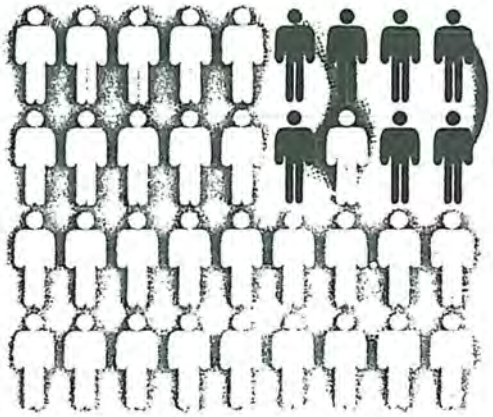

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Issues in utilizing epidemiologic data for the quantitative assessment of occupational risks

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Die Verwendung epidemiologischer Daten für die quantitative Beurteilung von beruflichen Risiken (Kurzfassung)

Eine Vielzahl der statistischen Methoden, die zur quantitativen Risikobeurteilung von beruflichen Gefahren verfügbar sind, wurde unter Verwendung von Daten aus Tierversuchen entwickelt. Obwohl die Bedeutung epidemiologischer Studien für die Beurteilung von Krebs- und Nicht-Krebsrisiken immer stärker anerkannt wird, hinkt die Entwicklung geeigneter statistischer Methoden zur Verwendung dieser Daten noch hinterher. Methoden, die für Daten aus Tierversuchen entwickelt wurden, sind im allgemeinen nicht auf epidemiologische Daten anwendbar, und das vor allem wegen der Unterschiede der Studiendesigns. Modelle, die zum Beispiel für die Risikoanalyse im Tierversuch entwickelt wurden (zum Beispiel das lineari-

sierte Mehrstufenmodell), sind im allgemeinen außerstande, Informationen zu den Auswirkungen verwandter zeitabhängiger Mit-Merkmale einzubeziehen – und eine Aussage zu diesem Punkt wird in den meisten epidemiologischen Studien in diesem Bereich gemacht. Dieser Vortrag bietet eine Übersicht über die speziellen Probleme, die bei der Verwendung epidemiologischer Daten für die quantitative Beurteilung von Berufsrisiken auftreten, und die für die Lösung dieser Probleme geeigneten statistischen Methoden. Zur Illustration dieser Themen werden Arbeiten der Autoren zur Risikobeurteilung von beruflicher Exposition bei Chrysotilasbest, Cadmium, Methylenchlorid, 1,3-Butadien, Kohlenstaub und Silika vorgestellt.

Problèmes liés à l'utilisation de données épidémiologiques pour l'évaluation quantitative des risques professionnels (Résumé)

La méthodologie statistique disponible pour l'évaluation quantitative des risques professionnels a été mise au point avant tout pour le traitement des données provenant des tests biologiques sur l'animal. Bien que l'on reconnaisse de plus en plus l'importance des études épidémiologiques pour l'évaluation des risques de cancer et d'autres maladies, la mise au point de méthodes statistiques adaptées pour l'utilisation de ces données a tardé. Les méthodes mises au point pour le traitement des données provenant des tests biologiques sur l'animal ne sont généralement pas applicables aux données épidémiologiques, principalement en raison des différences de conception des études. Par exemple, les modèles mis au point pour les analyses de risque à partir de tests biologiques sur l'animal (par exemple, le modèle linéaire multi-étapes) ne peuvent généralement pas intégrer des informations sur les effets des co-variables liées au temps et la censure sur ce point est un trait commun à la plupart des études épidémiologiques dans ce domaine. Les auteurs présentent une vue d'ensemble des problèmes particuliers rencontrés dans l'utilisation des données épidémiologiques pour l'évaluation quantitative des risques professionnels, et des méthodes statistiques appropriées pour traiter ces problèmes. Les travaux conduits par les auteurs sur l'évaluation des risques de l'exposition professionnelle à l'amiante chrysotile, au cadmium, au chlorure de méthylène, au 1,3-butadiène, aux poussières de charbon et à la silice seront utilisés pour illustrer ces problèmes.

Introduction

Many of the approaches available for quantitative risk assessment of occupational hazards have been developed for analyses of animal bioassay data.

Methods that have been developed for animal bioassay data are often not applicable to epidemiologic data, primarily because of differences in study design and data structure.

