Taylor & Francis
Taylor & Francis Group

Inhalation Toxicology

International Forum for Respiratory Research

ISSN: 0895-8378 (Print) 1091-7691 (Online) Journal homepage: https://www.tandfonline.com/loi/iiht20

EPIDEMIOLOGIC APPROACHES TO RISK ASSESSMENT

Leslie Stayner, Randall J. Smith, Steve Gilbert, A. John Bailer

To cite this article: Leslie Stayner, Randall J. Smith, Steve Gilbert, A. John Bailer (1999) EPIDEMIOLOGIC APPROACHES TO RISK ASSESSMENT, Inhalation Toxicology, 11:6-7, 593-601, DOI: 10.1080/089583799197005

To link to this article: https://doi.org/10.1080/089583799197005

EPIDEMIOLOGIC APPROACHES TO RISK ASSESSMENT

Leslie Stayner, Randall J. Smith, Steve Gilbert

Risk Evaluation Branch, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA

A. John Bailer

Risk Evaluation Branch, Education and Information Division, National Institute for Occupational Safety and Health, Cincinnati, Ohio, and Department of Mathematics and Statistics, Miami University, Oxford, Ohio, USA

The use of epidemiologic data for risk assessment (RA) purposes has been increasing and should be expected to continue increasing in the future. In part, this trend is related to the continued controversy surrounding the use of toxicologic data for predicting human risk (Ames & Gold, 1990). It is also perhaps a reflection of improvements in the quality and suitability of epidemiologic data for risk assessment.

An often cited reason for not using epidemiologic data in RA is the lack of good quality exposure data. However, as Smith (1988) has argued, 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, such as potential confounding, inadequate length of follow-up, selection biases, multiple exposures, and limited sample size (Stayner, 1992).

The use of epidemiologic data in quantitative risk analyses (QRA) has been particularly problematic. Hertz-Piccioto (1995) has proposed some criteria for their use in QRA, which include (1) a moderate to strong association, (2) confounding is unlikely or controlled for, (3) other strong biases are unlikely, and (4) a monotonic dose-response relationship was observed. Some of these criteria may be too restrictive, particularly the first one (moderate to strong association). Negative studies with good exposure data may be used to at least provide an upper bound on what human risks might be. In principle, high-quality epidemiologic data should always be incorporated in QRA whether or not a positive association was ob-

Presented 4 December 1997; accepted 17 December 1998.

Address correspondence to Dr. Leslie Stayner, Risk Evaluation Branch (Mail Stop C15), Education and Information Division, National Institute for Occupational Safety and Health, 4676 Columbia Parkway, Cincinnati, OH 45226, USA.

Inhalation Toxicology, 11:593–601, 1999
0895–8378/99 $12.00 + .00

served. The fourth criterion is described Hertz-Piccioto as not being absolutely "necessary," which we would agree with, since the sparseness of epidemiologic data frequently leads to the observation of irregular exposure-response relationships in categorical analyses.

Unfortunately, the development of appropriate methods for utilizing epidemiologic data in RA has lagged behind those developed for toxicologic data. This may in part be due to the dominance of toxicologists in RA and the reluctance of many epidemiologists to become involved in this process. The purpose of this article is to provide an overview of different approaches to more effectively utilize epidemiologic data in the RA process.

HAZARD IDENTIFICATION

Epidemiologic data has always played and will continue to play an essential role in the identification of human hazards. In fact, many hazards such as tobacco use, benzene, arsenic, and asbestos were first identified in epidemiologic studies well before an animal model was developed. However, in most cases epidemiologic studies can only reliably detect relatively high risks. For example, for lung cancer it has been estimated that occupational cohort mortality studies only have the statistical power to detect excess risks on the order of 1 in a 100, and at best 1 in a 1000 (Stayner, 1992).

Epidemiologic studies often yield conflicting results when excess risks are too small to be reliably measured by conventional epidemiologic methods. The limits of epidemiology in addressing many current environmental hazards with relatively low risk have been a source of controversy that was recently highlighted in a paper by Taubes (1995). A good example of this problem is the literature on electromagnetic frequencies (EMF). There have been many inconsistencies in the findings from the relatively large number of residential and occupational studies that have been performed to evaluate the EMF/cancer hypothesis. Some studies have reported an excess of leukemia or brain cancer, while others have not.

