8 RISK AND EXPOSURE ASSESSMENT FROM TOXIC CHEMICALS

Edited by
James Gillett and William R. Rish

with contributions by
Bev L. Huston, Duncan Murdoch, and Ortwin Renn

OVERVIEW

Basic Paradigm

The assessment of risk derived from exposure to chemicals causing measured, adverse health effects relies upon bringing together three streams of information:

1. the exposure pathway(s) from a source presenting a concentration of the chemical over space and time, taking into account the transport and transformation of the chemical through these pathways
2. the characterization of the nature of hazard, i.e., the toxic effects, caused by the chemical in the target organisms presented with that exposure
3. the dose-response relationship of the exposure to the effect, taking into account the age, size, physiological status, and other factors affecting the nature and intensity of effect(s)

Point 2 determines the process by which Point 1 is linked to Point 3, and is used later to place the nature of the impact into perspective for *risk management*, the series of decisions and actions by which risks are reduced.

Each of the above steps constitutes a body of science for which numerous questions remain, and answers to these are critical for risk assessment. There

are specific points that are especially important relative to concerns in the Great Lakes Basin ecosystem, and there are some generic questions that pertain to the risk assessment process, irrespective of geographic or regional issues, which are listed below.

- How will the risk assessment results be used?
- What mitigation and remediation methodologies might be expected to arise as heuristic outcomes of risk assessment?
- What is the explanatory power of risk assessments?
- How is uncertainty worked into risk assessment and its use and exposition?
- What is the nature of comparative risks and benefits, and how are they commensurated?
- How are risk assessments to be calibrated or verified?

Chemical Risk Assessments

Risk assessments are carried out in order to ascertain whether or how the risks attendant with a technology might be managed (Wilson and Crouch 1987). Each of the chemicals involved in human exposure must be subjected to a risk assessment for the general population, and particular attention should be given to site-specific assessments where high-risk chemicals are present in the environment **and** result in exposure to people.

One means of doing this for the large numbers of chemicals involved in the Great Lakes Basin would be to construct a set of pathways from contaminated media and biota to people and calculate the preliminary pollutant limit value [PPLV] (Rosenblatt et al. 1985). The PPLV is an expected equilibrium value that assumes all intermediate steps reach a steady state and can be compared directly to assessment goals. However, where actual values of residues in the intermediate steps are available, these would be preferred inputs (Anon. 1989), because these values represent both the achieved level and the range of values that might be encountered. Since many specific data needed for PPLV calculations are necessarily absent for a large number of the chemicals, and even for construction of the generic pathways of ingestion (food, water), inhalation (vapors, dust), and dermal exposures, and since there are important questions in assessing even a single chemical, a few representative chemicals are illustrative of the approaches that might be employed in examining the methodology. Alternatively, the risk analysis could focus on methods that can sort a group of chemicals by ecotoxicological concerns (Gillett 1983) or health effects (Jones et al. 1988).

Exposure. One of the most important elements in carrying out a risk assessment

is the determination of exposure. A number of factors must be considered in assessing exposure. These can be summarized as follows: chemical nature of the contaminant, type of exposure, populations exposed, and quality of the data base (i.e., suitability and credibility of analytical data, appropriateness of sampling and analysis, etc.).

(1) *Chemical Nature of the Contaminant.* The fate and toxicity of a chemical contaminant, such as a heavy metal, can vary considerably due to the speciation of the metal. For example, dialkyl mercury (R_2Hg) is considered to be more toxic than inorganic mercury, and it can move by vapor pathways and adsorption to sediments, mechanisms not pertinent for Hg^{+2}. The differences between Hg^{+2} and R_2Hg in pharmacodynamics and toxicokinetics alone may account for a significant part of the differences in the consequent risk assessment. Similarly, there are several different congeners of PCBs with differing toxicities.

Thus, when assessing the exposure of the population to a contaminant, there is a need to pay particular attention to the chemical form of the substance. While there is an increasing use of isomer-specified analysis, greater emphasis needs to be placed on developing isomer-specific analytical methods for various environmental substances, including speciation of inorganics.

(2) *Types of Exposure.* In the context of the Great Lakes, the most likely source of exposure to heavy metals and poorly degraded organochlorine compounds for humans is through consumption of fish. However, such exposure should not be looked at in isolation, and other sources of exposure must be taken into consideration in any risk assessment, i.e., a multimedia approach to exposure is required.

Just as route of exposure may be of critical importance, the timing and duration of exposure(s) may speed the response or result in increased resistance to an adverse effect. Cumulative damage incurred under one scenario may be repaired under another, less frequent or intense set of exposures.

(3) *Exposed Populations.* If consumption of fish is the major source of exposure to contaminants, then determination of consumption patterns of Great Lakes fish is urgently needed. At present, very little data are available on these patterns for various segments of the population, including demographic and ethnic groups. In addition, particular attention needs to be paid to sports fishermen and sustenance consumers. These analyses should include methods of preparation and processing in which residue retention and loss are followed.

(4) *Quality of the Data Base.* One of the difficulties in carrying out proper exposure estimates is the inadequacy of analytical data. Too often analytical methods are used that are unreliable, not reproducible, or insufficiently sensi-

tive. Use of such data can lead to gross overestimates and, in some cases, underestimates of exposure. If one is concerned about exposure through food, it is important that contaminant concentrations be determined in the edible portion. Where possible, exposure concentrations need to be determined directly (rather than estimated from bioconcentration factors or models) in doing exposure assessments. Bioactive metabolites, especially proximate carcinogens and activated forms of covalently reactive agents, need to be tracked throughout the exposure process. There is clearly a need for more research in regard to contamination in Great Lakes fish.

Figure 8-1 illustrates these activities for a typical risk assessment in which the available information (including estimated parameters and values) is brought together. It is presumed that the risk assessment is performed in order subsequently to carry out risk management.

Exposure Assessment Procedure

A number of authors have analyzed exposure from the Great Lakes Basin, and emphasis is clearly placed on ingestion as the major exposure route, with fish constituting the major component of the exposure. Cordle et al. (1982) assume a nonthreshold model based on extrapolation from animal experiments to conclude that there was increased risk of cancer from polychlorinated biphenyl (PCB) contaminated fish. Swain (1986) reported that extensive epidemiological studies of PCB ingestion in large cohorts (sports fishermen; mothers and their newborn infants) showed significant effects on development, cranial size, and birth weight. A model projected that the PCBs would be retained at detectable levels into the fifth generation, even if the initial generation of mothers stopped eating these fish forthwith.

The Committee on Assessment of Human Health Effects of Great Lakes Water Quality (CAHHEGLWQ) (1985) reported that the presence of tumors in Great Lakes fish suggests the presence of carcinogens and/or promoters in the water. It is assumed that the tumor occurrence indicates bioactive quantities of such chemicals in the fish flesh. However, the extrapolation to humans is fraught with considerable uncertainty in dose and latency relationships between fish and mammals. Although "direct transmission of cancer to humans by ingestion of fish cancerous cells (or tumor viruses) is almost certainly a misplaced concept" (CAHHEGLWQ 1985), these observations support a need to analyze contaminant concentrations in edible portions of fish tissues. All of these studies suggest that PCBs might be a logical choice for a risk-and-exposure assessment exposition.

