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Human and Ecological Risk Assessment

ISSN: 1080-7039 (Print) 1549-7860 (Online) Journal homepage: https://www.tandfonline.com/loi/bher20

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To cite this article: Paul Schulte (2003) Challenges for Risk Assessors, Human and Ecological Risk Assessment, 9:1, 439-445, DOI: 10.1080/713609874

To link to this article: https://doi.org/10.1080/713609874

Human and Ecological Risk Assessment: Vol. 9, No. 1, pp. 439-445 (2003)

Challenges for Risk Assessors

Paul Schulte[1]
National Institute for Occupational Safety and Health, Robert Taft Labs, MS C14, 4676 Columbia Parkway, Cincinnati, OH 45226; Tel(voice): 513-533-8302, Tel(fax): 513-533-8588; PSchulte@cdc.gov

ABSTRACT

At the early part of the 21st century, occupational safety and health risk assessors face a variety of challenges. In addition to technical issues, the challenges for risk assessors include: assessment of risks of mixtures/and synergistic effects; incorporation of biological information into risk assessments; development of different ways of presenting risk information to better inform policy makers and the public; better expressions of uncertainty and assumptions; and harmonization of assessments across agencies and countries. All of these challenges will occur against a background of unfolding understanding of human and other genomes. Risk assessors will be motivated and pressured to use genomic and related technologies, but ethical, social, and technical issues need to be addressed before widespread use.

Key Words: risk assessment, models, uncertainty, mechanisms, genomics.

INTRODUCTION

While over the last 25 years there have been many conferences and workshops on risk assessment, this workshop has a unique focus because it provides guidance to the field on research to improve risk assessment methods. To that end, we have brought together many of the people who have shaped the field of risk assessment to draw on their wisdom and experience. Risk assessment as it is currently practiced is a relatively young discipline that, while productive and informative, it is found to be wanting in several areas (Perera 1987; Paustenbach 1995; Samuels 1997; McMichael and Woodward 1999). It is quite difficult to make use in a predictive sense of the full range of information from animal, human, and other studies. The data available for quantifying risks are often sparse and estimation of risks have often not fully acknowledged the

[1] This paper was presented at the NIOSH Workshop on Research to Improve Risk Assessment Methods, held August 16-18, 2002, in Aspen, CO. Through administrative error, this paper should have been included in the workshop's proceedings, published in the *Journal of Human and Ecological Risk Assessment*, October 2002.

1080-7039/03/$.50

underlying uncertainties (Perera 1987; McMichael and Woodward 1999). Consequently, there is a need for improving and enhancing the approach.

The focus on the risk assessment methods is part of NIOSH's effort, in collaboration with numerous stakeholders, to develop and implement a National Occupational Research Agenda (NORA). NORA was developed in 1996 with input from 500 individuals and organizations from outside NIOSH (NIOSH 1996). It was created in response to limited resources and in recognition of the need to target research and develop mechanisms to promote collaboration. The goal of NORA is to provide a framework to guide occupational safety and health research nationally. The NORA process identified 21 priority research areas, of which >risk assessment methods, was one. NIOSH has been able to utilize NORA to form partnerships with other government agencies and organizations and leverage resources thus allowing for increased funding for grants and cooperative agreements; in FY99, NIOSH in conjunction with other agencies offered $1.55 million in RFA's for risk assessment methods. We hope this meeting will identify the research frontiers and stimulate further funding.

Risk assessment is a tool for society and decision-makers to choose actions when complete information on risks is not known. Hattis and Silver (1993) noted three scenarios in this regard: (1) when social policy decisions are in dispute; (2) when consequences of options are not subject to direct measurement; and (3) when scientific analysis of a hazard is incomplete.

