II. FRAMEWORK FOR THE INTEGRATION OF HEALTH AND ECOLOGICAL RISK ASSESSMENT

Glenn Suter, Theo Vermeire, Wayne Munns, and Jun Sekizawa

1. Introduction

What is included in the integrated framework?

In this document, we define the term integrated risk assessment as, a science-based approach that combines the processes of risk estimation for humans, biota, and natural resources in one assessment. Such an integrated approach can be applied to a wide variety of types of assessments including 1) assessments that predict the effects of proposed actions, 2) those that estimate the ongoing effects of past actions, 3) assessments of actions at particular places, and 4) assessments of risks from hazardous agents independent of location. Integration extends across all phases of the assessment process from the planning of the assessment to decision making.

Why integrate?

The objective of risk assessment is to support decision making by assessing risks of adverse effects on human health and the environment from chemicals, physical factors, and other environmental stresses. For practical reasons, the methodologies for human health and ecological risk assessment developed independently. However, with increased recognition of the need to more effectively protect both humans and the environment, it is time to consider a move to a more integrated, "holistic" approach to risk assessment.

The ability of environmental managers to make appropriate decisions may be limited by the incomplete or incoherent information provided by risk assessments that are too limited in scope. We believe that it is particularly important to integrate assessments of risks to human health and well-being with risks to nonhuman organisms, populations, and ecosystems. Decisions are not fully informed if they consider only one or the other. Protection of humans will not inevitably result in protection of nonhuman organisms and ecosystems. In most cases of environmental contamination or disturbance, some nonhuman receptors may be more exposed or more sensitive than humans (Suter 1993). Integration of health and ecological assessments is the focus of this paper, but additional types of integration may also be relevant to the risk manager’s needs (Annex A). A working glossary of key terms used in this framework is provided in Annex B.

Integration of health and ecological assessments provides five major advantages. Three of these address general concerns, while the last two relate to methodological issues:

> **Coherent Expression of Assessment Results** - Coherent results of integrated health and ecological risk assessments provide a strong basis for action to support decision making. However, when the results of independent health and ecological risk assessments are inconsistent and the bases for the inconsistency are unclear, decision making is complicated. This may occur because the results of the health and ecological risk

assessments are based on different spatial and temporal scales, different degrees of conservatism, or different assumptions, ranging from assumed parameter values to assumed land use scenarios. As a result, decision makers may find it difficult to decide whether, for example, the reported risks correspond to expected effects on humans that are sufficient to justify taking a remedial action that will destroy an ecosystem. As another example, consider a decision whether to license a new pesticide that poses an increased risk to humans and a decreased risk to aquatic communities relative to a current pesticide. If the ecological risk estimates are based on expected effects on a spatially distributed community while the health risks are based on provision of a margin of safety on an effect level for a hypothetical maximally exposed individual, the two estimates of risk can not be compared. Finally, if variance and uncertainty are not estimated and expressed equivalently for health and ecological risks, a decision maker can not determine the relative need for additional research to support future assessments. For example, variance in dilution should be either included or excluded in both assessments, and, if it is included, the same estimates should be used. Integration of health and ecological assessments can avoid these impediments to defensible decisions.

Interdependence - Ecological and human health risks are interdependent (Lubchenco 1998, Wilson 1998). Humans depend on nature for food, water purification, hydrologic regulation and other products and services which are diminished by the effects of toxic chemicals. In addition, ecological injuries may result in increased human exposures to contaminants or other stressors. For example, addition of nutrients to aquatic ecosystems and the resulting changes in algal community structure may influence the occurrence of water-borne diseases such as cholera as well as toxic algae such as *Pfiesteria piscicida* which kill fish and potentially affect humans. More subtlety, the occurrence of fish kills or the disappearance of formerly familiar birds may diminish people's sense of well being leading to both psychological and physical effects. As a result of this interdependence, assessments that do not integrate health and ecological risks are likely to miss important modes of action that involve interactions between effects on the environment and effects on humans.

Sentinel Organisms - Because nonhuman organisms often are more heavily exposed to environmental contaminants and may be more sensitive, they can serve as sentinels, suggesting potential sources of human hazards (NRC 1991, Burkhart and Gardner 1997, Sheffield et al. 1998). There are significant technical difficulties in extrapolating from nonhuman species to humans (Stahl 1997). However, if human health assessors reject the analogy, the public often makes it themselves. If the fish have tumors or the birds have deformities, the public that shares the environment with these organisms will be concerned, and assessors who have not integrated the health assessments with ecological assessments may have difficulty explaining why the public should not be concerned. Nonhuman organisms may also serve as sentinels for modes of action that have not been identified in humans. For example, opportunistic infections in marine mammals appear to be related to accumulation of polychlorinated biphenyls (PCBs) and organotin compounds which cause immunosuppression in laboratory animals (Ross 1998). This has raised concern for human populations that also accumulate these compounds through fish consumption (Takahashi et al. 1998).

Quality - The scientific quality of assessments is improved through sharing of information and techniques between assessment scientists in different fields. For example, in assessments of contaminated sites, human health assessors may use default uptake factors to estimate plant uptake, unaware that ecological assessors are measuring contaminant concentrations in plants from the site. Conversely, knowledge of mammalian toxicokinetics has been used in risk assessments for humans but is seldom used in assessments for wildlife. The data sets available for the safety evaluation of chemicals in human food and drinking water are relatively large and they are used to support intensive assessments. In contrast, ecological risk assessments for chemicals have relatively small data sets and few resources to perform assessments even though the receptors include thousands of species including plants, invertebrates, and vertebrates. Integration of efforts may help to alleviate this imbalance in quality.

Efficiency - Integration of human health and ecological risk assessments offers significant increases in efficiency. In fact, isolated assessments are inherently incomplete when both humans and ecological systems are potentially at risk. For example, the processes of contaminant release, transport, and transformation are common to all receptors. Although only humans shower in water and only aquatic organisms respire water, the processes that introduce the contaminants to water, degrade or transform them, and partition them among phases are common to both. Therefore, there are clear advantages in an integrated exposure model. The development of risk assessment methodology which takes into account insights from both human and ecological risk assessments will lead to improvements which can benefit both disciplines. This will provide benefits even where sector related risk assessments that do not have an integrated assessment as their goal (e.g., work-place risk assessments) are carried out.

What is the nature and purpose of this paper?

The purpose of this paper is to provide a common framework for integrated risk assessments. It will form a basis for performing future case studies of integrated risk assessment. For other discussions of integrated assessment, the reader is referred to US EPA (1997), Harvey et al. (1995), Harwell et al. (1992), Ludwig et al. (1993), Mennes et al. (1998), Vallentyne (1997), Van Leeuwen and Hermens (1995), Suter et al. (1995), and Vermeire et al. (1997).