Exposure Scenario. A brief explanation may be instructive, as understanding the exposure scenario will illustrate why risk assessment will be required, irrespective of the finding of probable health effects. Hatcheries on the Great Lakes

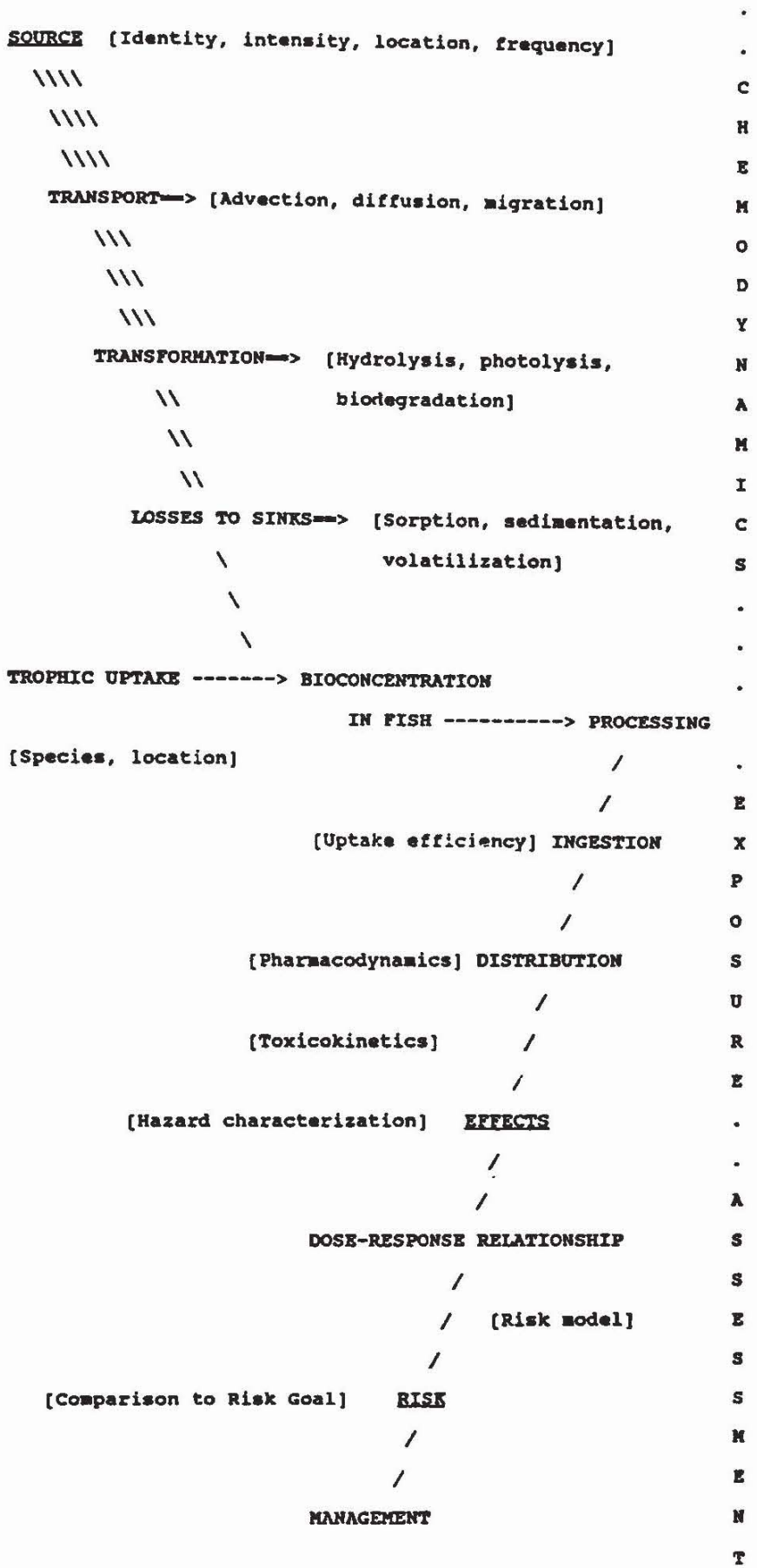

Figure 8-1. Chemodynamic and exposure pathways in risk assessment.

release literally tens of millions of young salmonid fish (principally chinook and coho salmon, lake trout, steelhead trout, and rainbow trout), of which only lake trout is native to the region. These fish feed on forage fish — smelt, alewife, sculpin, whitefish — which in turn feed on species emerging from or feeding on species in the sediment of the Great Lakes (Flint and Stevens 1989). Many toxic chemicals are sorbed to these sediments, but are mobilized by the activities of the benthic biota, either through bioaccumulation or by bioturbation (in which the sediment is stirred up by the animals' burrowing or forging activities).

The salmonids are all anadromous, that is, they normally migrate out of freshwater streams into the lakes, grow to maturity, then return to their stream of origin for reproduction. Typically, adult fish are harvested by sports fishermen at maturity when the fish gather to return to the stream (boat fishing in open water) or once they enter the stream (by bank fishing, including snagging and other nonangler techniques).

A very high degree of success is attained in this put-grow-take fishery; about 4–5% of the fish released are caught in the lakes or return to the stream. Thus, tens of thousands of metric tons of fish are generated (Flint and Stevens 1989). At least 50% of the survivors are caught, and many of these are eaten. Because of the chemodynamics within the food chain, these fish have relatively heavy body burdens of a wide range or organics (PCBs and related compounds; chlordane; and industrial intermediates and byproducts such as hexachlorobutadiene, octachlorostyrene, and hexachlorobenzene). Emphasis within the fishery on attaining trophy-sized fish has led to chinook, and to a lesser extent, coho salmon being the principal species released; chinook and lake trout are especially heavily contaminated.

Water concentrations within the Great Lakes are probably not in equilibrium with the sediments because of the slowness of mixing processes, so that drinking water concentrations of these same chemicals are essentially negligible. Many of the contaminants are no longer used or manufactured, but represent residues left from earlier decades, so inputs are a relatively small proportion of the total. However, some materials are continuously entering the system by long-range atmospheric transport, by leaking from waste disposal sites, or as use products in industry and households. Inhalation of these materials is also regarded as negligible.

The return of the contaminated salmonids not only directly exposes people to the sediment residues, but also results in wildlife exposure to contaminated fish not caught in the fishery and to the residues deposited by humans, wildlife, and the decomposing carcasses of unharvested fish. These residues may be taken up by stream or terrestrial biota or sorbed to soil, but eventually a portion reenters the Great Lakes. The overall effect of the fisheries program has been to redistribute the sediment burdens of toxic chemicals to a larger volume of

material, including tributaries and adjacent terrestrial ecosystems, while exposing potentially vulnerable populations of people and wildlife as the chemicals are cycled back and forth.

The abundance of fish, high expectations of anglers, and high earnings of the states/provinces (angling license sales, taxes on commercial enterprises), individual entrepreneurs (charter boat skippers, guides, restaurant and lodging owners, fishing tackle sellers, and marina sales), and communities (taxes, reduced welfare costs because of employment) drive the process to saturation (Lake Ontario is operating at 103% of theoretical capacity for anadromous fish [Flint and Stevens 1989]), while traditional native communities, indigenous poor, and wildlife are indiscriminately supplied with abundant, but contaminated, protein. Indeed, numerous conflicts arise as eager anglers violate private property to reach fishing spots, dead fish create a stench as they decay, and traffic jams rural roads. Yet one can also argue that the positive health effects of this activity are valuable, as anglers consume high-quality lipid rich in the anticholestemic omega-3 fatty acids and reduce stress through angling.

