COMMENTARY

Process and Assumptions in Risk Assessment

RONALD W. HART, Ph.D.*
and ANGELO TURTURRO, Ph.D.

National Center for Toxicological Research
Jefferson, AR 72079

Introduction

A key problem in regulatory research is how to assess risks to humans from hazardous materials under practical conditions of use and exposure. This assessment is important in order to make a priority listing of the risks associated with toxic substances, in order to devise techniques to cope properly with the ones identified, and in order to evaluate the success of programs to manage risk. Until the 1960s, concern was almost completely directed towards short-term effects (dizziness, nausea, cholera, etc.), leading to fairly simple risk assessments with easily measurable toxic endpoints in small groups (e.g., "If you eat this poisonous mushroom, you will vomit and probably die."). With the growth of our understanding of the chronic consequences of hazardous exposure, much of the focus has now shifted to chronic, long-term effects, for doses low enough to have no easily observable toxic effects, for populations in the millions. It is not a simple task to estimate the results of exposure to an agent on a complex toxic endpoint, such as in carcinogenesis, years after the initial insult. This is particularly true in a population with such confounding factors as diversity of lifestyle, diet, etc., and it is especially complicated if much of the data on adverse effects are derived from animal assays.

The quantitative prediction of adverse human health effects is an evolving science. In making risk assessment decisions, a number of scientific judgments and science policy are used. For instance, for carcinogenic risk there are over 50 components which require resolution. In actuality, these determinations are a series of assumptions used to bridge gaps in understanding and deficiencies in data. Use of each of these assumptions results in an attendant uncertainty which adds to the total uncertainty in a multiplicative fashion. Uncertainty in a risk assessment leads to complications in use of its results.

It is important to understand the process of risk assessment as a formalization of common-sense practices used in everyday life. However, many of these practices are implicit and consideration of the formal process may be useful.

Risk Assessment: The Process

Risk assessment, as noted in a recent government consensus document, generally can be divided into four parts: (1)
hazard identification; (2) exposure assessment; (3) hazard assessment; and (4) risk characterization.

**Hazard Identification**

Hazard identification entails a qualitative evaluation of both the data bearing on an agent’s ability to produce adverse health effects and the relevance of this information to humans. Many risk assessments used for regulatory purposes are terminated at this stage because this determination is sufficient. The major sources of information for this step are epidemiological studies, animal studies, short-term tests, both *in vitro* and *in vivo*, and other studies such as comparative metabolism and pharmacokinetics.

**Exposure Assessment**

This step evaluates the types (routes and media), magnitudes, time and duration of actual or anticipated exposures, and of doses when known, and, when appropriate, the number of persons who are likely to be exposed.

**Hazard or Dose-Response Assessment**

Hazard or dose-response assessment tries to estimate the relationship between the dose of a substance and the incidence of adverse health effects for the species of interest, usually humans. For all toxic endpoints other than cancer, a no-observed-effects-level (NOEL) and safety factors are usually used. For cancer, no NOEL is defined because it is usually assumed that there is no threshold. Instead, a dose-response curve is derived directly from animal or epidemiological data and then extrapolated to the dose region of interest, usually using one of a number of different models for extrapolation to low-dose.

**Risk Characterization**

Risk characterization involves estimating the probable incidence of an adverse health effect in humans, under various conditions of exposure, including a description of the uncertainties involved. Recent efforts\(^1\) can include a total evaluation of the qualitative evidence, the exposure information, the quantitative results, and can contain an evaluation of the uncertainty in these estimations for a particular agent as well as a summary of the assumptions that are used.

**Assumptions Used in Risk Assessment**

Each step in the process would quickly come to a halt unless a number of assumptions were used to patch the voids created by the lack of data and mechanistic understanding which exists for a particular chemical or toxic endpoint. Since what is known about the mechanism of a particular toxic endpoint or the distribution and effect of a particular chemical is so variable, the significance to that contributed by an assumption is also quite variable. However, some fairly common assumptions are denoted. There are assumptions of physical, chemical, and biological natures. The assumptions of a biological nature can be understood as extrapolation across conditions (i.e., from the conditions of the test to the actual conditions of human exposure) and extrapolation across species (from the species tested to humans).

**Hazard Identification**

1. **Extrapolation Across Conditions**
   
   A. Genetic factors are not confounding when generalizing the specific conditions in an epidemiological test to the total population.
B. Different physiological states, e.g., age, hormonal status, stress, disease, etc., are not confounding.
C. Diseases, especially tumors, act independently.

2. Extrapolation Across Species
A. Similarity in animal and human metabolism.
B. Exposure for a fraction of a lifetime of an animal (raised to some power, usually between 2 and 8) is equivalent to human exposure for the same fraction of a lifetime.