In the past, epidemiologic data has been often underutilized and misused in quantitative risk assessment (QRA). The explanation for this appears to be that risk assessment has been a field dominated by toxicologists and statisticians, and perhaps more importantly that few epidemiologists have taken an interest in this area. This situation appears to be changing as there has been a growing recognition of the importance of epidemiologic studies for cancer and non-cancer risk assessment. This trend has in part been fueled

by the growing skepticism towards the use of toxicologic data for predicting human risks [e.g. AMES and GOLD, 1990]. It also appears that more epidemiologists are becoming interested in participating in the QRA process.

SMITH [1988] has suggested that the primary limitation of epidemiologic data for QRA is the quality of the exposure data, and the primary limitation of toxicologic data for QRA is that it is based on the wrong species. He has also argued, that the uncertainty surrounding the exposure estimates for epidemiologic data is generally much smaller than the uncertainties surrounding the extrapolation of data from animal studies to predicting human risks.

There are, however, many other potential sources of uncertainty in using epidemiologic data for QRA [STAYNER, 1992]. Potential for confounding and other sources of bias (e.g. selection bias) may often severely limit if not completely invalidate the use of epidemiologic data for QRA. Inadequate length of follow-up may also be a serious limitation, particularly since we are generally interested in QRA in estimating lifetime risks and few epidemiologic studies follow a cohort for an entire lifetime. The fact that humans generally have multiple exposures complicates QRA for single agents; however, the fact that effects of hazards are studied in a real world context may also be viewed as an advantage that epidemiologic studies have over toxicologic studies.

Small sample size and resulting low statistical power may be the most severe limitation of epidemiologic studies particularly for detecting low level risks that are of potential public and regulatory concern. For example, the sample size that would be needed to have an 80 per cent chance (power) of detecting a lung cancer excess in a cohort study for varying levels of excess risk are presented in this slide. Most cohort studies would have an adequate sample size to detect an excess risk of 1 in a 100, which is estimated to require approximately 4,000 workers. However, very few cohort studies would include the more than 400,000 workers that would be required for detecting an excess lifetime risk of 1 in a 1000 which is a threshold for setting occupational standards in the U.S. [INFANTE,1995]. A study size of approximately 400 billion workers would be needed to detect a 1 in a 100,000 risk, which is greater than the world population (approximately 6 billion). Obviously, cohort studies are simply incapable of detecting excess lung cancer risks less than 1 in a 100,000 that are generally of concern in setting environmental standards.

Several attempts have been made in the past to use epidemiologic studies as a basis for validation of risk assessment models that have been developed using animal bioassay data [ALLEN et al., 1988; ZEISS, 1994]. Methylene chloride is a classic example in which several authors have used different methods for making comparisons between animal based RA models and epidemiologic findings, and have reached very different conclusions about their consistency [STAYNER and BAILER, 1993]. In this figure, the standardized mortality ratios and confidence intervals for lung and liver cancer reported in a study of Kodak workers exposed to methylene chloride is contrasted with those predicted from a QRA model based on an animal bioassay for liver and lung cancer. It may be seen from this graph that the confidence intervals from the epidemiologic study clearly encompass the intervals from the animal based QRA model at all of the exposure levels reported in this study. This result is actually what may be expected in using negative epidemiologic studies for testing QRA models based on animal data, since the variability surrounding the epidemiologic findings is often large.

Methods for Modeling Cancer Risks

A simple linear model based on the ratio of a relative risk (RR) estimate and the average exposure of an occupational cohort has been the most common approach used for developing cancer QRA models based on epidemiologic data [SMITH, 1988].

However, advances in statistical methods and computing now make it possible to develop far more sophisticated QRA models using epidemiologic data [STAYNER et al., 1995]. The results from applying several statistical and biologic models for estimating the relationship between occupational exposure to cadmium and lung cancer risks are illustrated in this figure. It has been suggested that "biologic" models such as the multistage model or the two stage clonal expansion model [MOOLGAVKAR and LUEBECK, 1990] may provide a better basis for QRA than statistical models. However, biologic models are, at one level, simply curve fitting exercises and these models are not necessarily any better than statistical models when (as in this case) no additional biologic information has been added to the model. On the other hand, when additional biologic information is incorporated into a biologic model the parameters from these models may be more biologically interpretable in comparison to the purely empirical models. It may be seen from this example that the choice of model may have a relatively large impact on the estimation of risk with risk estimates varying nearly an order of magnitude depending on the model used. It is difficult to say with epidemiologic data what kind of dose-response relationship is expected a priori. We have preferred to use empirical criteria of goodness of fit as a guide for model selection; however, one often finds that several models provide an adequate fit to the data. In this case, it is generally best to report a range of risk estimates from models that fit the data reasonably well.