One approach that is being increasingly used in an attempt to integrate and interpret the findings from multiple epidemiologic studies is meta-analysis. Meta-analysis may be defined as the "qualitative and quantitative analysis of a collection of epidemiologic results" (Berlin et al., 1993). Another approach that is being increasingly advocated is the "pooling" of epidemiologic data from multiple studies for use in a combined analysis (Friedenrich, 1993). Both meta-analysis and pooling have the potential of increasing the sensitivity of epidemiologic data for detecting low-level risks. For example, Kheifets et al. (1995, 1997) reported small but statistically significant excesses of leukemia (RR = 1.18, 95% CI = 1.12–1.24) and brain cancer (RR = 1.10, 95% CI = 1.05–1.06) in a recent meta-analysis of studies of individuals employed in electrical occupations (i.e., a surrogate for EMF

exposure). These papers are good examples of methods that should be used for exploring reasons for heterogeneity in meta-analyses of epidemiologic data, which may be expected due to differences in study design (Greenland et al., 1994). However, the small summary relative risks (<1.2) reported in these meta-analyses also illustrate the limitations of these techniques for resolving questions related to the detection of low-level risks. Most epidemiologists are reluctant to draw any causal conclusions from studies with relative risks less than 1.5, since it is generally difficult to rule out potential confounding or other sources of bias as an explanation for such findings.

VALIDATION OF ANIMAL BIOASSAY MODELS

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). These exercises have been the source of some controversy, and there is a need for development of appropriate methods for making these comparisons. 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 (Hearne et al., 1987; Tollefson et al., 1990; Stayner & Bailer, 1993). In Figure 1, 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 RA 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 RA 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 RA models based on animal data, since the variability surrounding the epidemiologic findings is often large.

DOSE-RESPONSE ASSESSMENT

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 RA models based on epidemiologic data (Smith, 1988). However, advances in statistical methods and computing now make it possible to develop far more sophisticated RA 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 Figure 2. It may be clearly seen from this example that the choice of model may have a relatively large impact on the esti-