The relationships in the food chain are illustrated in Figure 8-2 (based on Flint and Stevens 1989).

Risk Assessment Procedure

The first step is to define an acceptable level of risk for a particular hazard; in this case the Great Lakes Water Quality Agreement (CAHHEGLWQ 1985) suggests a risk of 10^{-5} (1 per 100,000 excess cancer deaths per 70-year lifetime exposure). The U.S. Environmental Protection Agency (U.S. EPA) uses a risk of 10^{-6} (1 per million) as a target for negligible risk.

Fish ingestion has several important parameters known to affect exposure. The species identity, age/weight, and location will determine the fish's body burden; the portion consumed and its quantity and frequency will determine the intake. The person's body weight (70 kg adult male, 50 kg adult female, and 10 kg child) determines the dose, while the age, sex, physiological and nutritional status, and chemical and disease history will contribute to the likely impact. The CAHHEGLWQ (1985) recommends that no adult eat more than 200 g of Great Lakes fish per week nor drink more than 2.0 L of Great Lakes water per day.

The U.S. EPA (1987) assumes that the number of exposed people is 2.69 (average size of U.S. family) times the number of licensed fishermen in the area. They assume an average fish consumption of 6.3 g/adult/day (total fish consumed in United States divided by adult population mass). The risk of cancer (q_i^*) is the *cancer potency* (CP) of the ith chemical (based on the upper limits of the 95% confidence interval of a multistage, one-hit, nonthreshold model of animal studies) times the *chronic daily intake* (CDI). CDI is the long-term water

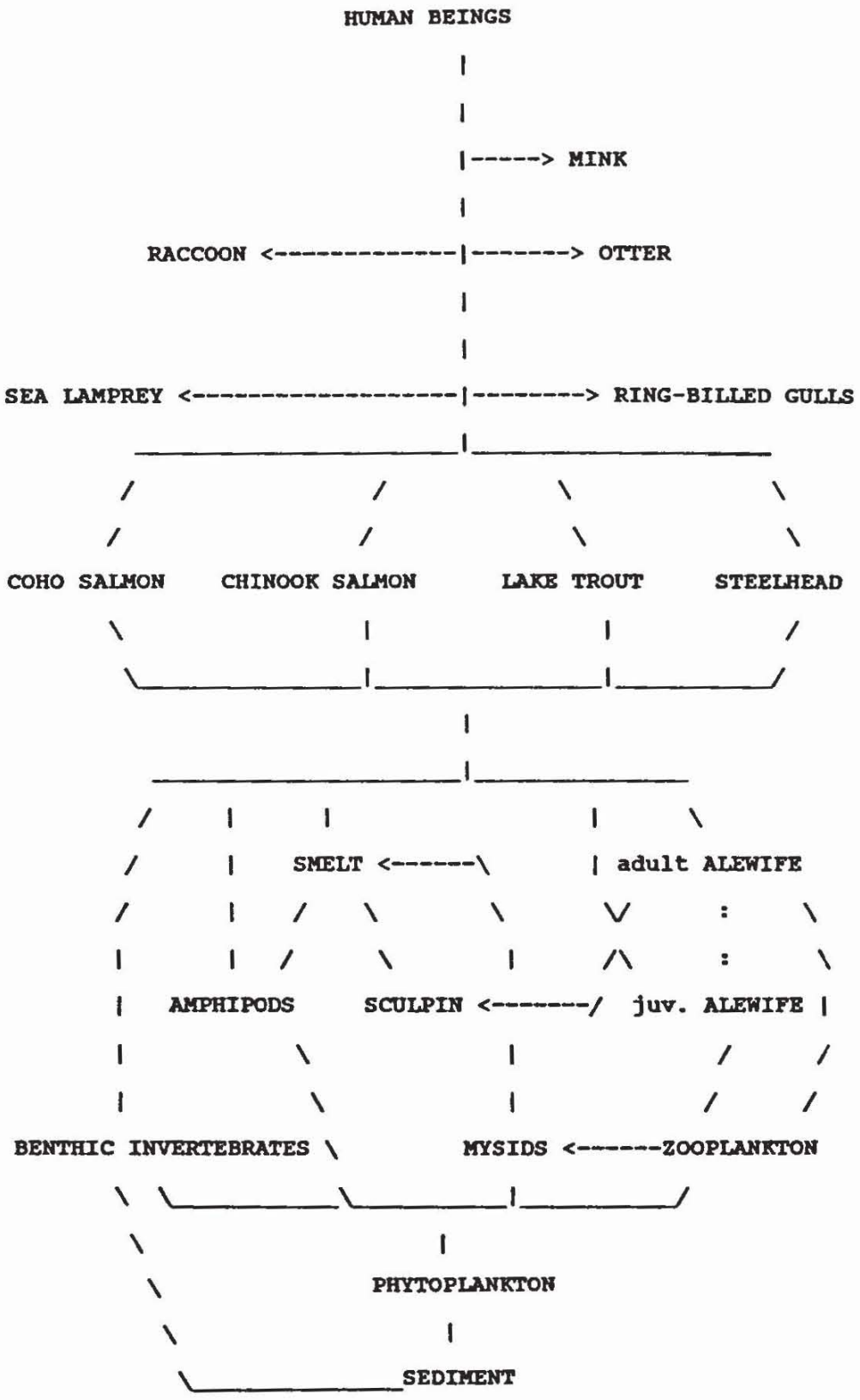

Figure 8-2. Lake Ontario food chain (Flint and Stevens 1989).

concentration times the consumption rate times the bioconcentration factor (BCF) for the chemical (irrespective of species, etc.) times the duration of exposure (fraction of year fishing occurs). Typical BCF values are 10,000 for PCBs, 54,000 for DDT, and 5000 for TCDD. CPs for these same chemicals are, respectively, 7.0, 0.34, and 1.56×10^5 (mg/kg/day)[1]. The actual residue value in the fish should be substituted for the water concentration times the BCF when known (Anon. 1989), so that if the average concentration of PCBs is 1 μg/g (1 ppm; Table 8-1), the calculated risk is 7 (mg PCB/kg human BW/day)$^{-1}$ × 6.3 g fish eaten/kg of human BW/day × 1 μg PCB/kg of fish consumed times 10^3 g/kg or 9×10^{-5}.

The Michigan Department of Natural Resources surveyed 25,000 fishermen and determined that the average daily consumption was 36.4 g of fish/adult; the CAHHEGLWQ (1985) recommended 28.6 g/person. However, based on data presented in Belton et al. (1986), sustenance fishermen might consume 200–225 g per adult/day for much of the year. The respective risks of these three groups of consumers are less than 5.2×10^{-4}, 4.1×10^{-4}, and $2.9–3.2 \times 10^{-3}$ excess cancer deaths per 70-year lifetime. In Ontario, 2 ppm of PCB in fish is accepted, for which the risks would be approximately double those calculated above, depending upon the presumed consumption rate, but the Canadian Federal Government has set a "tolerable dose" of 1 μg/kg/day, which is about 15% of that used in these calculations, so that the risk would be about 1.4×10^{-5}, or about that of the probative target of the CAHHEGLWQ (1985) recommendation.