Approaches using non-parametric smoothers such as splines or locally weighted regression methods [HASTIE and TIBSHIRANI, 1990] are a relatively new and promising tool for identifying exposure-response models. These methods can be used to estimate the exposure-response relationship within the range of the data and can provide support for the selection of parametric models for use when extrapolation beyond the range of the data is required. For example, a spline model and various parametric models were used to investigate the relationship between chrysotile asbestos exposure and lung cancer mortality which is illustrated in this figure [STAYNER et al., 1997]. The spline model results were found to be well approximated by an additive relative risk model, thus supporting the selection of this model for risk predictions.

Methods for Modeling Non-Cancer Risks

An attempt to identify a "threshold" dose below which there is zero excess risk has generally been the goal in risk assessments for non-carcinogens, and for some carcinogens as well. Risk assessors have generally attempted to identify such thresholds by collapsing the data into exposure categories and identifying the highest category without a significant increased risk as a no observed adverse effect level (NOAEL). Unfortunately, this is generally a misleading and inappropriate methodology for epidemiologic data. The choice of exposure categories is entirely arbitrary, since the exposure information in epidemiologic studies is generally continuous and not naturally categorical as it is in animal experiments. Thus the choice of different categorizations of exposure may influence the identification of the threshold level [BAILER et al., 1997]. Using epidemiologic data for non-cancer risk assessment is often further complicated by the fact that the response variable may be categorical, multinomial or continuous.

When the exposure data is continuous and the response variable is categorical or may be categorized, one approach is to simply fit parametric or non-parametric exposure-response models that are similar to those described above for cancer effects. For example, estimates of lifetime risk of coal workers pneumoconiosis as function of cumulative exposure to coal dust are presented based on a logistic model. These models may also be used to estimate a "benchmark" concentration, which is a level of exposure specified with a certain excess risk level (e.g. 10 per cent) [CRUMP, 1995].

Another approach that has been suggested is the fitting of models with a "threshold" parameter [ULM et al., 1990]. We have used this approach in a recent analysis of chrysotile asbestos [STAYNER et al., 1997]. The goodness of fit of the model (as judged by the deviance) was found to deteriorate as the threshold parameter was increased, suggesting that there was no threshold for either lung cancer or asbestosis. More commonly when threshold parameter are identified, their confidence intervals often include zero, i.e. no evidence of threshold present [BAILER et al., 1997]. It should be recognized that use of the term "threshold" for these model parameters may be misleading, and it might be better to describe this as a change point in the data below which there is no statistical evidence in the data for an adverse effect of exposure.

Finally, although epidemiologic risk assessment models have generally been based on estimates of exposure rather than dose a few authors have attempted to develop dosimetric models for humans that can be used for conducting true dose-response analyses [KRIEBEL, 1994]. For example, KUEMPEL [1997] has developed a dosimetric model for human exposure to coal dust. This model was used to estimate doses for a dose-response analysis of coal lung dust burden and coal workers pneumoconiosis. It was found that using estimates of dose rather than exposure generally improved the fit of the models. It was also observed that the pattern of coal dust retention in human lungs was dramatically different in human lungs than what would be predicted from animal based models. Humans appear to retain coal dust in the interstitium to a far greater extent than rodents.

Future Directions

The use of epidemiologic data as a source of information for QRA is likely to increase dramatically in the future. Many industries have instituted comprehensive exposure monitoring programs that will make it more likely that high quality exposure data will be available for epidemiologic analyses. Furthermore, the increasing development and application in epidemiology of biologic markers of exposure, effect and susceptibility may have a very large impact on the quality of epidemiologic data for QRA purposes [SCHULTE and MAZUCHELLI, 1991]. In closing, it should be emphasized that while epidemiologic data should have an increasingly important role it can never replace the crucial role of experimental studies in QRA. Epidemiologic and toxicologic data compliment one another, and it is only through the fullest use of both data resources that we can hope to fully characterize human risks from environmental and occupational exposures.

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