Uncertainty in Risk Assessment

Current Efforts and Future Hopes

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ABSTRACT: The incorporation of sampling variability in estimates of excess risk has been part of risk assessment practice for decades. Currently, there is a strong desire to incorporate understanding of biological mechanisms into the models used for exposure assessment and exposure-response modeling. In addition, representing population heterogeneity in the assessment of risks and the identification of sensitive subpopulations is of great concern. Finally, the communication of uncertainty and variability remains a challenge to risk assessors. Based upon the presentations of workshop faculty, a summary of current practice when addressing uncertainty together with conjectures concerning future challenges for addressing uncertainty, are presented.

It is my pleasure, and my challenge, to provide a quick reaction and summary to the presentations made at the Workshop on Uncertainty in the Risk Assessment of Environmental and Occupational Hazards. This workshop brought together an international collection of scientists from government, academia, and industry. As an organizing principle, the presentations were grouped into four categories based upon the National Academy of Sciences risk assessment model.[1] These categories included hazard identification, exposure assessment, exposure-response modeling, and risk characterization. Regardless of the category to which a presenter was assigned, all were asked to consider how we can improve understanding of the sources and magnitude of uncertainty in the risk assessment process. Speakers were also asked to explore how uncertainty in this process can be reduced and how uncertainty should be described, characterized, and expressed with a particular view towards policy implications. My summary follows the order in which presentations were made. As a caveat, before I begin, these observations represent what I heard in these presentations and should be read as one perspective of the meeting.

In his opening remarks, Dr. P. Landrigan introduced the concept of sensitive subpopulations. He focused on the risk assessment of children and warned against a simple treatment of children as "little adults". The exposure routes and patterns for children along with metabolism and developmental differences may place them at

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much higher risk of adverse health outcomes when exposed to an environmental hazard. After he addressed the uncertainty inherent in the risk assessment for sensitive subpopulations, Dr. Landrigan described how variability in food consumption distributions and pesticide residue distributions were convoluted to obtain a distribution of pesticides in children. This type of calculation, in which the distribution of an outcome attribute is constructed from distributions of input variables, proved to be a common theme of this workshop.

In the hazard identification session, Dr. C. Maltoni challenged us to consider the concordance of animal and human studies. In particular, he reminded us that if a lack of agreement is observed between human and animal studies, then careful consideration of the adequacy of each study type is needed. In addition, Dr. Maltoni strongly argued for the utility of animal studies in identifying human hazards. His presentation argued that the uncertainty associated with extrapolating to human risks from mammalian models may not be as large as many have claimed. The second presentation of this session was given by Dr. A. Ahlbom. He provided a summary of the vexing case of evaluating the potential risks associated with exposure to electromagnetic fields (EMF). The fundamental question underlying this presentation was what provides sufficient evidence of a hazard? Dr. Ahlbom suggested a structure for hazard identification that represents mechanistic belief as a prior distribution potentially modified by data. Implicit in this Bayesian formulation was the potential for controversy in defining the prior distribution. In this example, should the prior distribution for EMF effects be a distribution about zero (no effect) or about some positive value (suggesting an *a priori* belief in positive risk associated with exposure). One possible strategy is to start with a different prior distributions and then examine the posterior distributions. If the posterior distribution does not vary much with specification of prior probability distributions, then this eliminates this concern. Dr. M. Soffritti provided examples of other hazards that were difficult to evaluate. These examples included EMF and gamma radiation exposure. In particular, evaluating hazards associated with low carcinogenic risks is a special challenge. This evaluation requires large studies with low level exposures and lifetime follow-up of exposed individuals. The next speaker of this session, Dr. C. Portier, summarized recent activities in the United States for assessing the risks associated with EMF exposures. Noteworthy in his presentation was a description of a national sample that was conducted in order to generate a picture of current EMF exposure. This appeared to me to be an important general message for risk assessment: better assessment of the distribution of the exposures leads to stronger, and more valid, variability analyses. Dr. Portier also noted the challenge of risk communication. Labeling of EMF as a *possible carcinogen* was described as being too fuzzy, and potentially confusing. Finally, he discussed risk characterization issues for which the integration of the exposure-distributions and dose-response models was needed. The final speaker of the session, Dr. J. Huff, reviewed issues concerning the use of animal studies to predict human cancer risks. Since cancer is a very complicated disease that is multi-causal and multi-step involving multiple genes and mechanisms, perfect concordance between animal models and human responses is unreasonable. The concordance of effects between mammals but not necessarily between sites should be viewed as encouraging. In addition, he noted that data sets generated for screening purposes,

that is, qualitative cancer assessments, are often called upon to provide the foundation for quantitative dose-response projections.