2. Features of the Proposed Framework

The discussion of integration of ecological and human health risk assessment is facilitated by using a structure or framework that identifies the elements of risk assessment. Although several frameworks are being employed throughout the world, most approaches reflect four basic elements or steps: some form of problem definition, a characterization of exposure, a characterization of the relationship between effects and exposure, and a synthesis of this information to estimate risk. A convenient summary of environmental risk assessment/risk management frameworks used in The Netherlands, Australia and New Zealand, Canada, the United Kingdom, and the United States is offered by Power and McCarty (1998). Some of these are discussed below.

A distinction is used in this paper between risk assessment and risk management. We restrict risk assessment to the activities that provide the scientific information to be used in the decision making process. Risk management is the use of this and other kinds of information to select among possible alternatives and to implement the selected alternative. We maintain this distinction to focus attention on the scientific aspects of integrated risk assessment.

Recognizing the similarities in risk assessment frameworks currently in use, we used the U.S. Environmental Protection Agency's framework for ecological risk assessment (US EPA 1992, 1998) and associated terminology as a starting point. The ecological risk assessment (ERA) framework has greater general applicability than do human health frameworks, or those environmental frameworks derived directly from human health frameworks. The ecological frameworks are more inclusive because 1) they were developed to deal with a range of environmental stressors beyond toxic chemicals, 2) they must describe the nature and role of the environment in the risk process, and 3) they must explicitly deal with the identification of the endpoint to be assessed. A well developed body of concepts and terminology exist in the literature treating ecological risk assessment (e.g., Bartell et al. 1992, Suter 1993, Calabrese and Baldwin 1993, US EPA 1998).

Like the ERA framework, the integrated framework consists of three major components (Figure 1). During the first of these, *Problem Formulation*, the overall goals, objectives, scope, and activities of the assessment are delineated. The *Analysis* step consists of data collection and modeling exercises to characterize exposure in time and space, and to define the effects on humans and ecological systems resulting from exposure. The methods appropriate for the Analysis step may be stressor-specific, but also depend upon the nature of the systems identified to be at risk. Exposure and effect information are synthesized as estimates of risk in the *Risk Characterization* step. Ideally, these estimates are quantitative with respect to the level of risk expected under different exposure scenarios. Depending upon the kinds of information available, however, only qualitative estimates of risk may be possible.

The integrated framework shown in Figure 1 treats the relationship of risk assessment to risk management, stakeholder input, and data collection activities in a general manner. The risk assessment is performed by experts termed risk assessors. Risk management is the process of deciding what actions should be taken and is performed by individuals who may not be technical experts. Stakeholders are individuals or groups who have interests in the risk management. They may convey their concerns and provide data or models. The integrated framework shows risk management and stakeholder activities as parallel and concurrent activities that may interact in various ways depending on the legal context and the assessment problem. The US EPA's ERA framework and many others prescribe inputs by the risk manager to the Problem Formulation through a planning process which may also include stakeholders. Considerations of regulatory requirements and constraints (where appropriate), societal values, and of other issues relevant to the assessment enter the assessment process at this level. The results of the assessment ultimately are communicated to risk managers and stakeholders. In between the planning of the assessment and the communication of results, the scientists may work independently of the risk manager and stakeholder (as in the U.S.) or may accept input concerning the performance of the analysis and risk characterization. This framework allows for communication among these groups at any time, depending on the legal and cultural context.

Unlike some other frameworks, the integrated framework does not display the input of data because data may enter from various sources at various points in the process. Existing data may be collected and new data may be generated by the risk assessors. In addition, stakeholders may generate and supply data.

The integrated framework also does not explicitly represent or discuss the iteration of the assessment process. The process may be iterated any number of times if additional data or analysis is needed to support the risk management process.

Relationship to other Frameworks

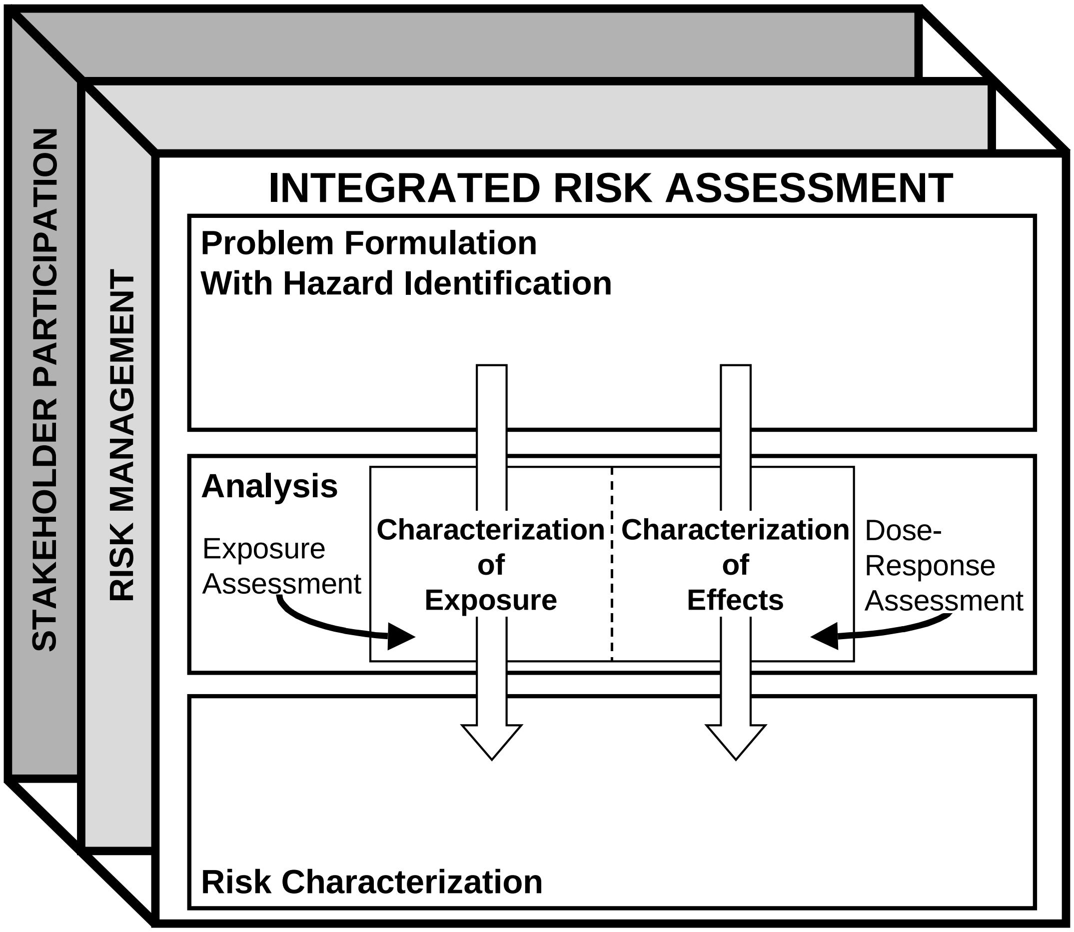
Most, if not all, of the frameworks for human and environmental risk assessment and management used today are based on the report "Risk Assessment in the Federal Government: Managing the Process," also called the "Red Book" by the US National Research Council (NRC 1983). This framework was originally designed for human health assessment only, but was later adopted for ecological risk assessment (Barnthouse and Suter 1986, US EPA 1992, Barnthouse 1993).