Exposure Assessment

1. Physical Assumptions
A. Certain spatial distributions of compounds, e.g. point estimates or distributions, can model real-life distributions.
B. Time variations of distributions, dependent on physical factors, are known.

2. Extrapolation Across Conditions
A. Media (i.e., substrate such as soil type) will not affect exposure.
B. Population characteristics (age, sex, etc.) will not affect exposure.

Hazard Assessment

Hazard assessment uses some assumptions which have been the source of lively debate over a long period of time. They include:

1. Extrapolation Across Conditions
A. Average dose is equivalent to dose varying in duration, frequency, and rate.
B. Target site dose is directly proportional to administered dose.
C. Adverse biological effects become greater with increasing chemical dose, and the model to extrapolate to low doses is known.

2. Extrapolation Across Species
A. Data available for more than one strain are combined using ad hoc techniques.
B. Standardized dosage scales (e.g., mg/kg body weight, mg/m² surface area) are used.

Risk Characterization

Risk characterization is dependent on all the assumptions which are used in its component processes, hazard identification, exposure assessment, and hazard assessment.

Many of the assumptions have multiple impacts and, therefore, can intervene in the process at a number of points.

The impact of the previous assumptions on the risk estimation can be immense. For instance, simply using a metamer of mg per m² rather than mg per kg-body weight can result in a difference in risk of an order of magnitude (see table I). Others have more profound effects.

The problem of uncertainty should not be underestimated, especially in using the figures generated by this process in setting action levels for agents. However, it should also be appreciated that this process derives the best scientifically-based guess that can be made currently. Attempts to quantitate better the process are actually a series of algorithms

<table>
<thead>
<tr>
<th>Species</th>
<th>ppm in Diet-day</th>
<th>mg/m²-Area-day</th>
<th>mg/kg Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>15</td>
<td>3</td>
<td>639</td>
</tr>
<tr>
<td>Rat</td>
<td>17</td>
<td>5</td>
<td>730</td>
</tr>
<tr>
<td>Man</td>
<td>47</td>
<td>37</td>
<td>25,500</td>
</tr>
</tbody>
</table>

to approximate better the complex biological processes underlying the interaction of organism and environment, and are in the vanguard for better understanding of the basic process involved in toxicology.

**Risk Assessment in a Clinical Context**

Although this methodology was used to define population risks for exposure to toxic substances, it is interesting to look at the process if used in another context. For instance, if one considers clinicians as risk managers, i.e., trying to control health problems in the presence or absence of a disease, a clinician may:

*Evaluate Hazard*—Determine which factors in a lifestyle are related to adverse effects (smoking, obesity), age-specific phenomena (menopause), genetics (family history), untoward drug effects.

*Assess Exposure*—Determine the extent of the factors (amount of smoking, extent of obesity, etc.).

*Assess Hazard*—Judge the impact of each hazardous factor at the level of “exposure.”

*Characterize Risk*—Integrate the impact of the lifestyle factors and exposure, to make evaluations of the status of the individual.

From this viewpoint, there are a number of useful key lessons to be learned from the experiences of risk assessment when used for evaluating risk from toxic substances.

1. It is critical and useful to evaluate the assumptions used and to estimate the uncertainty associated with the assumptions used. For instance, some important factors, such as smoking, effect of cholesterol levels, etc., are extrapolated across conditions (from the epidemiological studies which defined these risk factors). Other factors, such as drug dosages and screens for certain antibodies, frequently assume extrapolation across species. Each assumption has associated uncertainties, which should be kept in mind when making determinations.

2. Quantitation, though difficult, contributes significantly to ultimate control of the problem. Quantitation tests the process severely, exposing the areas of least knowledge, and leads to understanding. In this regard, it is useful that there are a number of clinical tests which give quantitative responses, which can better be compared against the results of control efforts. Quantitation such as this is important and should be expanded.

3. Biomarkers are useful. Significant advances in the evaluation of risk have come with the discovery of biomarkers for toxic effects. These biomarkers can be used to test experimentally the assumptions used. In essence, a number of clinical tests are biomarkers. A concerted program to exploit these biomarkers quantitatively might be very useful.

**Conclusion**

It is clear that the assumptions which underlie an assessment can lead to real uncertainty in the results of an assessment, and these assumptions can be as important as the assessment itself. It is important to see these uncertainties not as problems as much as an opportunity to understand the basic biological, chemical, physiological, and physical processes which are part of the interaction of an organism with agents. Placing the methodology in a new context, i.e., cross-talk in technology, can be useful in indicating areas to consider in other contexts.

**References**

2. Department of Health and Human Services
(DHHS), Committee to Coordinate Environmental and Related Programs (CCERP): Risk Assessment and Risk Management of Toxic Substances. A Report to the Secretary, DHHS, April, 1984.


