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Improving Risk Assessment: Priorities for Epidemiologic Research*

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ABSTRACT

The Epidemiology Work Group at the Workshop on Future Research for Improving Risk Assessment Methods, *Of Mice, Men, and Models*, held August 16 to 18, 2000, at Snowmass Village, Aspen, Colorado, concluded that in order to improve the utility of epidemiologic studies for risk assessment, methodologic research is needed in the following areas: (1) aspects of epidemiologic study designs that affect dose-response estimation; (2) alternative methods for estimating dose in human studies; and (3) refined methods for dose-response modeling for epidemiologic data. Needed research in aspects of epidemiologic study design includes recognition and control of study biases, identification of susceptible subpopulations, choice of exposure

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metrics, and choice of epidemiologic risk parameters. Much of this research can be done with existing data. Research needed to improve determinants of dose in human studies includes additional individual-level data (*e.g.*, diet, co-morbidity), development of more extensive human data for physiologically based pharmacokinetic (PBPK) dose modeling, tissue registries to increase the availability of tissue for studies of exposure/dose and susceptibility biomarkers, and biomarker data to assess exposures in humans and animals. Research needed on dose-response modeling of human studies includes more widespread application of flexible statistical methods (*e.g.*, general additive models), development of methods to compensate for epidemiologic bias in dose-response models, improved biological models using human data, and evaluation of the benchmark dose using human data.

There was consensus among the Work Group that, whereas most prior risk assessments have focused on cancer, there is a growing need for applications to other health outcomes. Developmental and reproductive effects, injuries, respiratory disease, and cardiovascular disease were identified as especially high priorities for research. It was also a consensus view that epidemiologists, industrial hygienists, and other scientists focusing on human data need to play a stronger role throughout the risk assessment process. Finally, the group agreed that there was a need to improve risk communication, particularly on uncertainty inherent in risk assessments that use epidemiologic data.

Key Words: risk assessment, epidemiology, statistical models, dose modeling, dose-response.

BACKGROUND

In the past, risk assessment has been largely performed by toxicologists and statisticians, and research methods in this field have mainly emphasized toxicologic and statistical issues. Epidemiologists have generally been under represented in the risk assessment process because most risk assessments have been based on toxicologic rather than epidemiologic data. This situation appears to be changing with more epidemiologists expressing an interest an participating in risk assessment (Samet *et al.* 1998; Hertz-Piccioto 1995; Stayner *et al.* 1995), primarily due to an increase in the availability of high quality epidemiologic studies that are available for quantitative risk assessment, and lingering questions about appropriateness of animal models for predicting human risk (Ames and Gold 1990; Huff 1999).

EPIDEMIOLOGIC RESEARCH NEEDS

The Workshop on Future Research for Improving Risk Assessment Methods, *Of Mice, Men, and Models*, held August 16 to 18, 2000, at Snowmass Village, Aspen, Colorado, included an Epidemiology Work Group. Prior to the meeting in Snowmass, members of the group were invited to develop descriptions of research areas that they believed would enhance the utility of epidemiologic studies for risk assessment purposes. After presentation of recommendations by approximately 20 members of the group, the priority areas were organized into four broad categories: (1) aspects of epidemiologic study designs that affect the validity of dose-response estimation; (2) alternative methods for estimating dose in human studies; (3) refined methods for dose-response modeling for epidemiologic data; and, (4) the range of health

outcomes for consideration in future risk assessments. Additional comments were made by members of the group with respect the importance of greater involvement of epidemiologists throughout risk assessment and communication.

Aspects of Epidemiologic Studies Affecting Dose-Response Estimation

Study Biases

All epidemiologic studies are vulnerable to biases, including nonrepresentative selection of study subjects, misclassification of exposure or health outcome, and confounding. The extent to which biases are recognized and controlled determines study validity. Nonetheless, bias is never fully eliminated and may cause distortion of findings that ultimately are incorporated into risk assessments. For example, occupational cohort studies are often prone to a selection bias known as the "healthy worker effect," which is due to selection of relatively healthy workers for employment and inappropriate comparisons with national or regional population disease rates (McMichael 1976). For risk assessment, a particularly serious aspect of this bias is related to the fact that workers must be healthy to continue working, which is sometimes referred to as the "Healthy Worker Survivor Effect" (HWSE) (Arrighi and Hertz-Picciotto 1996; Robbins 1987). It has been shown empirically that HWSE may lead to dampening of dose-response relationships, which may even appear negative in occupational cohorts (Steenland and Stayner 1991).

Incomplete or erroneous exposure assessment is a pervasive shortcoming of epidemiologic research that can lead to biased dose-response estimates (Armstrong *et al.* 1998; Thomas *et al.* 1993). Deficiencies in exposure assessment can be avoided in future research provided adequate resources are allocated. For existing epidemiologic studies on which risk assessments might be based, systematic efforts to address the direction and magnitude of bias can be attempted with sensitivity analyses. The Work Group strongly endorsed both improving exposure assessments for planned future studies and exploiting statistical methods to examine measurement error bias in available datasets.