Little details are available about the social, cultural, and ethnic distribution of anglers, but the relative risks vary by a factor of several hundred between those who rarely eat their catch and those who depend upon it for their principal source of protein (Belton et al. 1986). Whereas less than 3% of the anglers and crabbers in New Jersey consumed more than four meals per week from their catch, as much as 12% of Native American fishermen on the St. Lawrence River are sustenance or quasicommercial fishermen, i.e., consuming their catch themselves or bartering it within the community (H. Lickers, Mohawk Band Council, St. Regis, Ontario, personal communication). As with wildlife, human beings may create "hotspots" of exposure and outcome (Keith 1970).

The need for consistency in an assessment approach is evident, but that is far from the only problem. What should the endpoint measurements be, which effects should be selected as the basis for standards, what standard or advisory level should be employed as a goal, and who and where are the target populations? How large are these targets? Clearly, socioeconomic and cultural divisions, community traditions, and regard for the overall population must be considered.

Table 8-1 Mean Concentrations of Chemicals 1984-85

Species (Location)	DDT-R[a] µg/g	PCB[b] µg/g	PCDF[c,d] pg/g	PCDD[d,e] pg/g
Lake trout				
Ontario	0.89	2.8	70–160	100–200
Erie	0.13	0.3	25–55	>200
Huron	0.26	1.0	250–300	>200
Michigan	2.2	NA	70–160	>200
Superior	0.08	0.5	25–55	<10
Coho salmon				
Ontario	0.47	1.6		
Erie	0.05	0.4		
Huron	0.14	0.3		
Michigan	0.20	0.4		
Superior	0.03	0.1		
Rainbow smelt				
Ontario	0.19	0.55		
Erie	NA	NA		
Huron	0.08	0.20		
Michigan	NA	NA		
Superior	0.04	0.12		

[a]Bis-(p-chlorophenyl)-1,1,1-trichloroethane and homologs.
[b]Polychlorinated biphenyls.
[c]Polychlorinated dibenzofurans.
[d]Various species.
[e]Polychlorinated dibenzodioxins.

Choice of the "best" method of risk assessment depends on its end use. Forecasting health care costs requires accurate estimates; deciding on the registration of a new chemical requires conservatism in favor of public safety. A decision must be made on which sort of emphasis to give to estimates of risks from Great Lakes water pollution.

Human health assessments are targeted at the individual, the loss of which is to be avoided. Unfortunately, unless risk is commensurable and fully known, in terms of both positive and negative benefits, some individuals may be lost while saving others. Ideally, benefits would be retained while damage would be mitigated or corrected.

Uncertainty. A key issue in risk assessment is uncertainty, which can be apportioned among the various components of risk. Because *safety* is the "practical certainty that injury will not result" from exposure to the toxicant under the conditions recommended for use (NRC 1970), *risk* is the uncertainty that safety is present. We can know with certainty that a chemical is toxic, but find that the risk of adverse effect is now known with any degree of accuracy, because of variations in exposure or response. Krewski et al. (1987a) and Krewski and Murdoch (1988) have considered the statistical properties of the cancer bioassay methods and have determined that many thousands of animals would have to be tested, at great expense, in order to discern the sensitivity of present methods to features affecting uncertainty in the response. This is a key issue in interpretation of extrapolations at low doses, and the limited experimentation with very large assay numbers have been disappointingly uninformative.

At the other end of risk analysis, Morgan et al. (1980, 1982) and Rish (1988) have considered how uncertainty is generated in the analysis process itself. By formalizing the methods, assumptions, and means of parameter generation, they are able to describe the uncertainty of the method, exposure, and response in useful ways. A variety of simulation techniques permit this uncertainty to be displayed.

Dose Response Modeling

In the risk assessment process, a key set of assumptions has to do with how the dose response is estimated at low concentrations consumed over long periods of time, using either animal or even human data at higher concentrations for shorter periods of time.

The mathematically simplest form of the dose-response model is a linear one: At zero dose there will be no effect (or perhaps a background effect) and at nonzero doses the effect will rise in proportion to the dose. For carcinogenic modeling, there is some theoretical basis for such simple models (Murdoch et al. 1987). The essential assumptions in these models is that cancer develops from a single interaction of a target cell with a carcinogen. The target cell may have passed through still other stages to progress to cancer, but as long as one step in the chain is triggered by a single interaction, a linear model will result.

The theory above assumes knowledge and measurement of both the dose and the response. If the cell interacts with a reaction product from metabolism of a carcinogen (e.g., the arene oxides of polyaromatic hydrocarbons or covalently bound formaldehyde [Starr and Buck 1984]) or metabolism consumes a carcinogen before it has time to affect a cell (e.g., methylene chloride [Anderson et al. 1986]), then the saturability of metabolic processes may make the relation between exposure level and response nonlinear. Resolving questions of linearity at the low environmental doses of most carcinogens is essentially impossible —

even in animal bioassays, it may require inordinately large studies to show evidence of nonlinearity (Krewski et al. 1989). Furthermore, when the exposure is discontinuous or intermittent, the use of average exposures for a lifetime may seriously overestimate the risk (Kodell et al. 1987).

Linearity or additivity of effect is also questionable when mixtures of chemicals are considered. If two substances cause an effect by completely different mechanisms, or if they affect the same step in the same process, then multistage theory predicts the combined response to be the simple sum of separate effects, at least at low doses. However, it is predicted that substances affecting different steps in a multistage model may exhibit superadditive effects: Exposure to an initiator and a promotor may have weak effects separately, but in combination a multiplication synergy may result. The best example is asbestos fibers and cigarette smoke, which are seven times as effective together in causing cancer as each is separately (Hammond et al. 1979). It also seems possible that combinations of insults may have subadditive effects — competition for metabolic pathways may be one mechanism, or enhanced induction of a pathway leading to increased excretion of harmless metabolites may be another.

The difficulty for the risk assessor in modeling mixtures is the explosion of possible doses — every sample of fish is likely to contain a different chemical mixture, so that enough experimental measurements to verify a nonadditive model may just not be feasible. We are unsure as to the how these considerations apply to such inherent mixtures as toxaphene (177 congeners and isomers) and PCBs (up to 209 isomers) in comparing estimates based on their original (manufactured) form to the forms found in the field, where partial fractionation by physicochemical processes and abiotic and biotic transformations may have occurred on some variable basis.

Noncarcinogenic effects present great difficulties for these very same reasons. With outcomes that require substantial tissue damage, such as heart or neurological disease, the linear model becomes unreasonable. At low enough doses, one would expect no cases. Models predicting either dose thresholds or other strongly sublinear dose-response curves are applicable here, but are less tractable and less well understood. It may be that peak dose rather than average dose is relevant, if damage occurs when detoxification pathways are overwhelmed.

Developmental effects, fetal toxicity, and teratogenicity are also difficult to study with respect to a dose-response model. Because fetal development progresses so rapidly, very short-term exposures are relevant. The concentration present during a few critical days may determine the entire effect. Identification of susceptible times may be difficult. In any case, substances with long clearance times, such as lipophilic PCBs and dioxins, may accumulate in the body over periods of years, removing the possibility of any short-term control strategy. On the other hand, just because there is no effect in the developing animal

does not mean that toxicity to the pregnant or lactating animal should be ignored (U.S. EPA 1989).

