The International Programme on Chemical Safety

Integrated Risk Assessment
Report Prepared for the WHO/UNEP/ILO International Programme on Chemical Safety

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- Preface [pdf 7kb]

I.

- Executive summary [pdf 16kb]

II.

- Framework for the integration of health and ecological risk assessment [pdf 242kb]
- Annex A: Additional Types of Integration in Risk Assessment [pdf 7kb]
- Annex B: Working Glossary of Key Terms Used in this Document [pdf 10kb]
- References [pdf 12kb]

III. Case studies

- A. Persistent Organic Pollutants [pdf 299kb]
- B. Ultraviolet radiation effects on amphibians, coral, humans, and oceanic primary [pdf 79kb]
- C. Tributyltin and triphenyltin compounds [pdf 119kb]
- D. Organophosphorous pesticides in the environment [pdf 120kb]

IV.

- Meeting report of the international workshop on approaches to integrated risk assessment [pdf 34kb]

Preface

This report has been prepared for the WHO/UNEP/ILO International Programme on Chemical Safety by the following experts: Linda Birnbaum, US Environmental Protection Agency, USA; Terri Damstra, International Programme on Chemical Safety, USA; Jim Hart, Danish Veterinary and Food Administration, Denmark; Steve Hedtke, US Environmental Protection Agency, USA; Robert Kröes, The Netherlands; Robert MacPhail, US Environmental Protection Agency, USA; Erminio Marafante; Joint Research Centre; Italy; Wayne Munns, US Environmental Protection Agency, USA; Peter Ross, Institute of Ocean Sciences, Canada; Larry Reiter, US Environmental Protection Agency, USA; Jun Sekizawa, National Institute of Health Sciences, Japan; Glenn Suter, US Environmental Protection Agency, USA; Glen Van Der Kraak, University of Guelph, Canada; Gil Veith, US Environmental Protection Agency, USA; Theo Vermeire, National Institute of Public Health and the Environment, The Netherlands; and Michael Waters, US Environmental Protection Agency, USA.

Historically, human health and environmental risk assessment methodologies have generally developed independently. Regulatory agencies often use a chemical-by-chemical approach, focusing on a single media, a single source, and a single toxic endpoint. Many international and national organizations have expressed a need for an integrated, holistic approach to risk assessment that addresses real life situations of multichemical, multimedia, multiroute, and multispecies exposures. In response to this need, the International Programme on Chemical Safety (IPCS) convened a group of international scientific experts to develop approaches for integrated risk assessment.

In April 1998, IPCS convened an IPCS/OECD/EPA Scoping Meeting on Integrated Approaches to Human Health and Environmental Risk Assessment, in conjunction with a US EPA national symposium on Extrapolation in Human Health and Ecological Risk Assessment. A number of potential activities/issues related to integrated risk assessment were identified at this scoping meeting. In November 1998, a follow-up planning meeting was convened by IPCS to further identify mechanisms and approaches for integrated risk assessment. That planning meeting

agreed on a working definition of integrated risk assessment, developed a preliminary generic framework for integrated risk assessment, and proposed that a number of case studies be developed to evaluate the framework. IPCS convened a Framework Sub-Group meeting in July 1999 to review and revise the draft generic framework, and to develop criteria for identification of case studies and guidance for how the case studies would be developed. A meeting to further evaluate possible case study demonstrations of the generic framework was held in November 1999 and four case studies were chosen and their format/content finalized in July 2000. An international workshop was convened in April 2001 to evaluate the framework and demonstrate the benefits of integration using the four case studies.

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I. EXECUTIVE SUMMARY - APPROACHES TO INTEGRATED RISK ASSESSMENT

The goals of chemical safety programs encompass the prevention, assessment, and management of both short-term and long-term adverse effects to humans and the environment resulting from the production, use, transport and disposal of chemicals. The tools used internationally to assess and manage the risks of chemicals on human health have generally developed independently from the tools used to assess risks to the environment for practical and historical reasons. However, with increased recognition of the need to protect both humans and the environment more effectively, an integrated approach to risk assessment that addresses situations of multichemical, multimedia, multiroute, and multispecies exposures holistically is needed.

The UNEP/ILO/WHO International Programme on Chemical Safety (IPCS), in collaboration with the US Environmental Protection Agency (US EPA), the European Commission (EC), the Organization for Economic Cooperation and Development Cooperation, and other international and national organizations developed a working partnership to foster the integration of assessment approaches to evaluate human health and ecological risks. The overall goal of this project was to promote international understanding and acceptance of the integrated risk assessment process. Three specific objectives were identified to meet this goal: 1) enhance understanding of the benefits of integration, 2) identify and understand obstacles to integration, and 3) engage key scientific organizations to promote discussion of an integrated approach to risk assessment.

The term "integration" can have many meanings, and several opportunities exist within risk assessment generically for integration. For this effort, integrated risk assessment was taken to be "a science-based approach that combines the processes of risk estimation for humans, biota, and natural resources in one assessment." Although risk from chemical exposures was a primary concern, this definition does not limit the integrated risk assessment process to evaluation of chemical risks. It did, however, focus the efforts of the project on the scientific issues and needs of integrated risk assessment, and away from the varied regulatory and jurisdictional mandates and processes of individual governmental agencies.