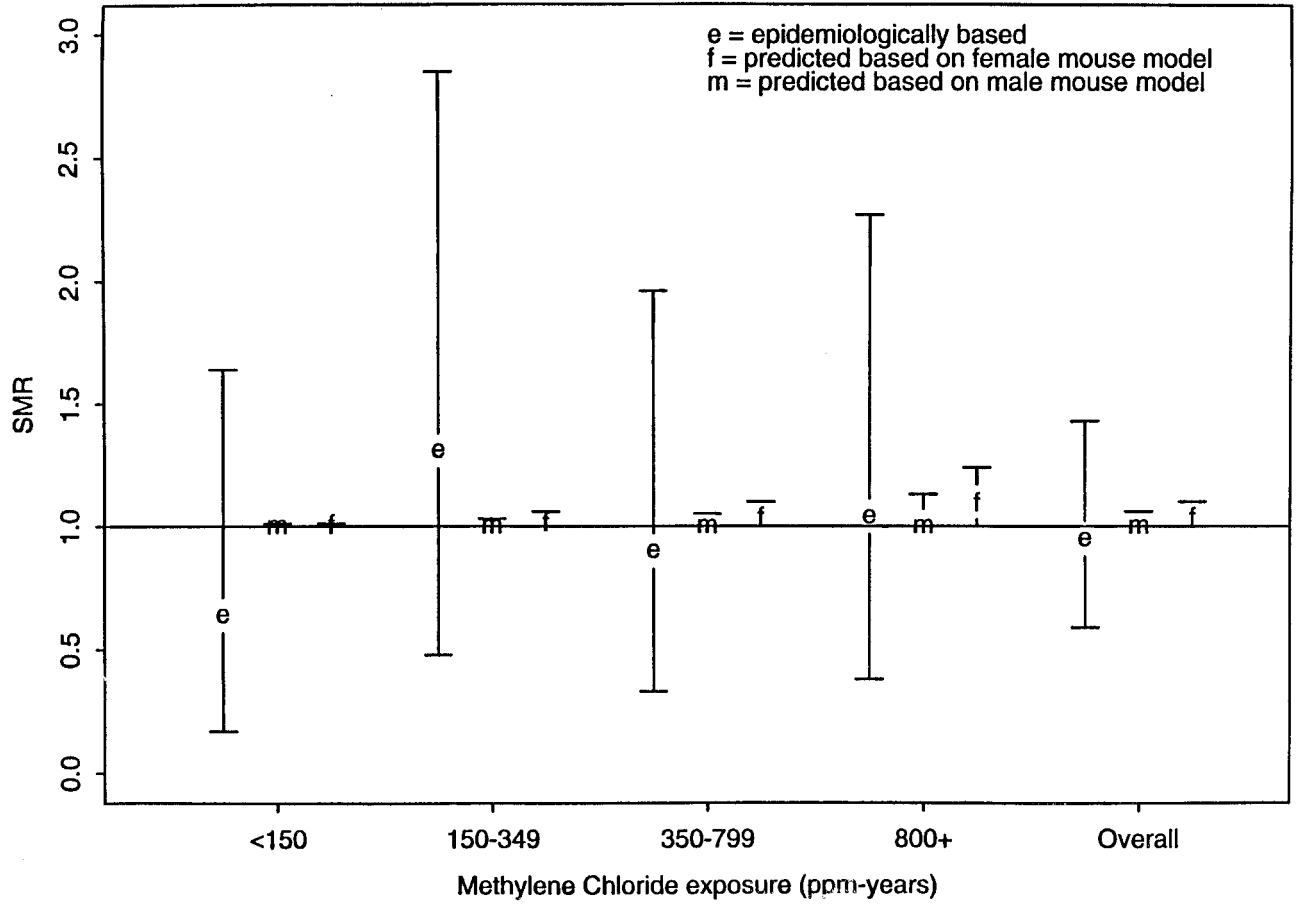

FIGURE 1. Standardized mortality ratios (SMR) and 95% confidence intervals with correction for the healthy worker effect (HWE) for cancers of the lung and liver combined. Adapted from Stayner and Bailer (1993).