Calibration

The problem of public interpretation of estimated upper bounds on risk (such as those produced by the linearized multistage model used by the U.S. EPA) has been much discussed. For assessing chemicals in the Great Lakes, the problem of combining risk assessments for tens or hundreds of chemicals arises. Estimates of risk may be summed (assuming additivity), but upper bounds become more and more conservative as they are summed. Thus, some form of calibration of the process is required, perhaps by epidemiological studies or by comparison of predictions with overall population rates of the disease.

This is not a trivial matter; the credibility of quantitative risk assessment may indeed rest upon finding a means of calibration of the process. Three features operate against achieving functional calibration:

1. multiple mechanisms of carcinogenicity, in which some agents share variously common bases but also have chemical and species-specific mechanisms
2. the significant role of cell proliferation (and the variable means by which this occurs) in producing tumors from lesions once they have been initiated and promoted
3. unresolved questions regarding repair and spontaneous remission, which merge with the issue of intermittent dosing (Kodell et al. 1987)

These questions are tied into factors such as nutritional, physiological, and disease status within the population and the concurrent effects of these and other chemicals on other systems influencing outcome (such as the immune system and metabolic competence of the liver, kidney, and intestine systems).

Regional Scale Assessments

At the present time methods are just being introduced (O'Neill et al. 1982) to permit the assessment of risk to geographic regions larger than a watershed. Are these needed for assessment of toxics in the Great Lakes Basin, or should we be focusing on smaller units, for which more discrete exposure scenarios and pathways can be described and quantified for a discernibly vulnerable population? Would these regional methodologies be understood and used? What implications do the temporal and spacial scales, and the geographic and demographic diversity, have for the risk assessment process per se?

Current analysis of regional risks have generally been limited to jurisdic-

tional issues by local and regional governments. Landscape ecology is just beginning to receive sufficient scientific notice as to be useful. Regional ecotoxicological risk assessments, which are derived and used on a much different basis than human health risk assessments, have had limited consideration by scientists (Hunsaker et al. 1989). Ecological risk assessment at the level of a lake or watershed is becoming more common in protection of natural resources, the assessment of damage from spills and accidents, and prioritization of remedial and mitigative actions, as in waste dump-site assessment. These ecological assessments are not used quantitatively or econometrically in the same fashion as health assessments.

In spite of some imposing difficulties, there is much to be said for regional-scale assessments, especially as related to the Great Lakes Basin. The geologic, political, and cultural histories tend to have more similarities, and smaller differences, within the region as compared to those in other regions. The sheer size of the Great Lakes themselves promotes regional considerations, even when we know that portions of any given lake may be radically different from other parts of the same lake. The region has been studied as such by a variety of institutions, so that there are useful data bases on soil and water quality, biota, and a variety of human activities pertinent to risk assessment. Agricultural and industrial activities, for example, are similar. Although the geopolitical lines are clear and very important, the differences between entities on either side are relatively small: High population areas are separated by sparsely populated farm and forest lands, and manufacturing areas are closely associated with the lakes and their bays and rivers.

Ecosystem theory suggests that hierarchical evaluation of processes leads to the revelation of otherwise unnoticed strengths and vulnerabilities (O'Neill et al. 1982). Thus the ecosystem is usually less readily perturbed than its components, some of which may disappear as a part of a response to a chemical stress. This same theory suggests that the time constants on pertinent rates at the landscape scale will be on the order of fractions of years to decades, making observation difficult for humans in a given professional lifetime.

Explanatory Power of Risk Assessment

Requirements. Risk assessment is an attempt to identify, and, if possible, quantify, the magnitude and probability of adverse effects as a result of an event or activity. There are a number of conditions needed for risk assessments:

- previous experience with the type of event or activity and the alleged effects associated with them
- known, or at least hypothetical, pathways linking the event (i.e., the exposure to a hazardous agent) and the potential effects

- empirical data to confirm and quantify the nature, magnitude, probabilities, and related uncertainties with respect to the pathway
- methodologies to integrate data into the pathway

Risk assessment must define which outcomes should be labeled *adverse*, in a biologic sense; present emphasis is on carcinogenic effects, with morbidity, developmental effects, miscarriages, etc. being underrepresented as endpoints driving assessment. The risk assessment must define the scope of hazards and their interactions (including interactions with other lifestyle factors, such as smoking or being overweight), as well as determine who may be expected to be affected and to what degree by the risk (general population, elderly and sick, infants, pregnant women, etc.). Moreover, assumptions about the circumstances of exposure (what type of persons, in what age or health condition, in what situation, etc.) must be specified.

Assumptions must be employed to define the parameters (including typical climatic and weather patterns, soil/sediment types, latitude for solar irradiance, etc.) for modeling dispersion of pollutants or the expected environmental concentration of an agent. Finally, a number of assumptions are generally made in extrapolating dose-response relationships from toxicological or epidemiological studies, including interpretation of animal data and treatment of background "noise."

In addition to limitations imposed by the nature of required assumptions, a group of general constraints are imposed on the risk analysis. Each individual has a unique physiognomy and is exposed to a unique set of hazardous materials and physical stresses. Ideally risk analysis should provide a risk profile for each individual, but this is neither possible nor useful for policy purposes. Hence, some degree of abstraction and generalization in risk assessment is unavoidable.

Limitations. To yield useful risk analyses, all above-mentioned conventions need to be specified and determined. There is no absolute scientific method that can specify these conventions. Rather, plausibility, intuition, consensus among scientists, and expert opinions guide the process of specifying these parameters. This process inevitably abstracts from potential differentiations, such as regional dispersion, temporal exposure, susceptibility to a hazard, and others. Although "averaging" is unavoidable, it may obscure the "true" magnitude of a hazard, if

- the timing of the exposure is crucial to the outcome
- the risk affects humans in special phases of their development
- the risk is only effectively relevant for certain types of persons or
- the risk is confined to special or rare situations

In these cases, the risk assessment may indicate a very low risk for the total population exposed to the hazard, but substantial, adverse health effects may occur in certain subpopulations.

At the same time, averaging over time and populations may give the impression of a "substantial danger" if a very large population is equally exposed to a very small individual risk, such as low levels of radiation. In essence, risk assessment relies on many judgmental and subjective procedures, which can all be justified vis-á-vis the problem, but not scientifically proven.

Merits. In spite of the mixture of theoretical, empirical, and arbitrary components, risk assessments have substantial explanatory power for problems encountered in managing costs, benefits, hazards, and gains for both individuals and communities. The assessments serve as a conceptual framework to integrate more specific studies on chemical fate and dispersion, exposure, dose-responses, and ultimately, risk management. The risk assessment process forces scientists to examine the elements of the critical pathway from a source to a potential vulnerable target (individual or population) and to seek out those component processes that have potential impacts on the outcome of the total analysis. Comparatively, risk assessments determine the "general" magnitude of a risk factor or set of factors, and thus may guide prioritization of risk management steps.

By forcing the integration of disparate information sources and theories from diverse disciplines, risk assessment often leads to articulation of more refined hypotheses about the causal pathways; the basic underlying biology, chemistry, or physics; and the relationship to special populations at risk.

Drawbacks. In spite of these utilities, there are a number of features of risk assessments that can cause difficulties in communicating about the risks from a given situation. For example, special caution needs to be taken when using risk assessments to put a hazard in perspective with other, more familiar hazards for risk managers or the public. A housewife may reject the analysis if it suggests that the health of her family is more threatened by her feeding them mushrooms than by trace quantities of a volatile organic chemical in the drinking water!