Two fundamental reasons for integrated risk assessment are: 1) to improve the quality and efficiency of assessments through the exchange of information between human health and environmental risk assessors; and 2) to provide more coherent inputs to the decision-making process. With respect to the latter, human health and ecological risk assessors often provide decision makers with inconsistent input that results in contradictory impressions of the nature of risks. This results from differences in approach that should be eliminated in an integrated approach.

A generic framework and associated documentation were developed to communicate how an integrated risk assessment could be conducted. Recognizing the similarities in risk assessment frameworks currently in use internationally, the integrated risk assessment framework is based on US EPA=s framework for ecological risk assessment and its associated terminology (US EPA 1998). Ecological risk assessment frameworks have greater general applicability than do human health frameworks (or those environmental frameworks derived directly from human health frameworks) in that they 1) were developed to deal with a range of environmental stressors beyond toxic chemicals, 2) must describe the nature and role of the environment in the risk assessment process, and 3) must explicitly identify the endpoint to be assessed. Further, a well developed body of concepts and terminology exist in the literature treating ecological risk assessment that support integration.

The integrated framework consists of three primary assessment phases. 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, although only qualitative estimates of risk may be possible in some circumstances. The integrated risk assessment framework treats the relationships among risk assessment, risk management, stakeholder input, and data collection activities in a general, parallel and concurrent manner. These activities may interact in various ways depending on the regulatory context and the nature of the assessment problem. Documentation developed to describe the framework details the purpose and activities of each assessment phase, identifies points of integration, describes perceived advantages of integration, offers examples clarifying key concepts, and defines relevant terminology. This integrated risk assessment framework received international peer review by diverse organizations and scientific experts prior to finalization.

Case studies were developed to help communicate the integrated risk assessment approach, to illustrate how assessments might be conducted, and to highlight the benefits of integration. Four assessment problems were selected for initial case study development based on 1) known linkages between human health and ecological effects and exposure to stressors, 2) the sufficiency of available knowledge of human and ecological effects, 3) the adequacy of information describing the stressor(s) and exposure to humans and ecological receptors, and 4) the degree of commonality in conceptual models relating stressors to ecological and human receptors with respect to time and spatial scale.

Using these criteria, the following case studies were developed by panels of scientific experts: 1) the risks of persistent organic pollutants (POPS) to humans and wildlife; 2) ultraviolet radiation effects on amphibians, coral, humans, and oceanic primary productivity; 3) risks of tributyltin and triphenyltin compounds; and 4) organophosphorous pesticides in the environment. Each case study describes integrated assessment activities relevant to all parts of the framework, identifying key points of integration, critical information needs, and the benefits of integration. Although not actual risk assessments from the standpoint of completeness and rigor of analysis, the intent behind their development was to demonstrate that integrated risk assessment leads to enhanced scientific understanding that facilitates high quality regulatory decisions, assists in the identification of emerging issues and therefore may be predictive, provides a resource-effective alternative to independent assessments, and improves the response time of regulatory decisions.

The concepts, approaches, and framework for integrated risk assessment were evaluated at an international workshop held in Ispra, Italy in April 2001. Sponsored by the IPCS and the EC, the overall objectives of the workshop were to promote international understanding and acceptance of integrated risk assessment as a decision support tool for environmental policy and regulation, and to identify the science needed to conduct integrated risk assessments. This workshop was attended by over 40 invited participants, representing diverse international and national organizations and expertise. Using the framework and four case studies to focus deliberations, workshop participants were asked to identify: 1) the benefits of and obstacles to integrated risk assessment, 2) the research needed to facilitate implementation of integrated risk assessment and how an integrated approach informs the international research agenda, and 3) mechanisms and actions that can be taken to facilitate practical application of integrated risk assessment by regulatory bodies.

A principle benefit of integrated risk assessment identified by workshop participants was the improved effectiveness of the assessment process through exploitation of shared data and models, and the transferability of knowledge of mechanisms and modes of actions across risk endpoints and stressors. Participants also concluded that there would be general reductions in assessment uncertainties, an increased likelihood of identifying unexpected and emerging risks, and reductions in overall assessment costs relative to independent ecological and health assessments. However, several obstacles hindering acceptance and implementation of integrated risk assessment were identified, including the traditional disciplinary barriers that exist between ecological and human health research and assessment that are emphasized by differences in terminology, and the institutional, political, and cultural barriers that are codified in law and regulation in most countries. Concern also was expressed that integrated risk assessments would be perceived as inherently more complex, and that they might result in higher costs initially as integrated assessment protocols are worked out. Few insurmountable barriers of a strictly technical nature were identified.

With respect to the research needed for effective integrated risk assessments, workshop participants identified harmonization of exposure characterization and surveillance methods and models as critical. Further, they recommended development of common risk

endpoints across taxa, and improved understanding of mechanisms of action at multiple scales of biological organization as means to improve extrapolations of data and information. Development of methods and measures that facilitate comparison of risks among endpoints was identified as a way to improve the value of assessment conclusions to risk management decisions. Participants also recommended development of improved cost/benefit methods both to support decision-making and to be used to demonstrate the benefits of integrated risk assessment.

Finally, workshop participants expressed their commitment to promote and facilitate acceptance and implementation of integrated risk assessment, suggesting that removal of terminological and other non-scientific barriers might be accomplished through integration of educational and training experiences. Enhanced funding of integrated risk research, and continued communication of the advantages and benefits of integrated risk assessment to key organizations and the scientific community as a whole were recommended as important in this regard. Several communication activities were suggested, ranging from presentation at scientific meetings and publication in the scientific literature, to development of a web-based clearinghouse of relevant information. We hope that these collaborative efforts of the IPCS, EC, and other international and national organizations will help to establish the foundation of internationally-accepted guidance for integration of risk assessment.