Common denominators in all frameworks are the roles of science and political and societal values as essential parts of the process. What differs are the degree of separation of science from policy, the different roles of stakeholders (industry, non-governmental organizations, and governmental organizations other than the regulator) in each stage of the process and the relative emphasis on risk management as opposed to risk assessment (Power and McCarty 1998).

The US EPA's ERA process separates science from the risk management process and mainly allow stakeholder consultations in risk management stages prior to and following risk assessment which, itself, is considered a purely technical exercise. Other frameworks, including the redefined NRC framework (NRC 1996), the EU Risk Assessment framework for new and existing chemicals (EC 1996) and the FAO/WHO framework developed for risk management and risk assessment of food additives (FAO/WHO 1997) demand a greater role for risk managers and stakeholders in the risk assessment. The degree of participation of risk managers or stakeholders in the risk assessment process depends on the relative degree of concern about bias and relevance. If risk managers and stakeholders are intimately involved in the process, they may influence the selection of scenarios, models, and parameters to obtain desired results. On the other hand, if they are not involved, the risk assessment may not address issues that are critical to the decision. The proposed integrated framework (Fig. 1) does not specify the timing or degree of involvement.

Leaving aside the degree of interaction with risk management and stakeholders, all risk assessment paradigms follow essentially the same logic. In some cases the stage of problem formulation, as described extensively in the U.S. Guidelines for ERA, is addressed, harmonized and laid down in advance. For example, assessments of individual chemicals within an agency or regulatory program may all use a common formulation of the assessment problem (EC 1996, FAO/WHO 1997). Differences among paradigms for human health and ecological risk assessment are mainly with regard to terminology. The most significant difference is the use of "hazard identification" which is sometimes used to indicate the stage in which data are being evaluated and stressors of concern selected – and therefore part of "problem formulation" (e.g., NRC 1983), whereas in other schemes hazard identification is part of the characterization of effects (effects assessment), indicating the identification of adverse effects which a stressor has an inherent capacity to cause (e.g., EC 1996, FAO/WHO 1997, OECD 1995). Other differences are considered minor for the purpose of this paper and generally will not lead to confusion.

Figure 1. A framework for integrated human health and ecological risk assessment (modified from US EPA 1998).



Risk assessors, risk managers, and stakeholders perform parallel activities which may interact at various stages.

3. Problem Formulation

What is problem formulation?

Problem formulation is a critical phase of the risk assessment process. The first step to initiating problem formulation, and the assessment itself, is a planning dialog that clarifies the management goals, the purpose and scope of the assessment, and the resources available to conduct the assessment. The planning dialog considers whether a risk assessment is needed, and who should be involved in the assessment/risk management process. It also helps to ensure that the assessment will provide the information necessary to support the environmental decision making process (i.e., risk management). Risk managers, risk assessors, and other stakeholders all bring valuable perspectives to assessment planning. This dialog may be initiated by presuming risk based on the characteristics of recognized stressors (stressor-driven), through direct observation of effects in the environment or in humans (effects-driven), or through a desire to evaluate potential risks to valued resources (resource-driven).

Problem formulation is the process by which the assessment is defined and the plan for analyzing and characterizing risk is developed (US EPA 1992, 1998). As an initial activity in problem formulation, information concerning known or suspected stressors, observed or hypothesized effects, and systems at potential risk is integrated to generate two types of products: assessment endpoints and conceptual models (Figure 2). Assessment endpoints are the specific attributes and entities to be assessed and protected (US EPA 1998). Criteria important for selecting appropriate assessment endpoints have been discussed by Suter (1989, 1990, 1993), US EPA (1998), and others. They generally include considerations of relevancy (with respect to the environmental systems, stressors, and societal values), applicability, and utility. The conceptual model is a representation of the relationships between the sources of the stressors and the assessment endpoints. It constitutes a hypothesis about how potentially significant risks arise. Ideally, the conceptual model should undergo rigorous review by risk managers, scientific peers, and other stakeholders to ensure that all concerns have been addressed and that the assessment will yield a scientifically sound and credible characterization of risk. The methods to be used in the assessment to evaluate the risk hypotheses reflected in the conceptual model are described in the analysis plan, the final product of problem formulation (Figure 2). Analysis plans provide the information necessary for risk assessors and risk managers to determine that the assessment will provide the kinds and quality of information necessary to make environmental management decisions.

What is integrated?

Assessment questions - An integrated approach offers the opportunity to develop and focus on assessment questions common to both health and environmental perspectives. It would ensure consistency in the spatial and temporal scopes of the two kinds of assessment, thereby enhancing the consistency of support information and processes used in environmental decision making. An integrated approach also helps to ensure adequate consideration of risks to humans through evaluation of risks to other organisms that influence human health and welfare.

Impetus for the assessment - An integrated approach has obvious utility in stressor-driven assessments, which are assessments that evaluate risks associated with specific stressors (e.g., new chemicals) in the environment. However, the impetus for an assessment may also be observed exposure (e.g., mercury in fish) or effects (e.g., mass mortality of birds). In those cases, the implications of those observations for both humans and nonhuman endpoints should be considered.

Assessment endpoints - Integration would foster coherence in endpoints used to assess health and ecological risks. Knowledge of the environmental fate or mode of action of a stressor can elucidate the susceptibility of potential human and ecological endpoints. In addition, knowledge of ecological susceptibility can suggest what indirect effects on humans may be identified as endpoints.

Conceptual models - Conceptual models in integrated assessments would reflect common sources and transport pathways of environmental stressors. Humans would be considered another potential receptor on these pathways. Such models would reflect a more complete list of risk hypotheses related to the environmental stressors, including incorporation of multiple sources, multiple exposure pathways, multiple direct effects, and the possibility of indirect effects.

Analysis plan - An integrated approach offers substantial opportunity for enhanced efficiency of sample and analysis activities, as well as other data gathering activities. Models can be selected to describe exposure (transport and fate) and effects in a manner that maximizes utility in assessing risk to humans and the environment, and that have similar data needs. Assumptions supporting those models and other analysis approaches would be made in common, and results of planned analysis activities would be expressed in similar fashion. Sampling, analysis, testing, and other data generating activities can be conducted to ensure relevance to human and ecological risks at minimum cost. Finally, if the assessment will be iterated, an integrated approach might foster the development of parallel tiers, which use common data and models. For example, both health and ecological assessments may begin with a screening assessment that will use a common set of conservative assumptions and then move to a more focused and realistic assessment.