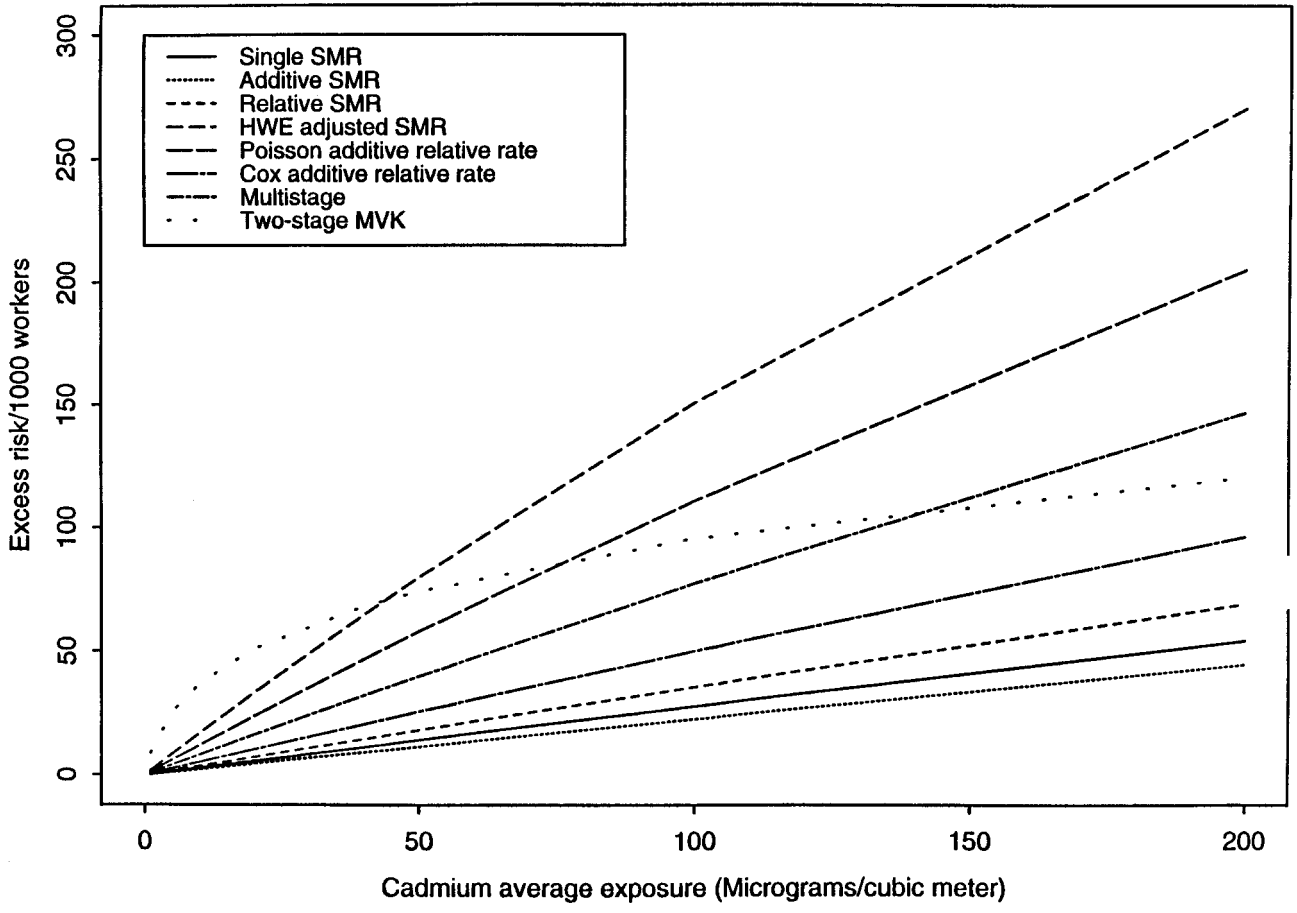

FIGURE 2. Comparison between lifetime excess lung cancer risk estimates derived from alternative models for occupational exposure to cadmium. Adapted from Stayner et al. (1995).

mation of risk. 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.

Approaches using smoothers such as splines or locally weighted regression methods (Hastie & Tibshirani, 1990) are a relatively new and promising tool for identifying exposure-response models. These methods can be used to estimate an exposure-response relationship within the range of the data and can suggest 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 Figure 3 (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.

The identification of a "threshold" dose below which there is zero risk is generally an issue in risk analyses for noncarcinogens, and increasingly for some carcinogens as well. Authors have frequently attempted to identify such thresholds by collapsing their data into exposure categories and identifying the highest category without an 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 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). Another approach to this problem is to fit models with a "threshold" parameter (Ulm, 1990). We have used this approach in a recent analysis of chrysotile asbestos, and failed to find evidence of a threshold for either asbestosis or lung cancer (Stayner et al., 1997). In addition, confidence intervals for threshold parameters may be estimated that often include zero, that is, 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. 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 the using estimates of dose rather than exposure generally improved the fit of