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

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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).

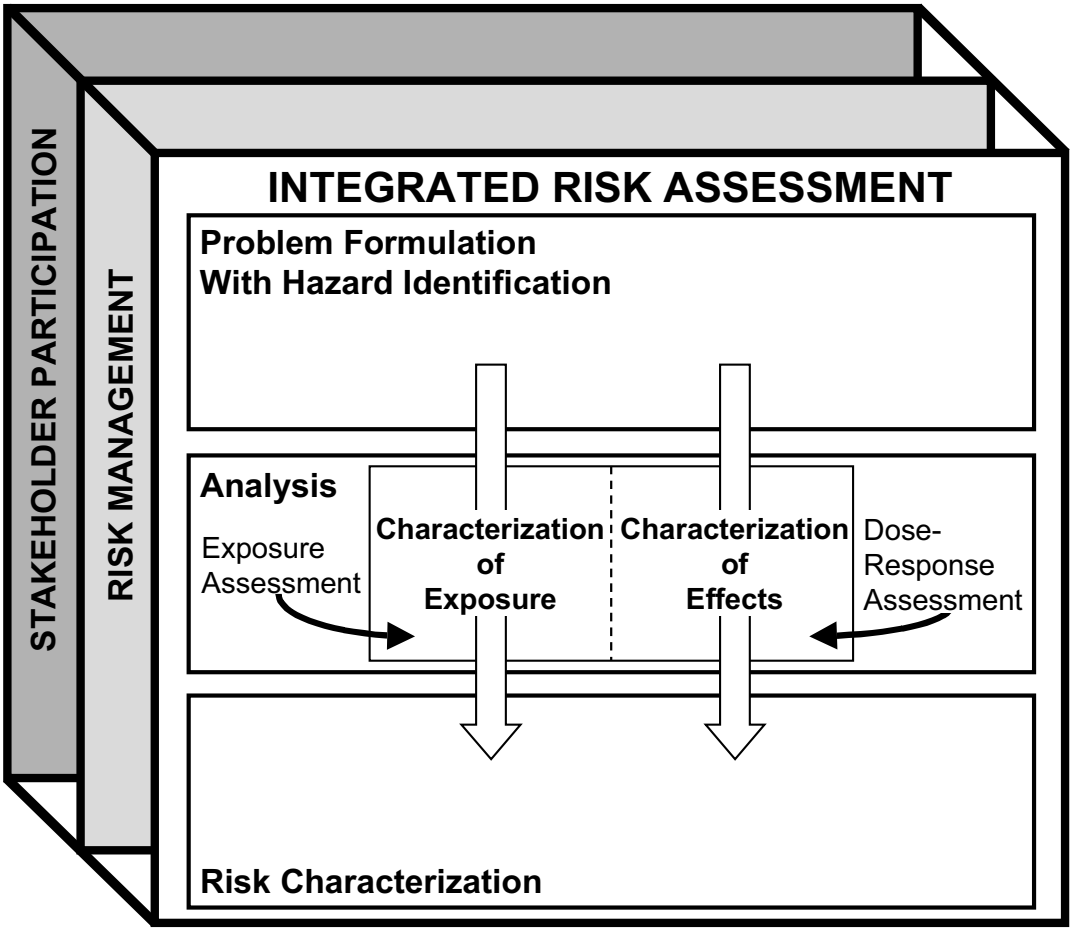
Common denominators in all frameworks are the roles of science and political and societal values as essential parts of the process. What differs are the degree of separation of science from policy, the different roles of stakeholders (industry, non-governmental organizations, and governmental organizations 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.