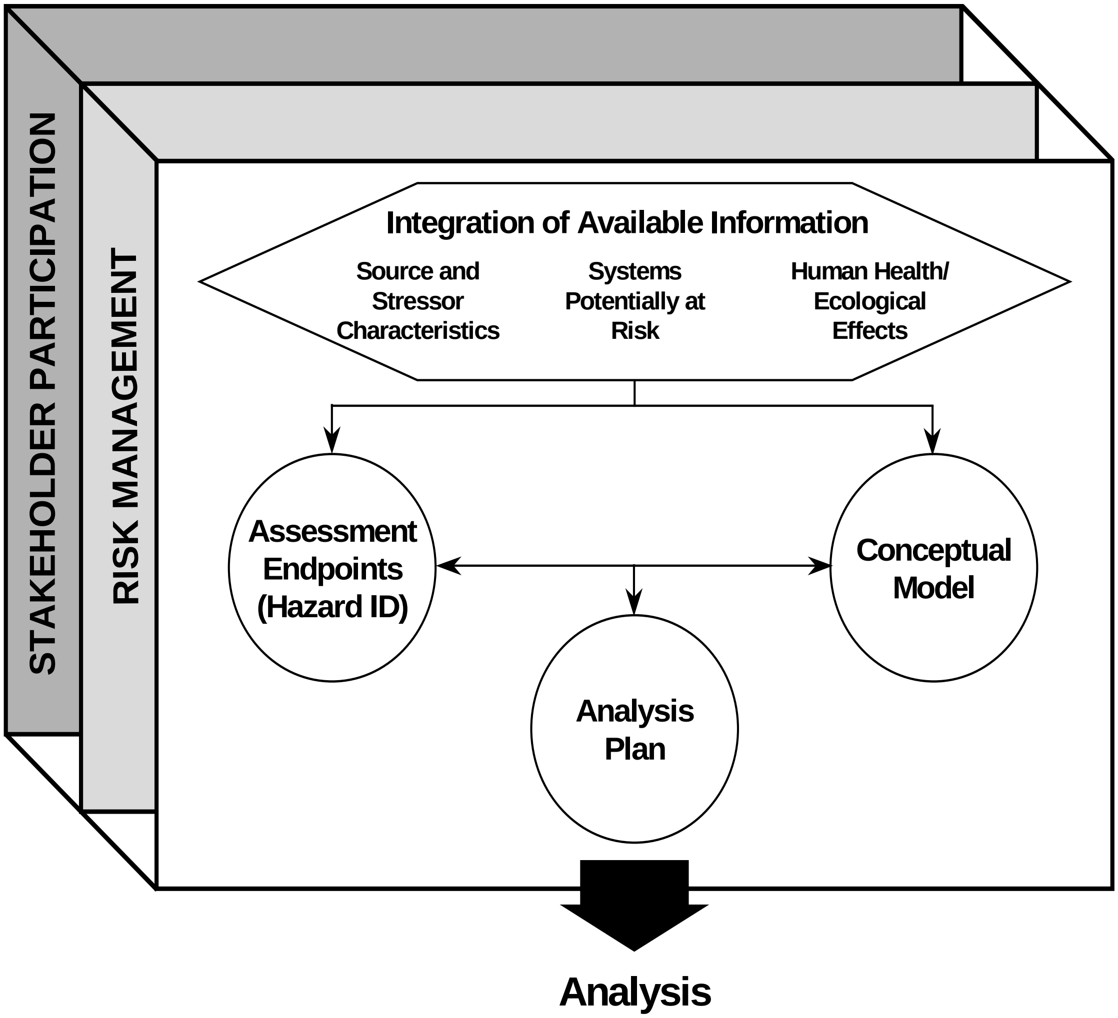


Figure 2. The problem formulation stage of an integrated risk assessment. Risk management and stakeholder activities are parallel and may interact with the problem formulation process to a greater of lesser extent depending on circumstances (modified from US EPA 1998).

4. Characterization of Exposure

What is characterization of exposure?

Characterization of exposure is the estimation of the concentrations, doses, or degree of contact of chemical, physical or biological stressors to which human individuals or populations, nonhuman individuals, populations, or ecosystems are or may be exposed. The objective of exposure characterization is to measure or model exposure in terms of routes, intensity, exposure media, spatial scales and time scales, using units that can be combined with the characterization of effects. The spatial scale refers to the geographical dimension of the problem: examples include the area around a point source, a region, or the globe. The time scale has aspects of duration, frequency, and timing.

Exposure characterization requires the evaluation of:

- Data completeness, quality and relevance for the aim of the risk assessment.
- Stressor characteristics: the identity and properties of the chemical, physical or biological stressor.
- Sources and emissions: identification and quantification of all sources and a correct description of industry and use category.
- Distribution pathways: conversion of the conceptual model to a quantitative model of relevant distribution routes and routes of exposure for endpoint organisms and ecosystems.
- Transport and fate: quantification of important transport, transformation, and degradation processes within the distribution pathways.
- External and internal exposure models: external exposure is estimated in terms of contact between a stressor and an organism which can be estimated from transport and fate models and knowledge of the organism’s behavior, whereas internal exposure is estimated as dose to target organs and requires consideration of toxicokinetic processes such as uptake, transport, and metabolism.

The uncertainty in the exposure estimates should also be addressed. Tiered approaches are generally preferable, beginning with simple conservative screening models and proceeding to more realistic and complex models generating probability density functions of exposure.

What is integrated?

Sources and emissions - In an integrated approach it is often useful to consider the whole life cycle of a stressor so as to identify all potential emission sources which may lead to exposure of humans or nonhuman organisms (Fig. 3). Emissions may occur at all stages. Sources must identified which lead directly or indirectly to exposure of both humans and nonhuman species.

Distribution pathways - Having identified all emission sources, exposure pathways from these sources to environmental compartments and finally to receptor organisms or ecosystems should be identified as well as the commonality of these routes for different receptors.

Transport and fate models - Exposure pathways common to two or more receptor organisms or ecosystems can be described by common transport and fate models, including aspects such as advection and diffusion, partitioning, bioaccumulation, and abiotic and biotic degradation. These processes are determined by the characteristics of the stressor, the receiving environmental compartment, and the receptor organism or ecosystem.

External and internal exposure models - Most stressors must contact target organisms to cause an effect. Contact and internal transport and fate may be modeled similarly for different organisms.

Measures of exposure related parameters - The application of common descriptions of sources and emissions and common models for transport, fate, contact and toxicokinetics implies that, for all parameters that are not receptor-specific, the same value and units should be chosen. This applies to both measured parameters and parameters for which default values need to be estimated by expert judgement.

Analytical tools - Integrated exposure assessment requires the application of the same quantitative methods such as methods for sensitivity and uncertainty analysis. Monitoring strategies should also consider aspects important for an integrative approach, particularly in relation to spatial scales and time scales.