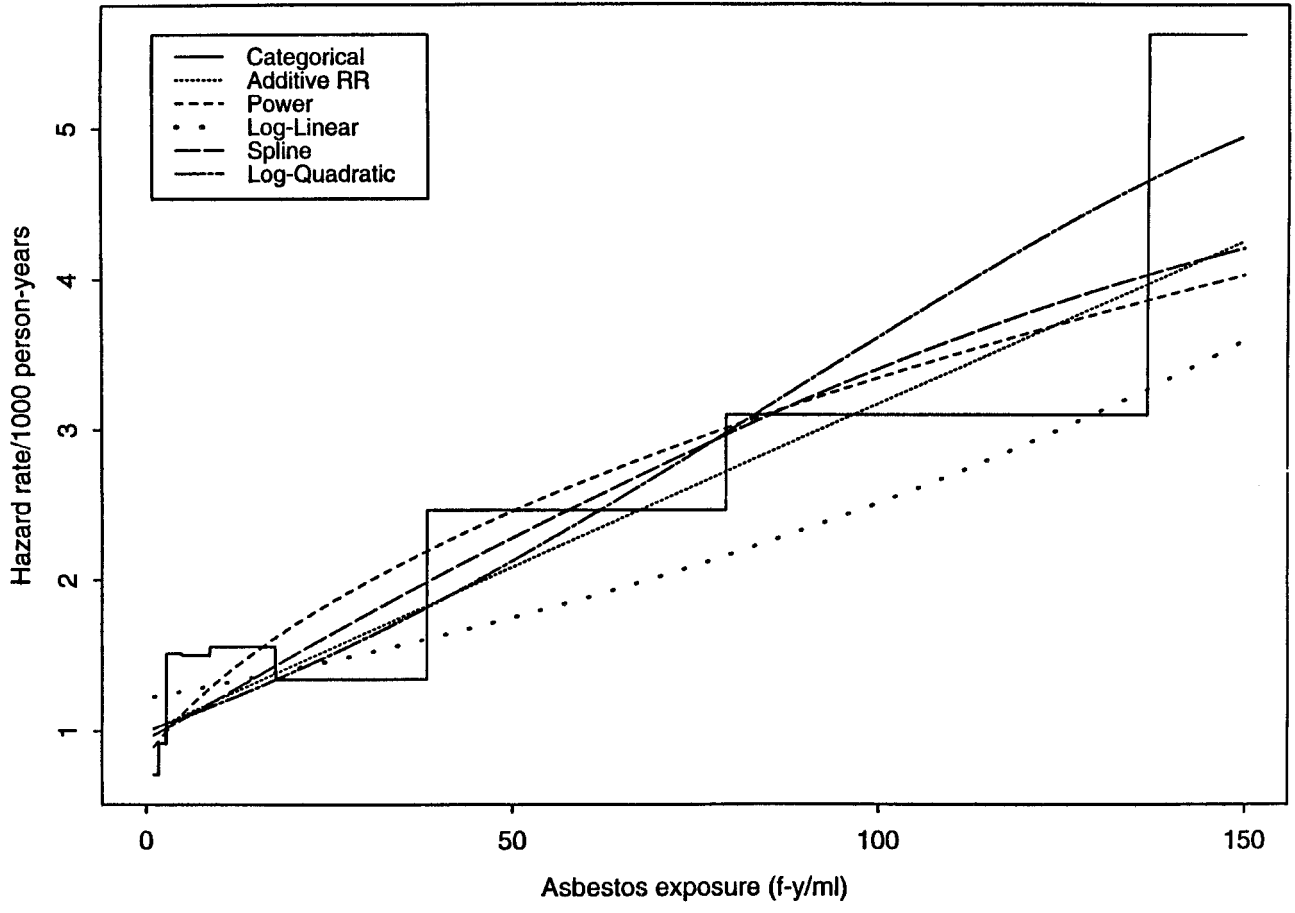

FIGURE 3. Lung cancer mortality rates as a function of cumulative asbestos exposure predicted by alternative models for white males, age 50 yr in 1940–1969. Adapted from Stayner et al. (1997).

the models. In general, it should be expected that measures of dose will improve RA models using epidemiologic data whenever the dose is not directly proportional to the exposure, as might be encountered in saturable processes.

FUTURE DIRECTIONS

The use of epidemiologic data as a source of information for RA 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 are likely to have a very large impact on the quality of epidemiologic data for RA purposes (Schulte & 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 RA. 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.

REFERENCES

Allen, B. C., Crump, K. S., and Shipp, A. M. 1988. Correlation between carcinogenic potency of chemicals in animals and humans. *Risk Anal.* 8(4):531–557.

Ames, B. N., and Gold, L. S. 1990. Chemical carcinogenesis: Too many rodent carcinogens. *Proc. Natl. Acad. Sci. USA* 87:7772–7776.