Kinetic models are often employed in exposure assessment as a means to extrapolate across routes of exposure, or across species. In the first presentation of the session devoted to uncertainty and variability in exposure assessment, Dr. L. Edler looked at how uncertainty could be incorporated into these models. His particular interests were in physiologically-based pharmacokinetic (PBPK) models. He commented that the basic formulation of these models involved a fundamental uncertainty issue—how many compartments should be included in the model? (As an aside, this may not be as important as the kinetic description of the compartments.) This was a structural uncertainty question. A related question addressed which parameter was most influential. He also raised the question of how uncertainty should be incorporated in a PBPK model—as a parameter distribution? Range of values? Can we consider correlation between model parameters? An uncertainty raised by Dr. Edler that may be overlooked was the differing laboratory analytics. This lab-to-lab variability in estimating PBPK model traits should also be considered in any uncertainty analysis. Finally, what factors influence the choice of error structure, for example, additive or multiplicative errors? Dr. P. Schulte then provided an overview of molecular epidemiology and how this might give us better understanding of the mechanism of the pathway from exposure to disease. He noted the importance of validation of biomarkers, both in terms of laboratory reproducibility and in terms of epidemiology utility. Finally, he challenged the audience to consider that more information does not necessarily reduce variability in the system. The more details we appreciate about exposure, susceptibility, and disease, the more we may appreciate our ignorance of other important issues. Dr. ten Berge addressed the definition of cumulative exposure metrics for safe dose assignment and stressed the importance of considering survival-adjusted analysis methods. Dr. A. Salvan took up the theme of toxicokinetic models again. He contrasted statistical models with PBPK and minimal physiologic toxicokinetic models in the context of dioxin risk assessment. In essence, the models range from completely empirical to extensive mechanistic models. Some compromise between these extremes is required. Dr. Salvan also noted that different estimation methods may inject yet another source of uncertainty in an analysis. Since human studies often include observations with incomplete data records, another source of uncertainty arises from whether such observations are omitted from an analysis or whether imputed values are supplied for the missing variables. Dr. H. Kromhout and Dr. D. Loomis presented an analysis of a large study of workers occupationally exposed to EMF. They identified numerous potential uncertainties in the assessment of EMF effects. Exposure assessment was a difficult exercise with concerns about the definition of job exposure matrices, the effects of duration and the effects of exposure intensity present. The effects of employing the wrong exposure measure are haunted with concerns about imprecision, and attenuation in the dose-response model is of greatest concern. Drs. Kromhout and Loomis used simulation studies to explore measurement error issues and presented dose-response with *bands of uncertainty* associated with different exposure patterns and window/lag assumptions. Dr. A. Woodward raised exposure assessment issues in the context of evaluating environmental tobacco smoke (ETS) exposure. He commented that the proper choice of an exposure measurement meth-

od depends upon its intended use, and that biomarkers and questionnaires possessed similar predictive validity for ETS. Dr. Woodward raised the important issue of uncertainty induced by different values and expectations. For example, risk tolerant and risk sensitive individuals, in a risk assessment based upon the same data, will be influenced by their very different frames of reference. The final session in the exposure assessment section was presented by Dr. A. Zavatti. Dr. Zavatti described the development of monitoring and prevention strategies. He argued that a network of specialists was required to manage resources for sustainable development and use of environmental resources.

The third session that focused on uncertainty in dose-response modeling was the home of many statistical talks. In the first presentation, Dr. R. Kodell provided a probabilistic structure for uncertainty factors that are commonly employed in non-cancer risk assessments. By characterizing the distribution of uncertainty factors with a log-normal distribution, he illustrated that the current defaults may correspond to an approximate 99th percentile for combined uncertainty factors. Dr. L. Ryan gave an overview of issues in developmental toxicology. She highlighted the challenges that arise when multiple endpoints are considered. If multiple responses might be considered for dose-response modeling and quantitative risk estimation, should the most sensitive site be considered or should we model the likelihood of at least one adverse response? The former may not be as protective as is widely believed. In addition, Dr. Ryan noted that the default omission of non-responders (non-pregnant in the context of teratology studies) may seriously bias the results. Dr. L. Stayner reviewed sources of uncertainty when employing human data from epidemiology studies for risk estimation. Included in this uncertainty list was the choice of best data set that might be addressed by multiple analyses, misspecification of the dose-response model which might be addressed by presenting multiple model projections, and all of the uncertainty inherent in observational study designs (causality, confounders, etc.). For retrospective cohort studies, the reconstruction of historical exposure patterns necessitates an analysis of uncertainty and variability. Dr. Stayner illustrated the use of Monte Carlo techniques to generate a distribution of parameter estimates for use in evaluating lung cancer responses in railroad workers exposed to diesel. He advocated reporting ranges of risk estimates for risk communication. Dr. K. Ulm introduced an alternative dose-response that accommodated thresholds in dose-response levels. Thresholds can be viewed as an estimated alternative to the no-adverse-effect level. With new German cancer guidelines including categories for nongenotoxic thresholds and genotoxic, low potency carcinogens, threshold ideas have become more important. Both of the talks by Drs. Stayner and Ulm described the uncertainty of the shape and form of the dose-response models that are used in risk estimation. Dr. K. Crump described a statistical meta-analysis based upon the distribution of p-values over different studies. This presentation predicted a larger number of liver carcinogens than have been observed by the United States National Toxicology Program. Dr. D. Krewski closed this session with a discussion of residential radon cancer risks. He presented the interesting idea of decomposing total variability/uncertainty into constituent parts. He described a characterization of model uncertainty and variability in a multiplicative model. He defined variability as the distribution of a component, and uncertainty as the distribution of a parameter that is a characteristic of the variability distribution. This definition led to discussion