Box 1. Commonality of exposure and effect in wildlife and humans.

Similarities in physiology (e.g., immune system), exposure (e.g., diet), mechanism of toxicity (e.g., *Ah*-receptor), and effect (e.g., immunotoxicity) provide a means of evaluation and comparison in wildlife and humans. Certain wildlife species, including the fish-eating birds and marine mammals, have suffered from the adverse effects of persistent organochlorine pollutants (POPs) as a result of their dietary exposure to these mixtures. A combined “weight of evidence” from laboratory studies, captive studies of wildlife, and studies of free-ranging populations of wildlife have implicated the dioxin-like compounds (the planar PCBs, dioxins, and furans) in immunotoxicity and related virus-associated mass mortalities. The position of these organisms at the top of freshwater and marine food chains results in their exposure to high levels of persistent, fat-soluble chemicals which bioaccumulate. Like wildlife, all humans are exposed to complex mixtures of POPs, and certain human consumer groups (e.g., Inuit, sportfishing families) share positions with wildlife at the top of the food chain. Increasing evidence of POP-related toxicities in humans exposed through their diets have been strengthened by evidence from wildlife. Certain wildlife species can therefore serve as “sentinels” for human health risks for complex mixtures of

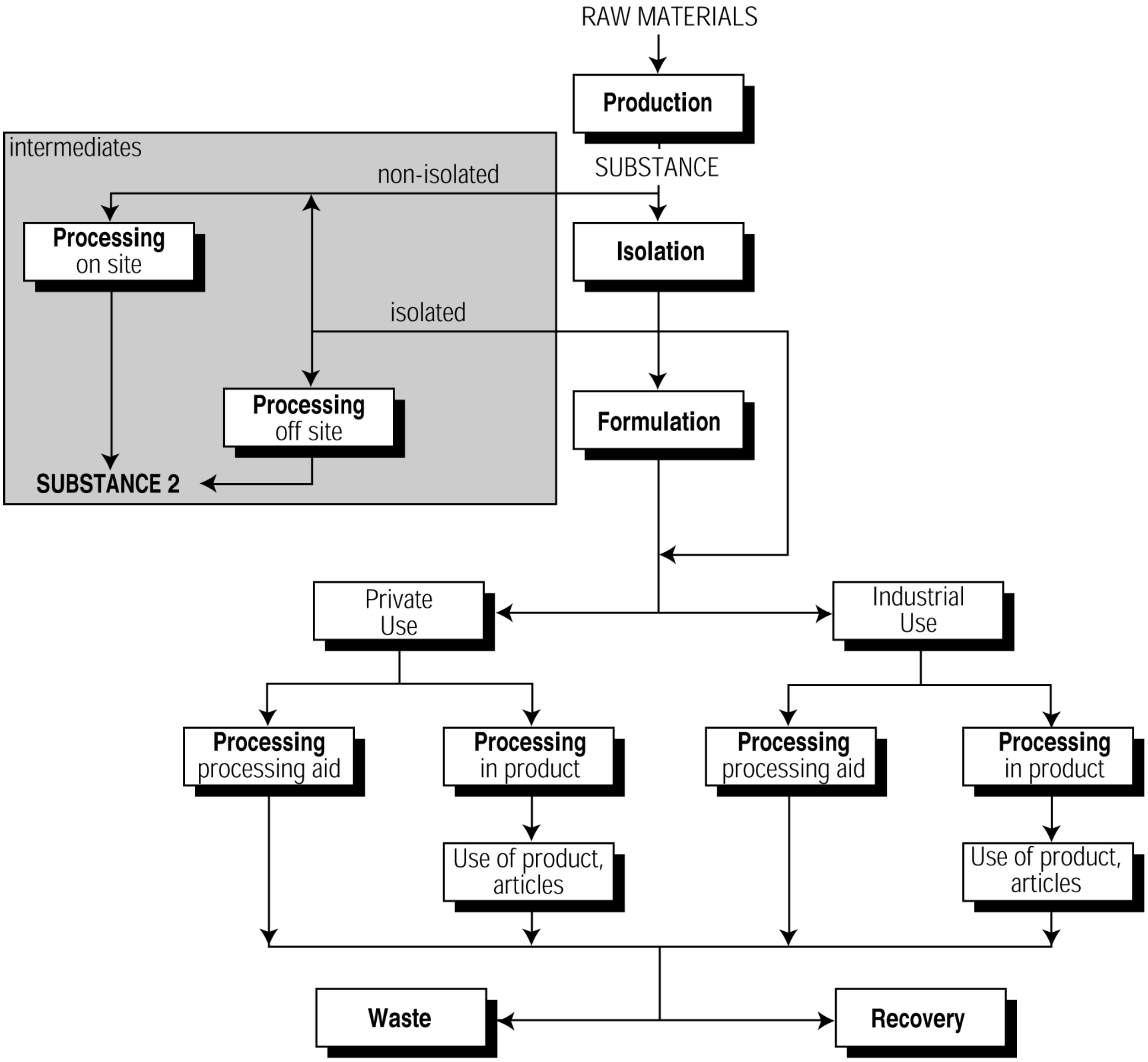


Figure 3. The life cycle of a chemical substance. Emissions to the environment can occur at any point in this cycle.