Susceptibility

Little is known about the quantitative effect of various human factors (*e.g.*, genetics, gender, age, diet) on responses to toxic environmental agents. The results of epidemiologic studies generally reflect "average" responses of the population, but may poorly reflect risks to susceptible subgroups. Epidemiologists commonly perform stratified analyses and related methods to detect effect modification of toxic exposures by host factors. This practice and the reporting of important subgroup-specific findings are encouraged; advances in statistical methods to quantify interactive effects will be beneficial in this regard. Identification of susceptible subgroups and quantification of subgroup risks will undoubtedly increase in importance in the foreseeable future as new information emerges from the Human Genome Project. There will be a definite need for the development of improved statistical methods such as those of Greenland and Poole (1994) to handle the extremely large amount of information that will emerge soon from molecular genetic research. There will also be a need for research on statistical techniques to incorporate this information into the development of risk assessment models.

Choice of Exposure Metrics

Cumulative Exposure. A convenient exposure metric for many epidemiologic studies has been cumulative exposure: the product of exposure concentration (c) and time (t). The convention is simple, recognizes that both c and t are important, and is a reasonable default when peak exposure episodes, exposure intermittence, and other exposure patterns cannot be estimated. In the future, epidemiologic research should take greater advantage of advances in environmental exposure assessment techniques that enable measurement of time-varying exposure levels. Research that quantifies the relative effects of cumulative, peak, and average exposures should shed light on exposure/disease mechanisms. This would logically lead to risk assessments based on the most relevant exposure patterns, not limited necessarily to cumulative exposure effects.

Exposure Distributions. Exposure estimates are frequently summarized (*e.g.*, average exposure) for a job, time period, or geographical location. This practice is prone to misclassification in situations where there is considerable heterogeneity of exposure within classification units. For example, in the workplace, exposures for a given job type can vary greatly depending on specific tasks performed, use of protective equipment, and local ventilation. Modern computational resources allow the incorporation of these factors to generate exposure distributions that are more valid personal indicators than are group averages. Research on methods for incorporation of exposure distributions in epidemiologic dose-response analyses should therefore be encouraged.

Exposure Windows. Related to the subject of exposure distributions is the timing of exposure which can be critical to the effect. For example, for many cancers with long latency intervals, exposures immediately preceding diagnosis or death may not be etiologically relevant (Thomas 1988). In other situations, recent exposures may be especially important if there are acute or late-stage effects. The timing of exposure is critical, sometimes even to a few days, as in the case of exposure to the developing fetus. Epidemiologic research on a variety of health outcomes is needed that more fully explores relevant exposure time windows in order to reduce exposure misclassification and hence uncertainty in risk assessments. Experience to date with these analyses is limited.

Choice of Epidemiologic Risk Parameters

Relative risk (*e.g.*, rate ratio, odds ratio) is the most common measure used in epidemiologic studies, particularly for studies of chronic diseases. Epidemiologic studies seldom report measures of risk difference (*i.e.*, excess risk) that might be used to estimate attributable risk and effect modification other than on a multiplicative scale. Other measures of risk such as years of life lost or lifetime excess risk may be more useful for informing risk managers. The ramifications of using various risk parameters in dose-response assessments deserves further study.

Dose-Response Modeling in Epidemiologic Studies

Application of "New" Statistical Methods

A variety of "new" flexible statistical models are available for application to dose-response assessment (Thomas 1998). For example, general additive models are

increasingly being applied to model complex dose-response data (Hastie and Tibshirani 1990). Hierarchial models (Greenland and Poole 1994) are also being increasingly used to combine information from different studies. Further application of such models should facilitate some of the more complex aspects of dose-response estimation, such as determination of threshold doses and estimation of nonlinear effects from peak exposures.

Benchmark Dose

The use of the benchmark dose in risk assessment has gained wide acceptance, but it has generally been employed with animal rather than human data. How human data are utilized in a benchmark dose presents its own set of issues, especially ambiguities in estimating points of departure and taking into account dose uncertainties.

Determinants of Dose in Human Studies

Development of Better Human Data for PBPK Models

Risk quantification by PBPK modeling generally has been limited by scarce human data on parameters, including tissue volumes, blood flows, tissue partition coefficients, and metabolism of common environmental contaminants. Human exposure experiments using a broad range of population subgroups are needed to define the parameter distributions associated with differences in age, sex, race, and genetic factors. Thus, it is recommended that a panel of relatively common toxicants be selected for testing that includes: (1) lipid- and water-soluble gases and vapors; and (2) particles in a range of sizes to determine deposition, uptake, and distribution. Simple field testing approaches to assess human exposures need to be developed, such as automated methods to monitor gas/vapor breath levels, measure ambient particle exposures, and measure exhaled breath for particles. In conjunction with these approaches, biomonitoring of toxicants and their metabolites in accessible tissues may be beneficial. Such data should be gathered in a variety of community and workplace settings to obtain representative samples for the population.