While risk assessment can be traced back to 3200 B.C. (Covello and Mumpower 1985), modern risk assessment in the occupational arena is interlinked to the development of occupational exposure limits (see Hewett [1996] and Paustenbach [1998] for a history of occupational exposure limits). The first occupational exposure limits published in Germany in the 1880s, were driven by the growth of the chemical industry and development of toxicology as a discipline. These early risk assessments were based on determining a no observed adverse effect level as illustrated by the work of Gruber (1883) and Lehman (1886) (Cited in Paustenbach [1998]). Gruber concluded, after exposing 2 hens and 12 rabbits and himself to carbon monoxide that, "the boundary of injurious action of carbon monoxide lies at a concentration in all probability of 500 ppm, but certainly not less than 200 ppm." Thus, in a primitive way, he demonstrated a no-effect threshold risk estimate and lower bound on the estimate. He addressed issues of animal-human extrapolation by using human data (N=1) to compare with the animal data. For the most part, toxicological studies to identify NOEL, NOAELS, LOEL, etc., drove occupational risk assessments and standard setting for much of the twentieth century. Beginning in the 1930s the protection of human health from chemicals in the workplace, the marketplace and the environment became a commonly recognized goal (Friess 1987). The process involved the identification of some form of human dosage versus response relationships for undesirable health effects, the assessment of risk for those effects under specified modes of exposure to the chemical in question, and, finally, the setting of permissible exposure limits based on some form of societal perception of acceptable risk (Friess 1987). By the 1970s, the risk assessment process began to include review of epidemiologic data as well as animal data. By the 1990s, the Food and Drug Act of 1938, the Delaney Clause of 1958 (21 U.S.C 348(c)(3)(A)), the BEIR V Report (1990), and nearly 25 pieces of major health, safety, and environmental legislation that began in 1969 had shaped and helped establish the field of modern health risk assessment (Paustenbach 1995).

In addition to many technical issues there are large-scale challenges for occupational safety and health risk assessors today and in the near future. These include:

- Assessing risks of mixtures/and synergistic effects
- Assessing risks in subgroups
- Incorporation of biological information into risk assessments
- Development of different ways of presenting risk information to better inform policymakers and the public
- Better expression of uncertainty and assumptions
- Harmonization of assessments across agencies and countries

MIXTURES/SYNERGISTIC EFFECTS

Most risk assessments focus on a single substance, but many occupational exposures are to multiple chemicals or materials that are mixtures of chemicals (NRC 1988). Many of the problems for risk assessment of mixtures are related to toxicologic testing limitations. Testing complex mixtures present a formidable scientific problem (NRC 1988). There is need to assure that what is tested is what workers are exposed to because physical and chemical characteristics of mixtures may be different according to time, place, and handling. Beyond toxicologic testing, there is need to develop further methods for conducting risk assessments on workers exposed to mixtures that may act additively, antagonistically, or synergistically. Although some approaches to modeling risks of mixtures have been suggested (Moolgavkar *et al.* 1999), interpretation of the results is difficult.

RISK IN SUBGROUPS

There is considerable variability in response of human exposure of toxic substances. Variations in individual response can produce large errors in prediction of effects (Krewski *et al.* 1999). Conversely, group risk assessments can result in underestimates of the effects in various subgroups. New capabilities to identify groups on the basis of genetic polymorphisms related to metabolic capabilities and to compare those characteristics within and across species will provide new data on subgroup risks for risk assessors to consider. The problem for risk assessors is how much account should be taken of the differing risks experienced by identifiable subgroups within the population (Moolgavkar *et al.* 1999)

INCORPORATING BIOLOGICAL INFORMATION INTO RISK ASSESSMENTS

It is intuitive that the more realistic biologically based models for estimation of effects and construction of dose-response curves will do better than traditional methods of linear extrapolation, but this has yet to be widely demonstrated (McCellan

1995; Moolgavkar *et al.* 1999). How to incorporate biomarkers into risks assessments is an evolving topic that is being stimulated by the development of high throughput/high output technologies and approaches such as DNA microarrays, proteomics, and toxicogenomics (Rockett and Dix 1999). Interpreting and assessing the outputs of such technologies is a problem facing toxicologists, epidemiologists, statisticians and risk assessors (Henry *et al.* 2002).

In addition to the technical/scientific problems in summarizing, using, and interpreting such data is the risk of overloading the risk assessment community with large amounts of data or concerns about disparate mechanisms so as to delay public health action. While biologically based models appear useful and informative, their absence or incompleteness should not be reason to fail to take action in the face of other compelling but less mechanistic data.