Bailer, A. J., Stayner, L. T., Smith, R. J., Kuempel, E. D., and Prince, M. M. 1997. Estimating benchmark concentrations and other noncancer endpoints endpoints in epidemiology studies. *Risk Anal.* 17:771–780.

Berlin, J., Longnecker, M., and Greenland, S. 1993. Meta-analysis of epidemiologic dose-response data. *Epidemiology* 4:218–228.

Friedenrich, C. 1993. Methods for pooled analyses of epidemiologic studies. *Epidemiology* 4:295–302.

Greenland, S. 1994. Invited commentary: A critical look at some populat meta-analytic methods. *Am. J. Epidemiol.* 140(3):290–296.

Hastie, T. J., and Tibshirani, R. J. 1990. *Generalized additive models.* London: Chapman & Hall.

Hearne, F. T., Grose, F., Pifer, J. W., Friedlander, B. R., and Raleigh, L. 1987. Methylene chloride study: Dose-response characterization and animal model comparison. *J. Occup. Med.* 29:217–228.

Hertz-Piccioto, I. H. 1995. Epidemiology and quantitative risk assessment: A bridge from science to policy. *Am. J. Public Health* 85:484–491.

Kheifets, L. I., Affifi, A. A., Buffler, P. A., and Zhang, Z. W. 1995. Occupational electric and magnetic field exposure and brain cancer. A meta-analysis. *Journal of Occupational and Environmental Medicine* 37:1327–1341.

Kheifets, L. I., Abdelmonem, A. A., Buffler, P. A., Zhang, Z. W., and Matkin, C. C. 1997. Occupational electric and magnetic field exposure and leukemia. A meta-analysis. *Journal of Occupational and Environmental Medicine* 39(1):1074–1091.

Kuempel, E. 1997. Development of a Biomathematical Lung Model to Describe Respirable Particle Retention and to Investigate Exposure, Dose and Disease in U.S. Coal Miners. Dissertation. Cincinnati, OH: University of Cincinnati.

Schulte, P., and Mazuchelli, L. 1991. Validation of biological markers for quantitative risk assessment purposes. *Environ. Health Perspect.* 90:239–246.

Smith, A. H. 1988. Epidemiologic input to environmental risk assessment. *Arch. Environ. Health* 43:124–127.

Stayner, L. T. 1992. Methodologic issues in using epidemiologic studies for quantitative risk assessment. *Proc. Conf. Chemical Risk Assessment in the DOD: Science Policy and Practice*, ed. H. J. Clewell, pp. 43–51. Cincinnati, OH: ACGIH.

Stayner, L. T., and Bailer, A. J. 1993. Comparing toxicologic and epidemiologic studies: Methylene chloride—A case study. *Risk Anal.* 13(6):667–673.

Stayner, L. T., Smith, R., Bailer, A. J., Luebeck, G. E., and Moolgavkar, S. H. 1995. Modeling epidemiologic studies of occupational cohorts for the quantitative assessment of carcinogenic hazards. *Am. J. Ind. Med.* 27:155–170.

Stayner, L. T., Smith, R., Bailer, J., Gilbert, S., Steenland, K., Dement, J., Brown, D., and Lemen, R. 1997. Exposure-response analysis of respiratory disease risk associated with occupational exposure to chrysotile asbestos. *Occup. Environ. Med.* 54:646–652.

Taubes. 1995. Epidemiology faces its limits. *Science* 269:164–169.

Tollefson, L., Lorentzen, R. J, Brown, R. N., and Springer, J. A. 1990. Comparison of the cancer risk of methylene chloride predicted from animal bioassay data with the epidemiologic evidence. *Risk Anal.* 10:429–435.

Ulm, K. W. 1990. Threshold models in occupational epidemiology. *Math. Computer Modeling* 14:649–652.

Zeiss, L. 1994. Current applications, limitations and future prospects. In *Chemical risk assessment and occupational health*, eds. C. M. Smith, D. C. Christiani, and K. T. Kelsey, pp. 113–122. Westport, CT: Auburn House.