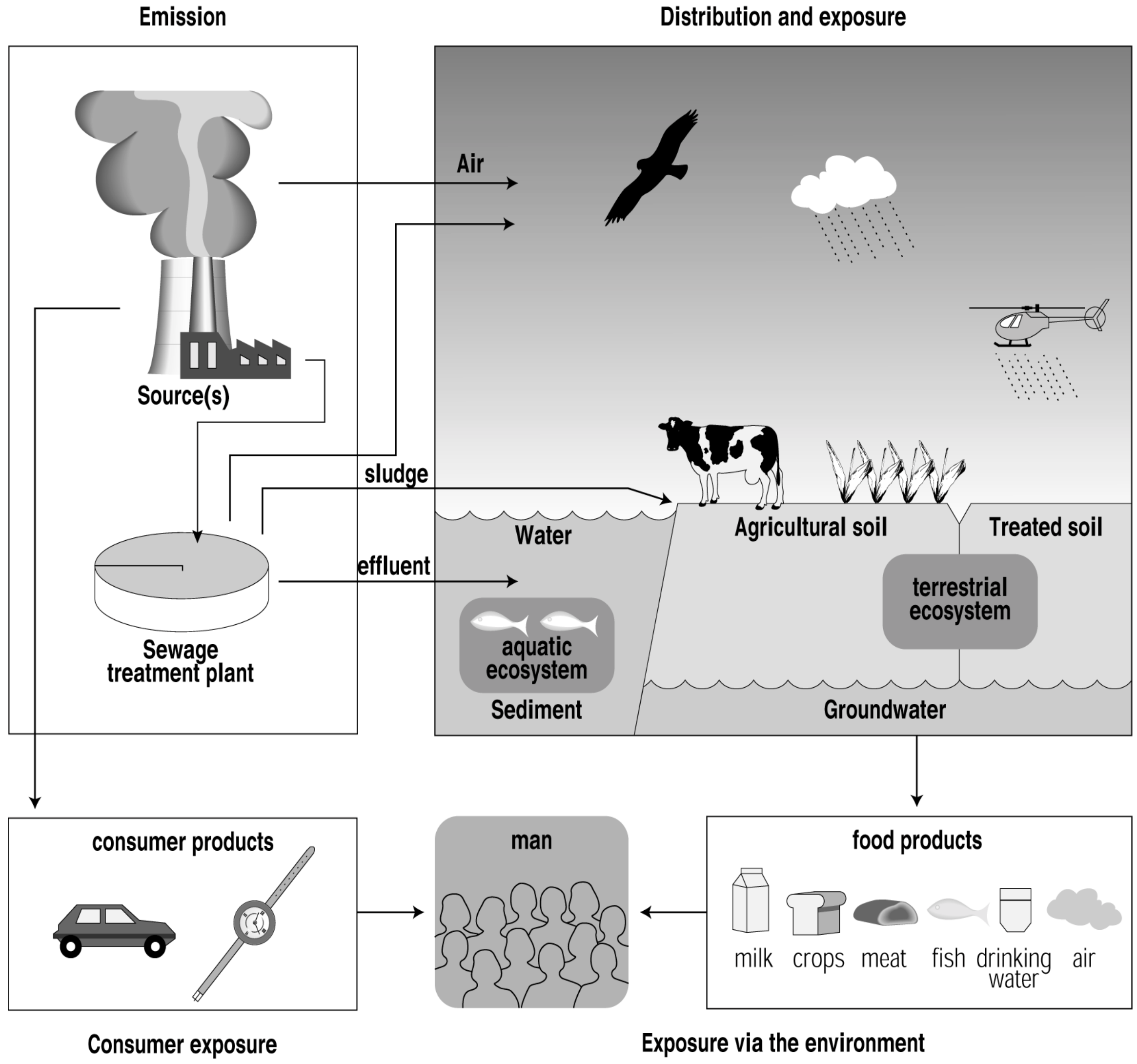


Figure 4. Routes of exposure of human and nonhuman organisms (van Leeuwen and Hermens 1995).

5. Characterization of Effects

What is characterization of effects?

Characterization of effects (also termed hazard characterization) consists of two distinct stages:

1. Hazard identification: the identification of adverse effects that a stressor has an inherent capacity to cause to human individuals or populations, or environmental populations or ecosystems, or natural resources;
2. Exposure- response analysis: the estimation of the relationship between level of exposure to a stressor, and the incidence and severity of an effect.

The hazard identification is normally part of the problem formulation in the US EPA frameworks, but it may be revisited during the characterization of effects if new data suggest additional hazards.

Characterization of effects requires:

- Evaluation of data completeness, reliability, and relevance for the aim of the risk assessment.
- Evaluation of the nature, intensity and time scale of adverse effects with a causal relation to the stressor.
- Identification of the modes of action.
- Quantification of the relation between the response to stressor and exposure.
- Extrapolations relating experimental and other data to the assessment endpoints including humans or ecosystem attributes.
- Evaluation of indirect effects.

What is integrated?

Reported effects and modes of action - As appropriate, integration of the characterization of effects should be based on an understanding of the common modes of action of stressors in a range of organisms including humans. In addition, identification of similarities in the nature, intensity and time scale of effects between species, as well as in the susceptibilities of different receptors, will allow a better understanding of the actual risk to these organisms and help in the identification of issues of concern.

Biomarkers and indicators - Common mechanisms of action identified across species may lead to the identification and application of biomarkers and other indicators of effect common to humans and other ecological receptors. Knowledge of the applicability of such measures of effect will improve the ability to estimate effects to other species in the assessment. Additionally, standardization of such measures will enhance the ability to understand the magnitudes of effects across a variety of receptors.

Box 2. Mode of action or potential common mechanisms behind the toxicities.

Some common mechanisms might be found to explain complex toxicity profiles (IPCS in press a&b). Essentially all of the effects of TCDD, as well as related PCDDs, PCDFs, and coplanar PCBs, are mediated by binding of the contaminants to a specific cellular protein, the Ah receptor. The Ah receptor is highly conserved, being present and functional in essentially all vertebrate species. It functions as a ligand activated transcription factor controlling proliferation, differentiation, and apoptosis in a tissue and developmental stage specific manner. The Ah receptor is a member of the PAS family of basic helix-loop-helix regulatory proteins, which can heterodimerize and control circadian rhythms, differentiation, and oxidative stress. Dioxin and related compounds are reproductive and developmental toxicants, immunotoxic, neurotoxic, and carcinogenic in multiple species, including domestic and laboratory animals, wildlife, and people.

Exposure-response modeling - Making use of the commonalities of mechanisms of actions among humans and ecological receptors is the real strength of the integrated approach. Based on common mechanisms of action, stressor-response modeling for humans and other species in the environment would use the same principles. Ideally, such efforts would result in continuous models of exposure-response (e.g., benchmark dose models), as opposed to an hypothesis testing approach which yields statistics like the No- or Lowest-Observed-Adverse Effect Levels. This is important to integrated assessment because, use of NOAELs and LOAELs does not allow comparison of the nature and magnitude of effects between human and ecological receptors. Toxicity equivalent factors and similar approaches used to combine or interconvert responses to stressors with common modes of action may be common to human and nonhuman species.

Extrapolations - Extrapolations bridge the gaps between observed effects on experimental or field-monitored organisms and the effects that must be estimated for assessment endpoints. Extrapolations are required between species, specific subpopulations, temporal and spatial scales, and modes of exposure. Common extrapolation procedures for humans and nonhuman species can be pursued including uncertainty factors, uncertainty distributions, allometric models, species sensitivity distributions, intertaxa regressions, and pharmacokinetic/pharmacodynamic models.

Direct and indirect effects - Integration of the characterization of effects should consider both direct and indirect effects resulting from exposure to the stressor. Indirect effects result from relationships among environmental processes. Integrated analyses of effect should recognize the potential cascading influences of one or more stressors. For example, direct toxicity to fish may result in loss of piscivorous wildlife and reductions in human welfare.

6. Risk Characterization

What is risk characterization?

Risk characterization is the phase of a risk assessment that: 1) combines the results of the characterizations of exposure and effects to estimate the risks to each endpoint, 2) estimates the uncertainties associated with the risks, and 3) summarizes the results for presentation to the risk manager and stakeholders.

What is integrated?

Combining exposure and effects - In the simplest case, an exposure estimate is used to estimate effects in an exposure-response model. Integration becomes more difficult when effects have been observed in the field and causation must be assigned or when multiple lines of evidence are available.

Box 3. Integration of knowledge on diverse effects in various organisms.