Risk assessments are ill suited for:

- determining the social, cultural, or political acceptability of a hazard
- addressing issues of equity and "time discounting"
- indicating the magnitude of a problem if exposure or effects are linked to special subpopulations or specific situations
- comparing highly divergent types of risk

- comparing the relative risks of different hazards, if the level of uncertainty varies considerably among three risks, or if the underlying mechanisms are so different as to rest on divergent or contrary assumptions
- public education programs, if other issues, such as equity and selective exposure to hazards, are not included in the program
- risk management uses, if the input data are insufficient or highly controversial

Although one can assess the risks for any situation, if settled scientific understanding of the underlying basis is lacking, the uncertainty can simply obviate the effort. Worse, critical assumptions may be manipulated to create an impression of high uncertainty, when in fact there is considerable certitude that the risk is high in certain situations and low in others.

KNOWLEDGE BASE

Substantial information exists on the concentrations of toxic chemicals in the Great Lakes Basin ecosystem, the effects that they may cause in experimental animals and human beings, and even the risks to health posed by various types of exposure. Part of the problem is, indeed, that there is so much information, some of which is erroneous, out of date, and/or of unknown quality. As noted earlier, risk assessment is an information-intensive activity. In particular, proper assessments require multidisciplinary evaluation of specific information on the following:

1. the characteristics (nature, intensity, location, seasonality, duration, frequency, etc.) of the source or sources
2. time/space concentrations of potential toxicants
3. the fate, transport, and transformation in the environment (chemodynamics) and in people (toxicokinetics), including detoxication and activation mechanisms
4. the exposure-related behaviors of people (is a pollutant repellant or aversive, or is it attractive?)
5. behavior-related exposures (how much time does a person spend in contact with the exposure concentration, or how much of what kind of foods are ingested?)
6. the mechanism(s) of action in initiating a toxic response and the underlying biological basis for the adverse outcome
7. any known interactions with existing genetic, nutritional, physiological, or disease states
8. the size, location, and relationship to sources of exposure of subpopula-

tions characterized by special vulnerabilities to a particular toxicant or stress
9. the temporal framework for the assessment (acute, chronic, or occupational)
10. any data inferring (wildlife, experimental animals) or more directly conferring (epidemiological, clinical, and occupational medicine studies) validity about assumptions employed in the analysis

For the key chemicals already identified previously (e.g., polyhalogenated organics, heavy metals), much of the data needs listed above already exist and have been employed in risk assessments. Some are available from on-line data bases or in other readily used forms. In addition, there are a number of other resources (regional U.S. EPA offices, state and local agencies, cooperative extension service) and specific assistance directives employed for assessment (U.S. EPA 1985, 1986, 1987). On the other hand, for even the most heavily studied chemicals, there are still basic deficiencies requiring the use of a variety of estimation techniques for parameters in modeling fate and effects.

Along with the needed data are the numerous risk assessment tools: models of chemical fate, uptake, storage, excretion, and metabolism; sets of analytical techniques appropriate to the range of concentrations and media encountered in exposures; on-line data sets of population characteristics and chemical residues; statistical procedures employed in experimental design and data analysis; and set procedures for calculating specific outcomes and the degree of uncertainty about those outcomes.

CRITICAL INFORMATION NEEDS

A thorough analysis of existing risk assessments for selected chemicals reveals serious deficiencies. The more explicit the assessment, the less these deficiencies create their own uncertainty to add to that inherent in risk posed by the chemical. For example, with PCBs we know that certain congeners (isomers) are probably much less active or less readily retained in biological tissues, whereas others are especially bioactive, recalcitrant to degradation, and/or likely to be retained and passed through the food chain (Safe 1984). Thus, isomer-specific toxicologic and chemodynamic data are needed (Luu et al. 1985).

By focusing particularly on food chain exposure, and even more tightly on that from fish consumption, the assessments can be improved by information of the following types:

1. the age, size, and flesh residues of game and commercial fish species consumed by people
2. the effects of processing and preparation on residues

3. the frequency, amount, and timing of fish consumption by location and season
4. the characteristics of the fish-consuming public (age, sex, status) along with identifiers of socioeconomic, cultural, or geographic status that can be used to estimate the size and location of likely vulnerable groups (e.g., sustenance fishing)
5. existing confounding or amplifying exposures to other chemicals (alcohol, tobacco, occupational chemicals or nutritional deficiencies)
6. concurrent exposure to PCBs and other chemicals through other sources (vegetation, potable water, meat)

Items 1, 2, and 6 should be isomer specific when possible. As important as the foregoing are, sound risk assessments may be practically impossible to prepare well in the absence of particular kinds of guidance provided by others. These would include:

- the intended use of the assessment (standard setting, priority setting, research analysis, or selection of risk management actions) that may control the level of detail developed
- the acceptable (or negligible) risk goal within a given time or set of times (e.g., number of excess cancer deaths per average lifetime)
- the technical understanding of those using the assessment product (professional engineer? city council member? litigating attorney?)
- the level of quality assurance within the assessment process itself
- the time by which a decision must be made

HUMAN HEALTH ISSUES

Experts discussing risk and exposure assessment issues are challenged to analyze the proposition: What data has to be ignored to accept the assumption that there are no human health effects from toxics in the Great Lakes Basin ecosystem? A detailed response depends, in part, on the outcome of the evaluations of exposure and toxicity data and the analysis of clinical and epidemiological data. It also depends upon the socially derived goals for "healthiness." Nevertheless, it is practically immaterial to risk assessment whether that proposition is valid or not. Ultimately, the assessments have to be made and the main questions are on which chemicals, to what depth, and for what purpose.

Support for the Hypothesis

It is entirely possible that the proposition is valid (i.e., that there are no human

health effects from Great Lakes toxics), in spite of evidence from laboratory animals and field populations, existing risk assessments notwithstanding. For example, the current exposures are more than an order of magnitude less than two decades ago and less ubiquitous. There is no evidence of a spate of environmental cancer for which a delay in expression has long been posed. Massive effects from earlier exposures should be seen, but rather, tumor registries and direct surveys reveal declining cancer rates (except for smoking-related tumors in lungs and gastrointestinal tract in women and for breast cancer). Occupational health studies have not revealed massive cancer rates for suspected chemicals not already explicitly identified as human carcinogens.

Moreover, humans may differ significantly in their sensitivity to carcinogens and genotoxic chemicals, as compared to wildlife or lab animals, because of species-specific abilities to detoxify the chemicals or repair any damage caused to a level indistinguishable from the background elicited by radon, naturally occurring carcinogens in the food supply, etc. The potential damage may simply never be achieved in reality. Animal evidence is just not conclusive for people, especially if there are indeed species-specific thresholds for action. Hopefully, the evidence will not be ignored in seeking solutions to protect wildlife, fisheries, and plants. It would be rather shameful to be so chauvinistic for our species.

Some might even criticize the analysis of this proposition as self-serving, since it is put forward by scientists, some might characterize as expecting to build or enhance their careers on the basis of it being invalidated. A similar criticism would arise if those examining the proposition were known to be biased in support of the null hypothesis or if its examiners had been selected as exclusively from the private sector as this group was from the public sector. This type of issue pervades the risk-assessment process, since innumerable assumptions must be made without generally agreed-upon criteria based on "settled science."

