Common Themes at the Workshop on Uncertainty in the Risk Assessment of Environmental and Occupational Hazards

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The workshop entitled "Uncertainty in the Risk Assessment of Environmental and Occupational Hazards", which was held during September 21–26, 1998 in Bologna, Italy in the historic council chamber of the Bologna Town Hall, was a collaborative effort of the European Ramazzini Foundation and the International Statistical Institute. The workshop had three objectives: (1) to improve understanding of the sources and magnitude of uncertainty in the risk assessment process; (2) to discuss and disseminate means for reducing such uncertainty; and (3) to describe, characterize, and express uncertainty in risk assessment, with a particular view towards its implications on policy. The workshop sessions revolved around the themes of uncertainty and variability in the four components of a common model of the risk assessment process. The presentations were grouped into sessions that considered uncertainty in hazard identification, exposure assessment, exposure-response modeling, and risk characterization. The workshop was designed to be highly practical. The uncertainties associated with the assessment of health risks of electromagnetic fields and of dioxin were the focus of more than one presentation. The perspectives of participants from academia, industry, and government enriched discussions about the evaluation and communication of uncertainty and variability throughout the risk assessment process.

The municipal council chamber in Bologna played host to a three-day workshop devoted to uncertainty in the risk assessment of environmental and occupational hazards. The sessions were organized into four components reflecting hazard identification, exposure assessment, concentration-response modeling and risk characterization. These four sessions were based on a common risk assessment paradigm suggested by the National Academy of Sciences in 1983.[1] After three days of deliberations, we noted ten general issues that appeared in more than one presentation and discussion. Here is what we heard and saw, or thought we did.

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1. Heterogeneity in responses should not be treated as just another source of uncertainty. Imagine a population for which several human studies indicate that some compound C is carcinogenic, but that quantitative assessments derived by similar methods range from 5 to 45 cases per thousand exposed—a ninefold difference. (This would be very small uncertainty in many risk assessment contexts.) Imagine now that you discover that the adverse effect is limited to persons who lack a detoxifying enzyme, and that a nonrandom segment of the population is so affected. The true risk is zero for some and 50 for others, with risks in the study populations determined by enzyme status, although we do not know the status of the next person we will encounter. This seems to be fundamentally different from the situation in which there are serious measurement problems, or errors in default assumptions, or other kinds of uncertainty.

There is a problem with this. Whether we call something heterogeneity or uncertainty depends on our state of knowledge. In an extreme *clockwork* universe every person has probability zero or unity of some dread outcome under any fixed set of circumstances—but we still do not know individual risks because we cannot tell what is going on cell by cell, molecule by molecule. Both variability (from unknown causes), as is reflected by this heterogeneity, and other uncertainties, are measures of our ignorance.

Some speakers highlighted special kinds of heterogeneity in risk, including:

- children are not little adults;
- sensitive subpopulations;
- synergies with prior, concurrent, or later exposures to other agents.

Some of these variations can be removed by appropriate scaling (e.g., by body weight) or other transformation (e.g., to a power of body weight as a surrogate for metabolic differences) but analytic methods that reduce the range or impact of variation (e.g., logarithmic transformation)—especially at the high end of risk—may run directly contrary to what is needed in protecting the public health.

2. Laboratory animal and human observational studies may lead to quite different risk estimates, but data often agree that a risk exists despite variations in specific outcomes or magnitudes of risk. Thus, there was a strong sense that animal studies offer a valid and important tool for identifying human hazards. In general, moves toward biologically-based models, and away from the familiar *default assumptions,* may simply replace a few large uncertainties with many small ones and offer no guarantee of any improvement in the product. However, this may provide a more honest depiction of our state of knowledge about potential hazards. Possible explanations of differences include substantial laboratory-to-laboratory variation in estimates of parameters that are critical in PBPK models.