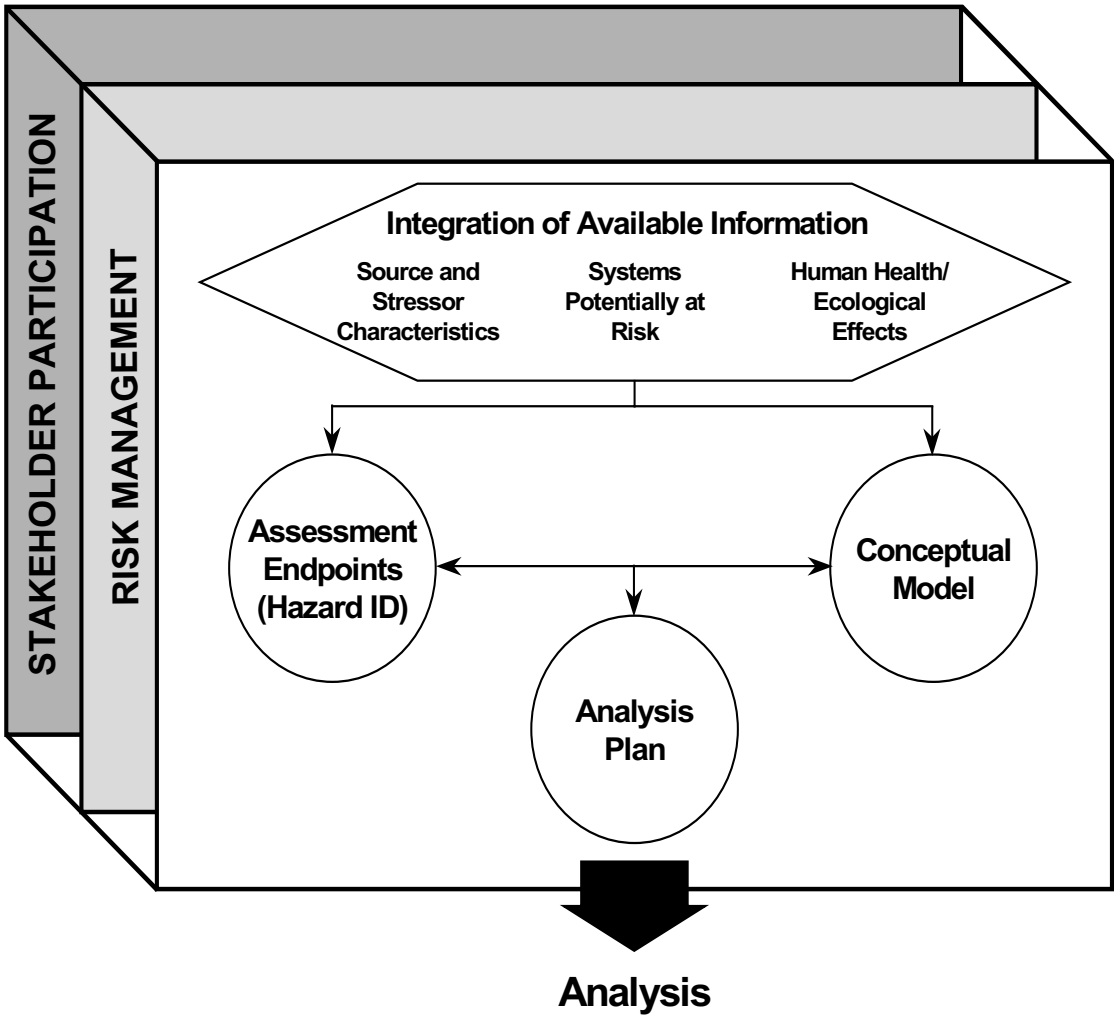


Figure 2. The problem formulation stage of an integrated risk assessment. Risk management and stakeholder activities are parallel and may interact with the problem formulation process to a greater of lesser extent depending on circumstances (modified from US EPA 1998).