Organotin compounds show wide variety of effects at different concentrations to each different aquatic organisms (IPCS 1990, in press a). In case of triphenyltin compounds (TPTs), toxicological profiles for environmental organisms and humans are as follows. EC$_{50}$s for inhibition of reproduction, germination or carbon fixation of fresh water and marine/estuarine algae occur at 1-5 µg/l level, imposex (development of male characteristics in females) in gastropods at 1ng/l, LC$_{50}$s for 48 hr exposure with daphnids at 10-200 µg/l, NOEC for reproduction of the same species in 21-day exposure at 0.1 µg/l, 30-day LC$_{50}$ and 30-day NOEC with fathead minnow larvae at 1.5 µg/l and 0.15 µg/l, respectively. TPTs also show varieties of health effects in laboratory animal species, including effects on immune system, such as decrease in immunoglobulin concentrations, lymphopenia, and thymus or splenic atrophy in rats and mice, reproductive/developmental effects (mostly LOAELs are in several mg/kg range or lower), hyperplasia/adenomas on endocrine organs or decrease in white blood cells at 0.3 mg/kg bw or lower in rat 2-year study. Similar effects at similar concentrations were seen for tributyltin compounds, too. Integration of knowledge of these toxicity profiles will shed lights on characteristics of toxicity of these compounds and may elucidate potential common mechanisms between environmental organisms and humans. Because thymus reduction, decrease in numbers of lymphocyte, and inhibition of gonad development in fish species by tributyltin were reported (Shimizu and Kimura 1992), organotin compounds may exert similar actions between environmental and laboratory organisms.

Determining causation - Causation must be determined when apparent effects are associated with chemical contamination or some other hazardous agent. Examples of apparent effects include cancer clusters, fish kills, and reduced tree growth. Various criteria have been developed in human and ecological risk assessment for determining causation (Rothman 1988, Fox 1991, Suter 1998). An integrated assessment would use a common set of evidence, common criteria, and common interpretations of those criteria to determine the cause of human and ecological effects that cooccur or are apparently associated with a common cause.

Combining lines of evidence - Risk characterizations often must derive a best estimate of risk from multiple lines of evidence. These may include results of toxicity tests of different species, results of single chemical and mixtures toxicity tests, and exposure estimates derived from different fate models and from environmental measurements. These lines of evidence may be quantitatively weighted and combined, the highest quality line may be chosen subjectively, an inferential logic may be developed, or some other process may be chosen. In an integrated assessment a common approach would be used to integrate multiple lines of evidence, and, as far as is appropriate, the chosen approach would be implemented in a consistent manner. In addition, evidence from ecological and human health risks would be integrated when appropriate. As a simple example, observed effects on piscivorus wildlife would be considered when estimating health risks to humans who consume fish. In this case, body burden or critical organ burden of the contaminants could be a common measure between animals and humans, normalizing for the wide range of species difference in metabolic activity and rate of food consumption. A more complex example is presented in Box 5.

Box 4. Uncertainty analysis in integrated risk assessment for organophosphate pesticides.

Consider the local risk assessment of human exposure to organophosphates pesticides via non-target crops next to a spraying area based on known application rates. The estimation of the total intake can be based on modeling of the following exposure pathways:

1. drift of the organophosphate through air, subsequent deposition, and transfer via crops and cattle and air to humans;
2. leaching to surface water or groundwater and transfer via fish and drinking water supply to humans.

In a deterministic assessment upper-bound estimates are based on conservative estimates of exposure and risk. In our example, worst case values will for instance be used for anatomical and dietary properties of humans and cattle, partition coefficients, bioconcentration factors and biotransfer factors. In uncertainty analysis, not only this upper-bound estimate will be estimated, but the full distribution of intakes of the affected population. This allows the risk manager to choose an appropriate level of uncertainty (e.g., the 50th or 99th percentile of the intake distribution), to separate individual variability (e.g., in human body weights or food intake factors) from true scientific uncertainty (e.g., in estimates of partition coefficients) and to consider benefits, costs, and comparable risks.

In this example the uncertainty analysis would require the following:

3. Definition of statistical distributions of key input parameters such as:

-variability in application rate, human body weights and food and drinking water intake factors, inhalation rates, fractions of food homegrown, and fat contents;

-variability and uncertainty in ingestion of grass, soil and air by cattle;

-uncertainty in percentage of drift, leaching/deposition/degradation/dilution rates, the ratio of plant dry mass to fresh mass, partition coefficients, bioconcentration and biotransfer factors;

4. Generate a distributions of exposure through simulation.

Compare this exposure distribution with a fixed value of the Acceptable Daily Intake (ADI) and determine the probability that this ADI is exceeded. Note that the assessment may be further developed by taking into account the variability and uncertainty in the human effects assessment.

Uncertainty - Uncertainty is at the heart of risk assessment. Through uncertainty analysis, the risks of various stressors can be expressed in a common form (e.g., the probability of occurrence of specified effects on human and ecological endpoints). However, the treatment of uncertainty in risk assessment is inconsistent and the terminology is diverse. An integrated assessment should start with a common concept and terminology of uncertainty (e.g., distinguish variance from true uncertainty), and as far as appropriate should use common analytical methods.

Box 5. Regional integrated assessment of human and ecological condition.

Assessment problems have characteristic spatial scales which are determined by the distribution and dynamics of stressors and receptors. Many important problems are best characterized at regional scales. Examples include the health and ecological risks from irrigation drain water in California's Central Valley, from nitrogen deposition in Central Europe, and from the shrinkage of the Nile Delta due to reduced sediment input. Regional-scale assessments present challenges and opportunities for the integration of human health and ecological risks. Issues that arise at regional scales include:

1. the transport of contaminants through regional watersheds and atmospheric dispersion resulting in exposures far from the point of release;
2. the potential for cumulative effects due to the regional distribution of diverse human activities;
3. changes in human perceptions of the aesthetic quality of landscapes due to changes in regional land-use patterns and ecological succession;
4. the problem of characterizing the condition of regions based on measurements with different spatial resolutions and sampling schemes;
5. prediction of the effects of human settlement patterns on loss of biodiversity and human exposure to wildlife and their diseases.

Methods for integrated risk assessments at regional scales are an area of active research. Many of these are being developed in the context of international evaluations of the effects of climate change (see, for example, Chan et al. 1999), and environmental monitoring and assessment programs evaluating condition at regional and national scales (e.g., the U.S. EPA's Environmental Monitoring and Assessment Program [EMAP]). Such efforts are bringing to focus the advantages as well as the complexities of integrated risk assessments at regional scales.