Opposition to the Validity of the Hypothesis

On the other hand, as noted earlier, the risk assessment process will continue, for several good reasons. Even if the data are weak, obfuscated, or not always appropriate for assessment purposes, and even in the absence of conclusive extrapolation techniques, the nonvalidity of the null hypothesis is very meritorious. If people will not pay attention to ecotoxicology, then maybe they will at least continue to pursue risk goals for health purposes. Acceptance of the null hypothesis does not provide any assistance to risk management, but rather leads to ambiguity of purpose and misdirection of resources.

A statistical argument can be made from an explicit reading of the proposition. All that would be necessary for nullification would be to find any credible

evidence to the contrary. The uncertainty itself of that evidence increases the risk above zero.

Is it ever appropriate to treat "no health effects" as a null hypothesis? Certainly our society (through the National Toxicology Program and the pesticide registration process) has already assumed the opposite hypothesis. U.S. EPA's linearized, multistage model, for instance, essentially assumes that all substances are suspected carcinogens and uses animal bioassay data to place upper bounds on their potential potency. Since hypothesis tests can never prove a null hypothesis, but can disprove it, the U.S. EPA approach does not demonstrate carcinogenicity, merely low (or negligible) risk. For a large number of compounds, there is now a practical certainty that they are not carcinogenic at nominal or environmental exposure rates. If the aim of the test of this proposition is to examine the evidence for human health effects, then the directions to the working groups are entirely appropriate. Null hypotheses have been used to represent expert consensus that a new experiment or design is attempting to overturn. Because evidence is persuasive regarding possible human health effects, and many scientists have been pursuing outcomes under a consensus that holds such health effects as at least possible and likely probable, the hypothesis is jarring. Moreover, the existing evidence that (1) high-dose toxicity implies the possibility of low-dose toxicity and (2) animal toxicity implies human toxicity, coupled with the hypothesis being scientifically untestable (by direct exposure of people), makes this instruction unpalatable.

Psychological Dimensions of Reversing the Burden of Proof

Finally, reversal of the burden of proof for as wide a range of agents as are represented in contaminated fish, water, soil, and sediments in the Great Lakes Basin ecosystem may be regarded by some as awkward at best and irrational at its worst. For each chemical to which the proposition does not apply, a set of restrictions, prohibitions, recommendations, and/or planned activities will have to be espoused. That one would immediately do this for any and all chemicals present in the system is inefficient and potentially devastating in its direct and indirect costs. Worse, it would destroy any credibility in the overall process. Hence, it is implicit in the undertaking that risk assessments will serve as a priority-setting function. This has indeed been the practice in California, where Proposition 65 has required a reversal of burden of proof (Kizer et al. 1988).

A third means of viewing this concern is to examine the situation where the probability of the adverse health effects is not zero, but not high enough to be significant per se. If essentially any exposure to a potentially hazardous material is sufficient to claim that the no-health-effects hypothesis has to be rejected, the use of such a tool may obscure real health hazards rather than illuminate the

magnitude. In terms of public policy, the outcome of the foregoing may be worthless, since there is no discrimination between low- and high-magnitude risks on which risk mitigation efforts could be based (in terms of risk-benefit or cost-effectiveness of risk-reduction methods). The policy value is therefore low and even counterproductive, if scarce resources have to be distributed randomly among different risk sources.

With respect to risk communication, the rejection of the no-health-effects hypothesis may easily be misinterpreted as a proof that there are biologically significant health effects related to the measured exposures. This inference would then be interpreted as a sign that danger lurks at every turn. The overall impression would be that our environment is so polluted that health effects are to be expected for any exposure that people face. In terms of risk perception, an overestimation of environmental risks may be the result for those persons highly aware of environmental quality and personal health, and a feeling of fatalism among those attaching less importance to environmental quality. Both responses can be seen as inadequate and undesirable.

Risk perception is complex and sometimes even contrary to expectations, but should not be allowed to dominate the scientific process (Krewski et al. 1987b). Without going into the details of risk perception, suffice it to say that the "hot spots" in exposure of small groups of people potentially viewed as more willing or able to accept higher risks may constitute 'ignored targets' of concern, even if the no-health effects hypothesis is accepted.

INTERDISCIPLINARY ASPECTS

Information Needed From Others

Detailed data needs on PCBs, DDT-R, PCDDs, PCDFs, and heavy metals — such as cadmium, lead, and mercury — were given above, along with ancillary information supporting the assessment. Risk goals are critically needed. However, some of these should receive particular attention. These would include:

1. exposure assessment involving long-range (global) atmospheric transport of toxicants
2. exposure and effects assessments of the specific forms of toxicants involved (e.g., PCB congeners, metal ion species)
3. specific exposures through consumption of fish, by species, amount, timing, and consumer, and including methods of preparation
4. methodology for summation of multiple toxicant exposures and for assessing nongenotoxic endpoints, especially developmental, immunotoxicological, neurological and behavioral, and reproductive endpoints
5. methodology for exposure and risk assessments at the regional scale

Information Directed to Others

Risk assessors need information from many other disciplines, and therefore need to develop mechanisms for closer interaction. This is especially true during detailed review of studies used to validate assessments, but nonetheless is true in the analysis of raw data regarding exposure and hazard. Nothing is more valuable than an expert, and the particular expertise needed comes from researchers in other disciplines, who have contributed information to this volume.

It should not be too surprising if proof of effects or of a statistically significant lack of effects are both absent or unattainable. The Great Lakes Basin ecosystem is not so particularly, highly contaminated as some parts of the scientific and popular press would have us believe. Within the two major U.S. EPA regions making up the bulk of the U.S. side of the basin, the frequency of samples higher than existing standards is rarely remarkably higher or lower than the average throughout the United States, although there are some admitted "hot spots" requiring attention. There are many transboundary risk assessment problems in the Basin. The source of materials, such as toxaphene, and especially transport by long-range airflow, needs examination.

Better assessment methodologies are urgently needed (and supporting basic biological understanding) for reproductive, neurobehavioral, immunotoxicological, and related nonlethal endpoints. Also needed are more appropriate means of evaluating mixtures and chemicals with short to intermediate half-lives in the environment from dispersed or infrequent sources.

In the absence of an adequate methodology, the best approach is to state the probability that a guidance value or goal will be exceeded. Unfortunately, there is almost no politician who will espouse a "goal" for human fetal deformity, neonatal neurobehavioral injury, or similar index higher than "zero." This is unfortunate in that we do not understand all sources of such injuries (although alcohol and smoking are leading candidates). Eliminating all of them is a highly desirable goal, but the uncertainty in the methodology will necessarily lead to upper bounds that are higher than zero for some chemicals with little or even no activity in regard to these endpoints.

There are a number of chemicals for which the response is biphasic, that is, the chemical is required or beneficial at low concentrations and toxic at higher concentrations, or even carcinogenic. The most dramatic agent in this class is selenium (Se), for which the range of concentrations encompassing the minimum requirement and the maximum tolerated dose without overt toxicity is less than two orders of magnitude in a wide range of species. A large study in China (involving 800,000 people studied over a >10-year period) indicates that Se intake is protective against cancer at lower levels, but possibly carcinogenic at higher levels (C. Campbell, Cornell University, personal communication). There is no theory or practice at present that permits risk assessment for such chemi-

cals. Similar problems occur with alcohol ingestion (1 glass/day of beer or wine shows lower cancer risk than either zero or >2 glasses). In general, where nutritional or other physiological or disease interactions are involved, one may assume a balance in risks, i.e., optimize exposure. However, that requires detailed knowledge of the population level, and even individual, nutritional requirements, a matter of considerable debate.