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

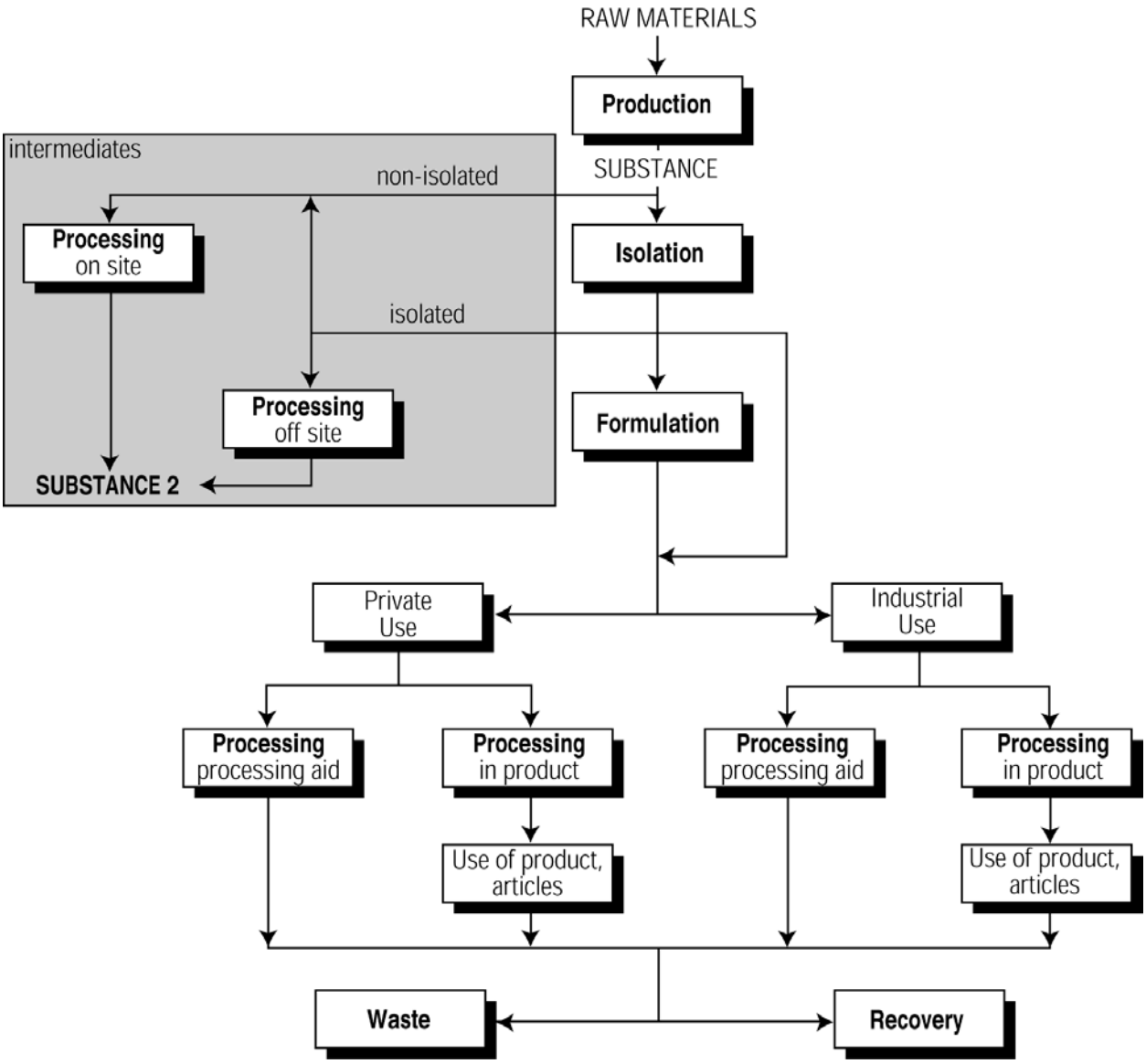


Figure 3. The life cycle of a chemical substance. Emissions to the environment can occur at any point in this cycle.

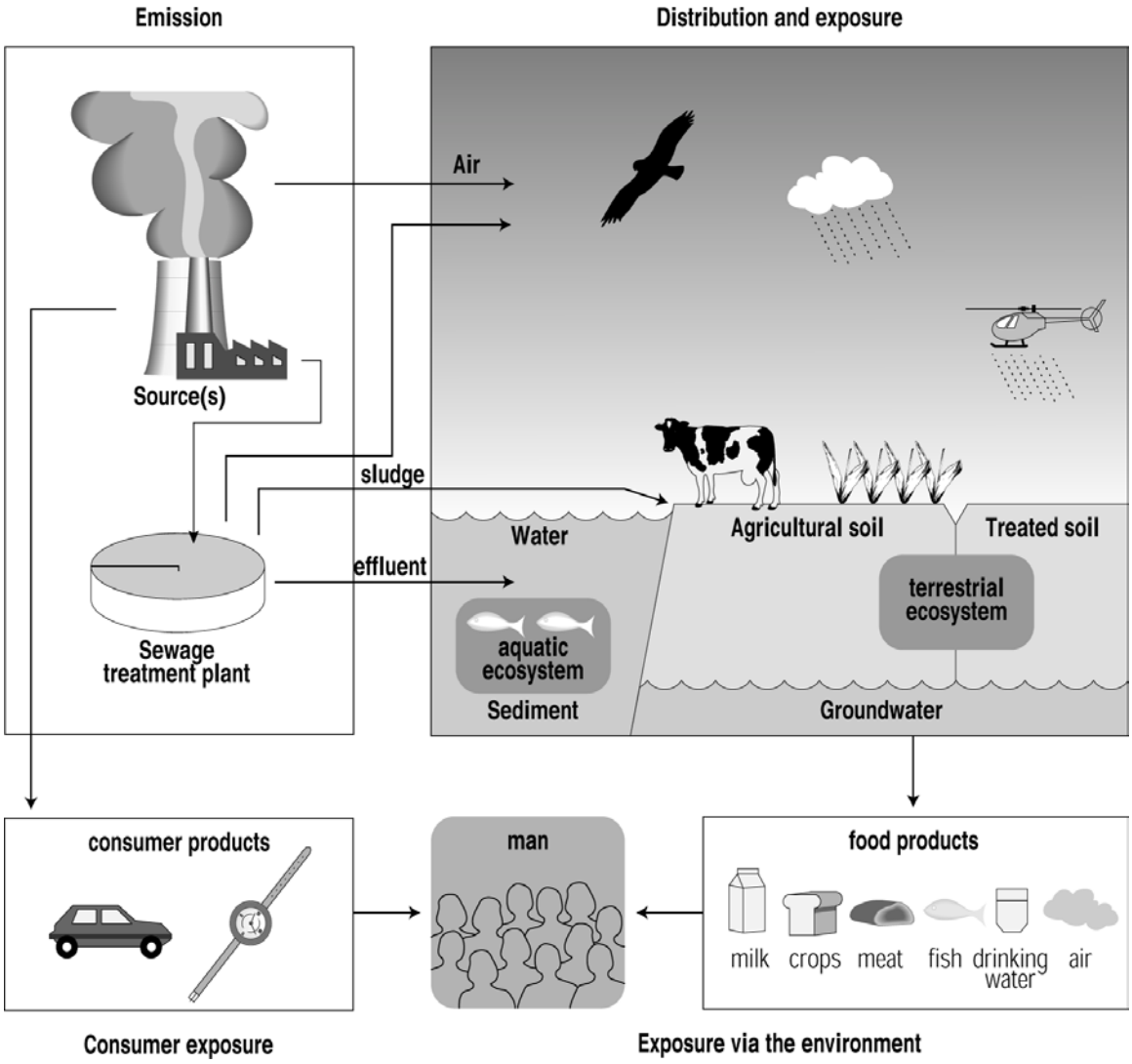


Figure 4. Routes of exposure of human and nonhuman organisms (van Leeuwen and Hermens 1995).

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.

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.

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.

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 50^{th} or 99^{th} 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.

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.

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.

Annex A. Additional Types of Integration in Risk Assessment

Multiple Agents — Assessments should integrate risks to humans and the environment from all agents that are relevant to the decision. For example, risks to aquatic life from pesticides are routinely considered, but, if the goal is to restore aquatic life in agricultural areas, the risk assessment should also include siltation, fertilization, and destruction of channel structure.