Biomarkers

Risk assessment for carcinogens, and other endpoints, is often hampered by extrapolations between animals and humans due to differences in toxicokinetic and toxicodynamic processes. Incorporating biomarkers of exposure, effect, and susceptibility into epidemiologic studies of occupationally and environmentally exposed cohorts has great potential to enhance the application of the studies in risk assessment. The application of biomarkers in epidemiologic studies is dependent on the availability of appropriate biological samples from exposed populations. Centralized repositories for archiving such samples would greatly facilitate the incorporation of biomarkers into epidemiologic studies. Sample repositories might be developed at appropriate Federal agencies or other large research institutes.

Biological Markers of Disease Susceptibility

Risk assessment for cancer has traditionally been built on stochastic models of the carcinogenesis process with parameters fitted to experimental or epidemiologic

data. It is generally accepted that cancer is a genetic disease, involving somatic mutations or other changes to DNA that can be induced by environmental exposures to carcinogens. It is also well established that some germ line mutations can produce a hereditary predisposition to cancer or an unusual sensitivity to environmental carcinogens. There is ongoing, widespread research in molecular genetics to identify polymorphisms involved in the metabolic activation of precarcinogens to their active form or their de-activation. Information derived from this research has great potential, ultimately, for characterizing especially susceptible subgroups within populations. Consequently, as new genetic marker information emerges, there will be an increased need for refined risk assessment methods that permit estimation of subgroup-specific risks.

Health Outcomes Needing Further Study

Historically, risk assessments based on epidemiologic data have focused mainly on cancer. The Work Group voiced a need for other endpoints to be studied as well. These include the following:

Reproductive and Developmental Outcomes. Reproductive and developmental effects have characteristics that make risk assessment for these endpoints more complex than for many other outcomes. For example, there is a wide range of specific endpoints, ranging from gonadal dysfunction, endocrine disturbances, and impaired reproductive performance to effects observed early in life, such as pregnancy wastage in subclinically or clinically detected conceptions, infant death, structural malformations, intrauterine growth retardation, deficits in development of structure or function, and transplacental carcinogenesis. Furthermore, the occurrence of an outcome may preclude another outcome or influence the shape of its dose-response. The role of repair and the timing of exposure are also key to understanding and quantifying risks from reproductive/developmental toxins.

Injury. Little research has been done on risk assessment for injuries, yet injuries are one of the leading causes of death and lost work time in the United States. Difficulties in studying injuries include problems of defining correct population denominators, estimation of appropriate doses, and poorly identified risk-modifying factors. Nonetheless, these should not be insurmountable problems for future epidemiologic research.

Cardiovascular and Respiratory Diseases. Cardiovascular disease is the leading cause of death in the United States, and there is evidence that exposure to various environmental agents, such as arsenic and fine particulate air pollution, may increase the risk of the disease. Respiratory diseases are currently of major public health concern. The increasing rates of asthma in the population offers a vivid example. Consequently, there is a clear need for including these diseases in future risk assessments.

OTHER CONSIDERATIONS

The Work Group discussed the need for increased representation of epidemiologists and industrial hygienists in the risk assessment community. It was noted that health risk assessment committees frequently do not include epidemiologists or exposure assessment scientists. Limited use of epidemiologic data and inadequate

training in risk assessment methods among epidemiologists and exposure assessors are the main reasons for this precedent.

It was felt that there was a need to develop guidelines for the skill combinations needed to adequately evaluate all studies when conducting risk assessment. Also needed are guidelines to be used in evaluating human studies in risk assessment projects. Increased training in risk assessment for epidemiologists is needed as well as additional support for epidemiologic research. There is a National Center for Toxicological Research; a National Center for Epidemiologic Research that emphasizes training in risk assessment might also be created.

Much of the research needed to improve risk assessments that use epidemiologic data can be done with existing data. The group decided that it was not necessary to conduct new epidemiologic studies to address the questions raised in the first area of research described above, "Aspects of epidemiologic studies affecting dose-response estimation". Re-analysis of existing data sets would be a logical starting point. Eventually, pooling of shared datasets to address low-level risks will be desirable. The Work Group endorsed this idea, but cautioned that appropriate attention will need to be paid to data confidentiality and protection of study subjects.

Finally, the communication of risk assessments to the general public in a manner that they can understand is a difficult challenge. Characterizing uncertainty is particularly difficult. Methods to characterize and explain uncertainty quantitatively and qualitatively are needed.

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