DIFFERENT WAYS TO PRESENT DATA TO DECISION-MAKERS AND THE PUBLIC

Risk assessors face two problems in terms of data. One is the type and quality of data they get and the other is how they express results of their analyses. The two are linked. Hattis and Silver (1993) describe this problem:

> Experimental scientists in the Baconian tradition (Kuhn 1977) are reluctant to build elaborate mathematical models having been conditioned to view such theoretical effects as unproductive speculation . . . . On the other hand, epidemiologists and biostatisticians, in seeking to reduce problems to forms of which their traditional curve-fitting tools are most easily applicable, often are led to produce data fits that satisfy statistical criteria, possibly at the expense of attainable biologic or mechanistic realism that is required to use the results in risk modeling.

Additionally, the question is how research designs can be improved to meet the needs of policymakers (Samet 2000). Completion of the risk analysis is not the end of the risk assessor's responsibility. There is also the necessity of developing the analysis in a way that can be communicated and informative.

Alternate ways of characterizing risk can have large implications for how decision-makers and the public may react. For example, expressing risk in terms of years of potential life lost (YPLL) or disability adjusted life expectancy (DALE) rather than using traditional relative measures such SMR, or OR or even AR may be more evocative (Park *et al.* 2000) and more likely to induce action.

BETTER EXPRESSION OF UNCERTAINTY AND IMPLICIT ASSUMPTIONS

The uncertain qualities of risk assessments have long been a concern of risk assessors (Bailer *et al.* 1999; Paustenbach, 1989). Still there remains a tension between acknowledging uncertainty on the one hand, and then wholeheartedly believing assessments conducted with such uncertainties on the other. Similarly, assumptions used in risk assessments are often acknowledged but quickly forgotten when results are expressed or used. Samuels (1997) characterized it this way:

> Put simply, risk assessment models (indeed all models) sequester data in much the same way that a lawyer marshals the premises and evidence of a legal argument to prove a priori presumption, which he/she promotes or defends.

The National Academy of Sciences (1975) expressed it another way:

> Value judgments about non-commensurate risk factors in a decision such as life, health, aesthetics and equity should be explicitly dealt with by the politically responsible decision-makers and not hidden in purportedly objective data and analysis.

Applying the responsibility to decision-makers of explicitly dealing with hidden assumptions does not relieve risk assessors of the burden of identifying in detail all assumptions and in some cases, implications of a risk assessment. This includes, at the least, incorporation of sensitivity analyses for key assumption and parameters.

HARMONIZATION OF RISK ASSESSMENT EFFORTS

World-wide, there are approximately 1700 occupational health standards for chemicals, yet more than 65,000 chemicals are widely used in commerce. Moreover, the global nature of economies and the transnational span of companies, argues for global harmonization of standards and risk assessment methods and the classification and labeling of chemicals (IPCS 1997; Lundberg 1994; Zielhuis 1991). Harmonization is defined as an understanding of the methods and practices used by various countries and organizations to develop confidence and acceptance of assessments that use different approaches. Additionally, coordinated approaches among various risk assessment and standard setting groups, world-wide, could result in a larger number of standards being developed.

CONCLUSION

The challenges to risk assessors in the early part of the 21st century will occur as human and other genomes become more understood. Increasingly, risk assessors will be motivated or pressured to use genetic information in risk assessment (Simmons and Portier 2002). While such information can be useful in understanding mechanisms and reducing uncertainty, there are technical, ethical, and social issues that will need to be addressed before this genetic information can be widely applied. These include privacy of genetic information, protection of worker confidentiality, implications for regulatory agencies, application to tort litigation, and potential for discriminatory use of genetic information (Henry 2002). There is also the risk of genetic reductionism that will reduce complex workplace phenomena to simplistic genetic explanations. Risk assessors will need to guard against such pressures in addressing the challenges described in this paper.

All of these challenges identified herein have both methodologic and philosophical components. I hope that the consideration of them will provide a framework for the deliberations at this workshop and stimulate our thinking about future research directions.

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