Multiple Routes — Assessments should integrate risks to humans and the environment from all routes of exposure that are relevant to the decision. For example, assessments of risks to humans from pesticides may need to consider routes of exposure other than diet.

Multiple Endpoints — Assessments should consider all potentially significant endpoints for both human and ecological receptors that are relevant to the decision. As is discussed in the text, a common mechanistic understanding can allow multiple health and ecological endpoints to be identified and assessed in a common and consistent manner. In addition, multiple endpoints may be integrated into one or a few common units such as Quality Adjusted Life Years (QALYs).

Multiple Receptors — Assessments should consider all classes of human and ecological receptors that are relevant to the decision. For example, health risks should be estimated for the entire exposed population, including all age classes, genders, and occupational groups, and not just the maximally exposed individual. Similarly, ecological risks should address the distribution of risks across the exposed biotic community and not just representative or sensitive species.

Multiple scales in dimensions — Extrapolations in risk assessment can occur in various dimensions including time (short to long), place (one site to other sites), space (local to regional), biological scale (small animals to larger ones), or mechanisms (molecular processes to physiology and organismal responses). Integration of information at various scales in various dimensions may be necessary to estimate risks in actual situations.

Life Cycle — Assessments may need to integrate the risks from the entire life cycle of a chemical or other product. These include risks from production of raw materials, manufacturing, use, and disposal of both the product and associated byproducts.

Management Alternatives — When decisions are based on comparison of alternatives, assessments should consider the risks from relevant alternatives in an integrated manner. For example, an assessment of risks from waste water should consider both the risks from the untreated effluent and the risks from alternative treatment technologies including disposal of sludges.

Socioeconomics and Risk — If effects on economies and social processes are relevant to the decision as well as those on human health and the environment, the

effects should be assessed in an integrated manner. Currently, such integration is largely limited to balancing the costs of a management action against the benefits. However, the interactions between environmental quality, health, and individual and social well being are much more complex. Adequate integration could require consideration of services of nature, human values and preferences, and other nonmarket mechanisms.

Annex B. Working Glossary of Key Terms Used in this Document

(modified from EC 1994 and US EPA 1998)

Analysis — A phase of integrated risk assessment that characterizes exposure to a stressor(s) and the ability of the stressor(s) to cause adverse effects to human or nonhuman receptors.

Assessment endpoint — An explicit expression of the environmental value or human condition that is to be protected, operationally defined by an entity (such as salmon or humans) and its attributes (such as age structure or liver function).

Characterization of effects — A portion of the analysis phase of integrated risk assessment that evaluates the ability of a stressor(s) to cause adverse effects to human or nonhuman receptors under a particular set of circumstances. Includes dose (concentration) - response (effect) assessment.

Characterization of exposure — A portion of the analysis phase of integrated risk assessment that evaluates the co-occurrence or contact of the stressor with one or more ecological or human entities. Equivalent to exposure assessment.

Community — In ecology, an assemblage of populations of different species within a specified location in space and time. For humans, a component of society bounded in a geographic sense.

Conceptual model — A written description and visual representation of predicted relationships between ecological and human entities, the stressors to which they may be exposed, and the sources of the stressors. Developed during the problem formulation phase of integrated risk assessments.

Disturbance — Any event or series of events that disrupts human or ecological structure and changes resource availability or the physical environment.

EC_{50} — A concentration that is statistically or graphically estimated to cause a specified effect in 50% of a group of test organisms under specified experimental conditions.

Ecological risk assessment — The process that evaluates the nature and likelihood of adverse ecological effects from exposure to one or more stressors. Likelihoods may be qualitative or quantitative.

Ecosystem — The biotic community and abiotic environment within a specified location in space and time.

Exposure — The contact or co-occurrence of a stressor with a human or nonhuman receptor.

Hazard assessment — The identification of the adverse effects which a stressor has an inherent capacity to cause. Hazard assessment activities occur in the problem formulation phase of integrated risk assessment.

Human health risk assessment — The process that evaluates the nature and likelihood of adverse human health effects from exposure to one or more stressors.

Integrated risk assessment — A science-based approach that combines the processes of risk estimation for humans, biota, and natural resources in one assessment.

LC_{50} — A concentration that is statistically or graphically estimated to be lethal to 50% of a group of test organisms under specified experimental conditions.

Lowest-observed-adverse-effect level (LOAEL) — The lowest level of a stressor evaluated in a test that causes statistically or biologically significant adverse changes in test organisms compared with the controls.

No-observed-adverse-effect level (NOAEL) — The highest level of a stressor evaluated in a test that does not cause statistically or biologically significant adverse changes in test organisms compared with the controls.

Population — An aggregate of individuals of a species (human or nonhuman) within a specified location in space and time.

Problem Formulation — A phase of integrated risk assessment that evaluates characteristics of the stressor(s), human/ecological system, and receptors, identifies assessment endpoints, develops one or more conceptual models, and develops an analysis plan.

Receptor — The ecological entity or human exposed to the stressor.

Risk characterization — A phase of integrated risk assessment that integrates exposure and effect information to estimate the likelihood and severity of adverse effects associated with exposure to a stressor.

Source — An entity or action that releases to the environment or imposes on the environment a chemical, physical, or biological stressor or stressors.