3. What is sufficient evidence to justify what kind of risk management response? Intervention may be based on levels of evidence ranging from a faint suspicion, to an equivocal laboratory finding, or to conclusive epidemiologic studies, with many steps between. Similarly, the level of interven-

tion can range from a little private worry, to voluntary personal avoidance, to public warnings, to strict labeling, to controlled use, or to outright prohibition, again with many intermediate steps. Somehow these two continuous scales, strength of evidence and risk management steps, should be linked. There appears to be little or no research on this topic, either theoretical or applied, although opinions are rife.

4. Each new study should be interpreted in a context of what is already known. This implies a Bayesian approach to each step of risk assessment. This is a fairly new and evolving approach in risk assessment. Interesting questions concerning the nature of a prior distribution may be related to risk management ideas. For example, should a prior distribution reflect a belief that a potential hazard has no adverse effect—perhaps as reflected in the distribution of an associated regression coefficient, with the hazard being centered at zero? Alternatively, should we start with a prior distribution that reflects a belief that the substance is hazardous? Answers to these specific questions are necessarily political and philosophical as much as they are scientific.

5. The more that a particular risk is concentrated on a small, identifiable subpopulation, the easier it is to identify and measure the risk, but the greatest population-wide hazards may be from very low exposures of millions of people. In the limit, if every person is affected by some exposure, the risk will merge into the background rate and be undetectable, or even unsuspected. The challenges to evaluating the risks associated with such small exposures are very great and these need to be addressed in well-designed and extensive animal and human studies.

6. Toxic hazards are complex. Cancer has multiple causes, with multiple steps, and a likelihood of response heterogeneity, as well as multiple biologic mechanisms of causation. Laboratory observations suggesting that risk has a threshold or sublinear form may not carry over to humans who live in a sea of toxic agents and may already be well along some biologic pathway before they encounter the new hazard, which could then create linear or supralinear risks. Reproductive responses are even more complex—aspermia, failure to ovulate or implant, birth defects, failure of nursing, and many others.

These complexities are well-understood by workers in the field, but not always by risk managers or by the public, who want sharp lines between what is risky and what is safe. Communicating this complexity to risk managers and to the public remains one of our great challenges in risk assessment.

7. All critical assumptions underlying the risk assessment process must be identified and, to the extent possible, validated. For example, the shape of concentration-response models, mechanism of toxicity, and questions of species extrapolation haunt most or all risk assessments. However, even the identification of assumptions may be difficult and incomplete. Sensitivity analysis can help to define the range of uncertainty, but this approach

depends on knowing all of the critical inputs and reasonable ranges for their values.

8. It has become a truism that the greatest uncertainties in risk assessment are likely to come from poor understanding of exposures. In addition to uncertainties about levels of exposure, we often do not know how to summarize the exposure captured by the risk. For example, for some reproductive hazard, should we use the cumulative exposure at low levels over a lifetime, or the maximum eight-hour time-weighted average during the third month of pregnancy, or something else? Choices of metrics for exposure are seldom justified or formally evaluated. This was stated or implied in several presentations, but not addressed in a direct way by any speaker.
9. Completion of a risk assessment document is not the end of the road. Contrary to the recommendations of the National Academy of Sciences in their 1983 *Red Book*, risk assessors must be involved in all later stages of risk management and risk communication, with special attention to uncertainty, however unpopular that may be.
10. There are many critical gaps in the data for specific toxic agents, but there are also gaps in matters that lie beyond concerns about toxic hazards taken one-by-one. Examples include the parameters needed in PBPK modeling, critical aspects of transport, general responses to very low exposures or background levels of risk, and many other things. Building databases may be less exciting scientifically and less appealing politically than the carcinogen-of-the-week approach, but it is essential for improvements in risk assessment, including reduction of uncertainty. Sensitivity analyses based on solid data will have more credibility than those based on a series of convenient *ad hoc* distributional assumptions.

Given these impressions, what is next? We believe that uncertainty and variability will always be a part of the risk assessment process. This implies a need to continue to develop the tools to appropriately accommodate these concerns in risk assessment. However, this activity will not be enough. A closer collaboration between risk assessment scientists and social scientists specializing in risk communication is needed. We must communicate uncertainty and variability to risk managers and to the public in order to be effective risk assessors.

REFERENCE

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