CONCLUSION

As a result of the foregoing discussion, the traditional approach in risk analysis that follows is recommended: An effect is only taken for granted if the deviation is significantly larger than expected from random distribution or from comparison with control populations. It is better to incorporate conservative judgments into the risk assessment methods than to change the burden of proof if the concern is to avoid underestimation of risks. In addition, special studies on selected populations may reveal significant effects that might be used as yardsticks for regulating the risk for the general public.

REFERENCES

Ames, B. N. Dietary carcinogens and anticarcinogens. *Science* 221:1256–1263 (1983).

Anon. EPA stress on data collection over modelling to affect rulemakings. *Environ. Policy Alert* March 22, 1989, p. 4.

Belton, T., R. Roundy and N. Weinstein. Managing the risks of toxic exposure. *Environment* 28:19–37 (1986).

Committee on Assessment of Human Health Effects of Great Lakes Water Quality (1985).

Cordle, F., R. Locke and J. Springer. Risk assessment in a federal regulatory agency: an assessment of risk associated with human consumption of some species of fish contaminated with PCBs. *Environ. Health Persp.* 45:171–182 (1982).

Flint, R. W., and R. J. J. Stevens. Lake Ontario: A Great Lake in Transition. Great Lakes Monograph No. 2. Buffalo, (NY: SUNY at Buffalo.1989), 121 pp.

Gillett, J. W. A pre-biologic screen (PBS) for ecotoxicologic effects. *Environ. Toxicol. Chem.* 2:463–476 (1983).

Hammond, E. C., I. J. Selikoff and H. Seidman. Asbestos exposure, cigarette smoking and death rates. *Ann. N.Y. Acad. Sci.* 330:473 (1979).

Hunsaker, C. T., R. L. Graham, G. W. Suter II, R. V. O'Neill, B. L. Jackson and L. W. Barnthouse. Regional Ecological Risk Assessment: Theory and

Demonstration. Environmental Sciences Div. Pub. No. 3273, (Oak Ridge, TN: Oak Ridge National Laboratory, 1989), 101 pp.

Jones, T. D., P. J. Walsh, A. P. Watson, B. A. Owens, L. W. Barnthouse and D. A. Sanders. Chemical scoring by a rapid screening of hazard (RASH) method. *Risk Anal.* 8:99–118 (1988).

Keith, J. O. Variations in the biological vulnerability of birds to insecticides, In: *The Biologocial Impact of Pesticides in the Environment*, J. W. Gillett, Ed. Environmental Health Sciences Series No. 1 (Corvallis, OR: Oregon State University, 1970), pp. 31–35.

Kizer, K. W., T. E. Warriner and S. A. Book. Sound science in the implementation of public policy: A case report on California's Proposition 65. *JAMA* 206:951–955 (1988).

Kodell, R. L., et al. Using average lifetime dose rate for intermittent exposures to carcinogens. *Risk Anal.* 7:339–345 (1987).

Krewski, D., M. J. Goddard and D. Murdoch. Statistical considerations in the interpretation of negative carcinogenicity data. *Reg. Toxicol. Pharmacol.* 9:5–22 (1989).

Krewski, D., and D. J. Murdoch. Quantitative factors in carcinogenic risk assessment. In: *Banbury Report 31 Carcinogen Risk Assessment: New Directions in the Qualitative and Quantitative Aspects.* (Cold Springs Harbor, NY: Cold Spring Harbor Laboratory, 1988), pp. 257–273.

Krewski, D., D. J. Murdoch and J. R. Withey. The application of pharmacokinetic data in carcinogenic risk assessment, In: *Pharmacokinetics in Risk Assessment: Drinking Water and Health*, Vol. 8 (Washington, D.C.: National Academy Press, 1987a), pp. 441–468.

Krewski, D., E. Somers and P. L. Birkwood. Risk perception in a decision making context. *Environ. Carcin. Rev. (J. Environ. Sci. Health)* C5:175–209 (1987b).

Luu, B., M. A. Denomme, R. Towner, S. M. A. Li and S. Safe. Polychlorinated biphenyls: correlation between in vivo and in vitro quantitative structure-activity relationships (QSARs). *J. Toxicol. Environ. Health.* 16:379–388 (1985).

Morgan, M. G., M. Henrion and S. C. Morris. Expert Judgments for Policy Analysis. BNL 51358. Upton, NY: Carnegie-Mellon University and Brookhaven National Laboratory, (1980).

Morgan, M. G., M. Henrion and S. C. Morris. Technological Uncertainty in Policy Analysis. Pittsburgh, PA: Carnegie-Mellon University, (1982).

Murdoch, D. J., D. R. Krewski and K. S. Crump. Quantitative theories of carcinogenesis. In: *Cancer Modeling*, J. R. Thompson and B. W. Brown, eds. (New York: Marcel Dekker, 1987), pp. 61–89.

National Research Council. Evaluating the safety of food chemicals. Food

Protection Committee, Food and Nutrition Board, Div. of Biology and Agriculture. Washington, DC: *Nat. Acad. Sci.* 0-309-01859-5, (1970).

O'Neill, R. V., R. H. Gardner, L. W. Barnthouse, G. W. Suter II, S. G. Hildebrand and C. W. Gehrs. Ecosystem risk analysis: a new methodology. *Environ. Toxicol. Chem.* 1:161–177 (1982).

Rish, W. R. Approach to Uncertainty in Risk Analysis. ORNL/TM-10746. Oak Ridge, TN: Oak Ridge National Laboratory, (1982).

Rosenblatt, D. H., et al. The preliminary pollutant limit value (PPLV) concept. *Military Med.* 151:645–647 (1986).

Safe, S. Polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs): Biochemistry, toxicology and mechanisms of action. *CRC Crit. Rev. Toxicol.* 13:319–393 (1984).

Starr, T. B., and R. B. Buck. The importance of delivered dose in estimating low-dose cancer risk from inhalation exposure to formaldehyde. *Fundam. Appl. Toxicol.* 4:740–753 (1984).

Swain, W. R. Human health consequences of consumption of fish contaminated with organochlorine compounds. In: Symposium on Trace Chemicals and Aquatic Life: Research and Management, Seattle, WA (1986).

U.S. EPA. Development of Statistical Distributions or Ranges of Standard Factors Used in Exposure Assessments. OHEA-E-161. Washington, D.C.: Office of Health and Environmental Assessment, U.S. Environmental Protection Agency (1985).

U.S. EPA. Superfund Public Health Evaluation Manual. OSWER Directive 9285.4-1. Washington, D.C.: Office of Emergency and Remedial Response/Office of Solid Waste and Emergency Response. U.S. Environmental Protection Agency (1985).

U.S. EPA. Superfund Exposure Assessment Manual. OSWER Directive 9285.5-1. Washington, D.C.: Office of Emergency and Remedial Response/ Office of Solid Waste and Emergency Response. U.S. Environmental Protection Agency (1987).

U.S. EPA. Proposed Amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants. EPA/600/FR-89/001. U.S. Environmental Protection Agency. Fed. Register March 6, 1989, pp. 9386–9403.

Wilson, R., and E. A. C. Crouch. Risk assessment and comparisons: an introduction. *Science* 236:267–270 (1987).