Stakeholder — A member of society concerned about the environmental issues associated with the assessment or who may be affected by management decisions that use the results of the assessment.

Stressor — Any physical, chemical (substance), or biological entity that can induce an adverse response. Synonymous with agent.

Trophic levels — A functional classification of taxa within a community that is based on feeding relationships (e.g., aquatic and terrestrial green plants make up the first trophic level and herbivores make up the second).

Uncertainty — The lack of information or knowledge about a phenomenon, process, or measurement. Uncertainty usually can be reduced through further measurement or study. (See variability.)

Variability — The true diversity or variability of a population. Variability cannot be reduced through further measurement or study. (See uncertainty.)

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III. CASE STUDIES

A. Persistent Organic Pollutants (POPs) in humans and wildlife

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Abstract:

Since the mid-1900s, the global environment has become increasingly contaminated by Persistent Organic Pollutants (POPs), including many with dioxin-like properties. These compounds generally have low water solubility, do not degrade readily in the environment, bioaccumulate in food chains, and have been linked to adverse health effects in both humans and wildlife. The presence of such compounds in terrestrial and aquatic food chains is relevant to those concerned with both human health and environmental protection because of the many common exposure pathways and biological effects among different species. In the past, some chemicals with health risks for humans have been identified following reports of adverse effects in wildlife. Integrating human and ecological risk assessments may improve society's ability to manage the design, manufacture, use and disposal of chemicals in a safe and efficient manner. This can be achieved by encouraging a rigorous and multidisciplinary approach to evaluating the sources, transport and fate of chemicals, and their associated health risks in all environmental compartments.

1. Background

Both humans and other organisms in the environment are exposed to Persistent Organic Pollutants (POPs), including contaminants which may have either "dioxin-like" properties (i.e. those POPs that bind to the Aryl hydrocarbon receptor (*Ah*R) and initiate toxic responses; 29 of the 419 PCB, PCDD and PCDF congeners are currently considered "dioxin-like") or "non-dioxin-like" properties (including many PCBs and organochlorine pesticides), through the dietary intake of food items. The primary sources of these contaminants to humans and top predators in the environment are foods or prey items from the freshwater and marine environment, and the terrestrial food chain. Concern about the risks that the "dioxin-like" contaminants present to humans and other high trophic level organisms has increased because of the "weight of evidence" generated through multiple scientific approaches in numerous laboratory animal, wildlife and human studies.

With a large body of multidisciplinary literature, this case study provides an opportunity to demonstrate the utility of an integrated human and ecological risk assessment process. Humans and wildlife are exposed to both the "dioxin-like" and "non-dioxin-like" POPs. We draw on evidence from studies of the transport, fate and exposure aspects of all POPs (i.e. both "dioxin-like and "non dioxin-like"), but focus on the risks associated with the "dioxin-like" compounds because of their particularly potent toxicity and our reasonable mechanistic grasp of this group of chemicals. This integration of human and ecological risk assessments may be less effective in the case of certain occupational exposures for humans, different classes of chemicals that are not generally released into the environment, or where chemicals do not bioaccumulate in the food chain. However, such is the nature of risk assessments; to quantify the relative risks presented by different chemical classes, whether these are small or large. Integrated human and ecological risk assessment represents a new direction for characterizing the risks which anthropogenic contaminants present to the environment, within which humans are an integral part.

During the last half of the 20th century, the global environment has become contaminated with a number of persistent, fat-soluble chemical contaminants, commonly referred to as the POPs. Contamination of the global environment with a complex mixture of POPs has resulted from deliberate discharges and applications, as well as from the inadvertent formation of by-products of incomplete combustion or industrial processes. Classes of these POPs include the organochlorine pesticides (e.g. DDT, chlordane, toxaphene), the polyhalogenated -biphenyls (PHBs; includes PCBs and PBBs), -dibenzo-*p*-dioxins (PHDDs; includes PCDDs), -dibenzofurans (PHDFs; includes PCDFs), and the polychlorinated naphthalenes (PCNs). Other problematic persistent chemical contaminants not included in the POP group include the organo-metallic compounds (organotins and methyl mercury). The vast number of compounds which can be detected in tissue samples from organisms inhabiting even remote parts of the world (Muir et al., 1992; Ross et al., 2000a) presents a considerable challenge to policy makers tasked with regulating industry and protecting the environment. Despite this challenge, considerable progress has been made in identifying the nature of global contamination by such compounds

and understanding some of the mechanistic aspects of toxicity associated with different compounds (see Figure 1).

Adverse health effects associated with exposure to POPs have been observed in both high trophic level wildlife and humans. The concept of a "wildlife-human connection" draws on this evidence of adverse effects in highly-exposed wildlife to predict the risk of adverse health effects in humans. While it is difficult to unequivocally establish whether these compounds are adversely affecting humans or wildlife in the environment, the accumulating "weight of evidence" strongly implicates POPs, as well as the "dioxin-like" POPs, in incidents of endocrine and immune dysfunction, reproductive impairment, developmental abnormalities, and neurological function in a host of vertebrate species.