Presentation of Results - The results of risk characterizations must be presented in a form that is easily understood without losing their accuracy or diminishing their information content. This requires skillful use of text, graphic, and tabular presentation. To diminish confusion and to promote coherent decision making, the results of health and ecological risk assessments should be presented in a common format that allows comparison of results. For example, if health risks are presented as "the maximally exposed human will exceed a safe dose due to eating fish from the lake," and the ecological risk is presented as "the probability of extinction of the local otter population is *x*," the results are both legitimate, but they are not comparable. An integrated assessment would use some common presentation of results (e.g., proportions of human and otters in a region experiencing reproductive impairment), and would explain differences in the magnitude of effects. Similarly, the uncertainties would be presented in a common form (e.g., cumulative frequency). This integrated risk characterization would greatly facilitate the task of communicating risks to risk managers and the public.

7. Risk Management and Stakeholder Participation

What is risk management?

Risk management, in contrast to the scientific process of risk assessment, involves making decisions concerning actions in response to estimated risks to humans or ecological systems. A risk manager defines the issues to be addressed by a risk assessment, selects among alternative management options, and determines the acceptability of risks associated with decisions. The deliberations and decisions integral to risk management involve many kinds of information. In addition to consideration of potential adverse effect estimated by the risk assessment process, the sociopolitical and economic implications of alternative options may be considered in the decision making process. Legal mandates and regulatory constraints define the nature of decisions (as well as the focus of the risk assessment) and limit the range of management options available. Engineering feasibility may further constrain the implementation of various options. Thus, the understanding of potential risk to humans and ecological systems contributed by risk assessment is but one consideration in the overall risk management process.

What is integrated?

Ideally, the net benefit of the regulatory, remedial or restoration decision to human health and the environment would be maximized. Given that there may be conflicts between human health and ecological goals and that economic and political considerations may mitigate against maximizing either health or ecological benefits, it is important, at minimum, to ensure that both health and ecological risks are fully and fairly considered. This requires that the results of health and ecological risk characterizations be presented in a manner that facilitates comparison and balancing.

Risk management decisions should be transparent and should use a clear and consistent logic. Integrated assessments should provide consistent expressions of health and ecological risks because they are needed for consistent decision logics.

What is stakeholder participation?

Stakeholders in the risk assessment process are members of society concerned about the environmental issues associated with the assessment and who may be affected by management decisions that use the results of the assessment. Potentially included as stakeholders in any particular risk assessment are representatives of industry, public interest groups, property owners, resource consumers, and other private citizens. Stakeholders can participate in risk assessments in a number of ways, including by assisting in development of management goals, by proposing assessment endpoints, by providing valuable insights and information, and by reviewing assessment results. Although the circumstances of stakeholder involvement vary widely among different risk assessments (depending on the regulatory and management context of the assessment), active stakeholder participation helps to ensure understanding of assessment results and the success of management actions.

What is integrated?

Stakeholder participation can be integrated during all phases of the risk assessment process. During problem formulation, stakeholders can provide input to development of management goals that address both ecological and human health issues. They also can help to identify ecological entities and human health issues that can become joint or complementary assessment endpoints. In both problem formulation and analyses phases, stakeholders can provide information and data useful to understanding exposure from stressors to humans and other receptors, possible effects resulting from that exposure, as well as the possible interactions of humans and nonhumans that influence exposure and effects. Integration of stakeholder involvement during risk characterization and risk management can improve the description, interpretation, and understanding of risks estimated by the assessment. Stakeholders input can be used to help identify the relative importance of risks to humans and ecological systems, thereby assisting the decision-making process and supporting management actions.

8. Risk Communication

What is risk communication?

Risk communication is an essential but difficult interactive process among risk assessors, risk managers, stakeholders, and other members of the public in which information about risks is exchanged (NRC 1989, Lundgren and McMakin 1998). Because ecological and human health risks are interdependent, there is a need for communication of health and ecological risks in an integrated manner.

Risk communication occurs first in the problem formulation when the risk manager explains the questions that he wants answered and the legal, policy, time, and resource constraints on the assessment. The assessors respond with the scientific and technical constraints on the assessment and provide scientific information to help clarify and sharpen the questions and define the scope of the assessment. After the assessment is completed, risk assessors communicate their results to the risk manager in a form that is useful for decision making including presenting the risks for alternative actions and uncertainties concerning risk estimates. Risk communication will also include stakeholders and the general public, but the timing and extent of this communication depends on the problem and context.

What is integrated?

Communication during the problem formulation should include the human health and ecological risk assessors, the risk manager, and, as appropriate, the stakeholders. If decisions about the purpose and scope of the assessment are not coherent, it will not be possible integrate the sampling, analysis and assessment processes or to perform consistent analyses or human and ecological risks.

When the assessment is complete, the human and ecological risk assessors should present a coherent message concerning risks. Even when human and ecological risk assessments are performed in a consistent manner, apparent inconsistencies often occur and must be explained.

Members of the public commonly assume that risks to nonhuman organisms are indicative of risks to humans. If this is not the case, the assessors must be prepared to explain the differences in diet, inherent sensitivity, route of exposure, or other factor that accounts for the difference.

One of the major sources of confusion in risk communication is inconsistency in the degree of conservatism. A way to avoid this confusion is for health and ecological risk assessors to present their best estimates of the consequences of the actions along with consistent estimates of uncertainty. Uncertainty is often difficult to communicate, and assessors should consider alternative forms appropriate to the audience.

9. Conclusions and Recommendations

Integration of health and ecological risk assessments has obvious advantages. The framework presented here should facilitate the processes of planning and performing integrated assessments. It should also facilitate environmental decision making by providing a consistent and coherent set of human and ecological risk estimates.

The implementation of this framework will require greater collaboration among risk assessors than is currently the case. For all risk assessments, an interdisciplinary team should perform the problem formulation. It should, in consultation with the risk manager, identify the stressors and sources, select the endpoints, define the environment, and develop a conceptual model. The team should then determine whether there are linkages between the sources of stressors and potentially significant responses of both human and ecological endpoints. If there are linkages to both types of endpoint receptors, the team should then plan and carry out an assessment that uses consistent data, exposure and effects models, and risk characterization. They should communicate their results in a consistent and integrated manner so that risk managers and stakeholders understand the implications of alternative actions. Finally, they should support the decision-making process by providing results in terms that are appropriate to the decision logic used by the risk manager.

Box 6. Interdependence of ecological and human risk assessment.

The interdependence of Inuit peoples in the Arctic and their environment led to an integrated approach to the risks associated with exposure of long-range transported atmospheric pollutants to the remote North. Despite living in a remote environment, the Inuit are now recognized as some of the most contaminated humans in the world. The subsistence-orientation of many Inuit communities, coupled with their position high in the marine food chain, necessitated an approach which combined a modeling of sources, pathways and fate of contaminants, and an assessment of risk which was weighed against benefits. Because of their consumption of large quantities of marine foods, including fish and marine mammal products, extrapolations were made to high trophic level wildlife from other areas, where adverse effects had been noted. In the context of these effects in wildlife, common exposures and shared mechanisms of toxic action between humans and such wildlife have guided efforts to predict and assess possible human health effects.