and debate, with some feeling that the definition was overly restrictive. Developing a shared definition and understanding of uncertainty and variability is an important step. Risk assessment researchers must reach an understanding of these issues before we can effectively communicate uncertainty and variability to risk managers and to the public.

The fourth and final session addressed uncertainty in risk characterization and communication. Dr. J. Bailar raised the issue that perspectives on uncertainty are discipline dependent. This was initially illustrated with an example of perspectives on synergy, where the same pattern of data led to different interpretations of the presence and direction of interaction. Dr. D. Hattis reported on his work to develop a database of human variability in parameters of PBPK models. He employed a log-normal probability model that he justified on the grounds of a multiplicative effects model. A major message to take away from this presentation was that highly variable traits may not be covered by tenfold safety factors. Dr. F. Bois described a detailed analyses of PBPK models. He suggested an approach in which PBPK model fitting fed into cancer data fitting, followed by the establishment of human risk. Variability would be appropriately incorporated at each of these three phases of analysis. Dr. Bois argued for the need for better model validation and modification of model parameters by data based on a Bayesian framework. In addition, identifiability of population parameters and interspecies and interpopulation uncertainty factors were noted to be not well established. Extensions of this work may ultimately include integration with transport and effect models. Dr. N. Yamaguchi raised issues of external and internal validity when characterizing hazards. He continued the earlier theme of Dr. Stayner and others by discussing uncertainty in epidemiology studies, mentioning unrecognized confounding and effect modification. He also noted that the perception of risks and hazards among the public was an important component that may determine support for risk assessment activities. The closing speaker of this session, Dr. C. De Rosa, commented on data gaps in risk characterization and emphasized the need to conduct the research necessary to address ignorance and uncertainty. He advocated an open model of risk assessment with full involvement of all stakeholders in the process. The need to assess and articulate uncertainty in the risk assessment process, to risk managers and to the public in general, was another conclusion in his presentation.

As can be inferred from the preceding paragraphs, we had a rich collection of presentations that generated much discussion. Dr. J. Bailar commented during one discussion period that "we never know as much as we think we know" to which Dr. L. Stayner added "there is more uncertainty than we capture in our uncertainty analysis". Appreciation of these observations will sober even the boldest of risk assessors and will serve to keep us all focused on the need to view the analysis of uncertainty and variability in risk assessment as an evolving exercise. We are not yet close to any established formal paradigm for this analysis. Perhaps the establishment of guidelines for sensitivity analyses of varying types might be an objective for future deliberations. Even if we agree on sensitivity/uncertainty assessment guidelines, will we be able to communicate these concerns to risk managers and to the public? Perhaps one of our communication headaches is associated with the linguistic difficulties that remain—uncertainty versus variability; sensitivity versus uncertainty analyses (not *versus* but tools to analyze sensitivity and uncertainty simultaneously?). As noted in

many of the presentations at this meeting, addressing *data gaps* to mitigate uncertainty should be a goal we all share. Even if we can adequately address these concerns, the expansion of this debate to consider humans as part of the larger ecosystem looms on the horizon. My intention is not to close on a depressing note. I am excited about the innovation and development of tools to incorporate uncertainty and variability in risk assessments. I believe this workshop addressed the goal of understanding the sources and magnitude of uncertainty in the risk assessment process. Furthermore, I believe the workshop also addressed the objective of describing, characterizing and expressing uncertainty and variability. I believe that more effort can and should be spent addressing the policy implications of uncertainty and the communication of uncertainty to the public.

ACKNOWLEDGMENTS

REFERENCE

1. NATIONAL ACADEMY OF SCIENCES. 1983. Risk Assessment in the Federal Government: Managing the Process. National Academy Press, Washington, D.C.