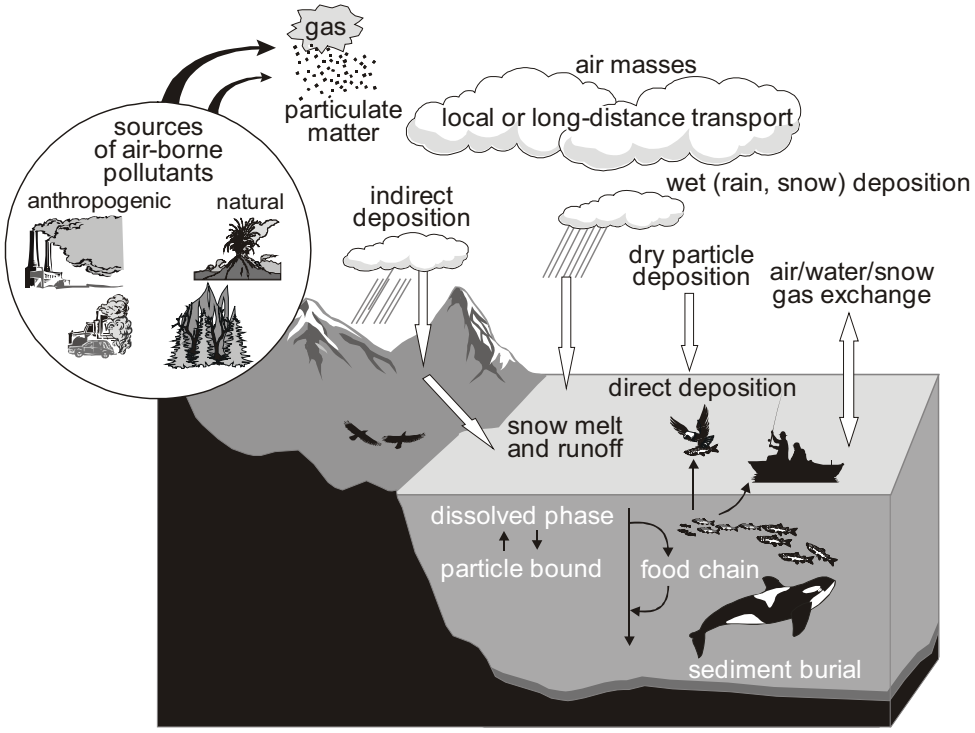

Figure 1: *In addition to direct effluent discharges, Persistent Organic Pollutants (POPs) and their "dioxin-like" components are distributed globally through atmospheric processes, ensuring that even remote human and wildlife populations are exposed. While populations inhabiting industrialized regions are often considered more vulnerable to higher level exposures, subsistence-oriented aboriginal peoples in the Arctic are at risk because of their heavy reliance on aquatic food resources.*

Effects observed in high-trophic level wildlife include the eggshell-thinning effects of DDT on fish-eating birds and their subsequent extirpation from large parts of the industrialized world (Hickey and Anderson, 1968; Wiemeyer and Porter, 1970); the relationship between PCBs

and developmental abnormalities in Great Lakes birds (Gilbertson et al., 1991; Tillitt et al., 1992); reproductive impairment among European seal populations (Helle et al., 1976; Reijnders, 1980); and captive feeding or free-ranging studies of birds, mink and seals in which reproductive effects, immunotoxicity and endocrine disruption have been observed (Bleavins et al., 1980; Reijnders, 1986; Brouwer et al., 1989a; Hakansson et al., 1992; De Swart et al., 1994; Ross et al., 1996a; Simms et al., 2000).

High trophic level organisms and certain human consumer groups occupy a similar niche, and are often exposed to similar types of environmental contaminants through dietary intake (see Figure 2). Certain human consumer groups, including sportsfishing families, immigrant communities, and aboriginal populations can be at increased risk because of exposure to environmental contaminants through their consumption of fish and other aquatic foods (Dewailly et al., 1989; Dewailly et al., 1994; Jacobson and Jacobson, 1996; Dewailly et al., 2000).

Evaluating the patterns, levels, trends, and effects of POPs in high trophic level consumers may therefore contribute to our understanding of both the contamination of aquatic ecosystems (freshwater and marine), and the risks posed to human health. Lessons learned from some of these more highly exposed groups of wildlife and humans are likely to be relevant to the health of the general public, where evidence is mounting that even relatively low exposures to POPs can affect human health. The use of wildlife as "sentinels" or "early warning indicators" has become an increasingly important issue in the area of human health (De Guise et al., 1995; Colborn and Smolen, 1996; Ross, 2000), although a more formally integrated human and ecological risk assessment is still lacking. Humans and wildlife share exposure to and effects of the POPs and the "dioxin-like" components of POPs, highlighting the utility of an integrated risk assessment.

2. Problem Formulation

Impetus for the assessment

Early reports of environmental contamination by POPs, high POP concentrations reported in top predators, adverse effects reported in certain wildlife (e.g. eggshell thinning following DDT exposure in fish-eating birds), adverse effects observed in laboratory animals, incidents of occupational or incidental exposures for humans (e.g. Yusho, Seveso incidents), and more recent evidence suggesting that humans are being adversely affected at low ("background") concentrations (Koopman-Esseboom et al., 1996; Weisglas-Kuperus et al., 2000) all point to a distinct need for an integrated approach to risk assessment. Concerns about the health of high trophic level wildlife or humans represent tangible and defensible reasons for carrying out a risk assessment of these chemicals for all of these groups. Common routes of exposure and similar patterns of effects in humans and wildlife underline the benefits to combining human and ecological risk assessments for many of the POPs.

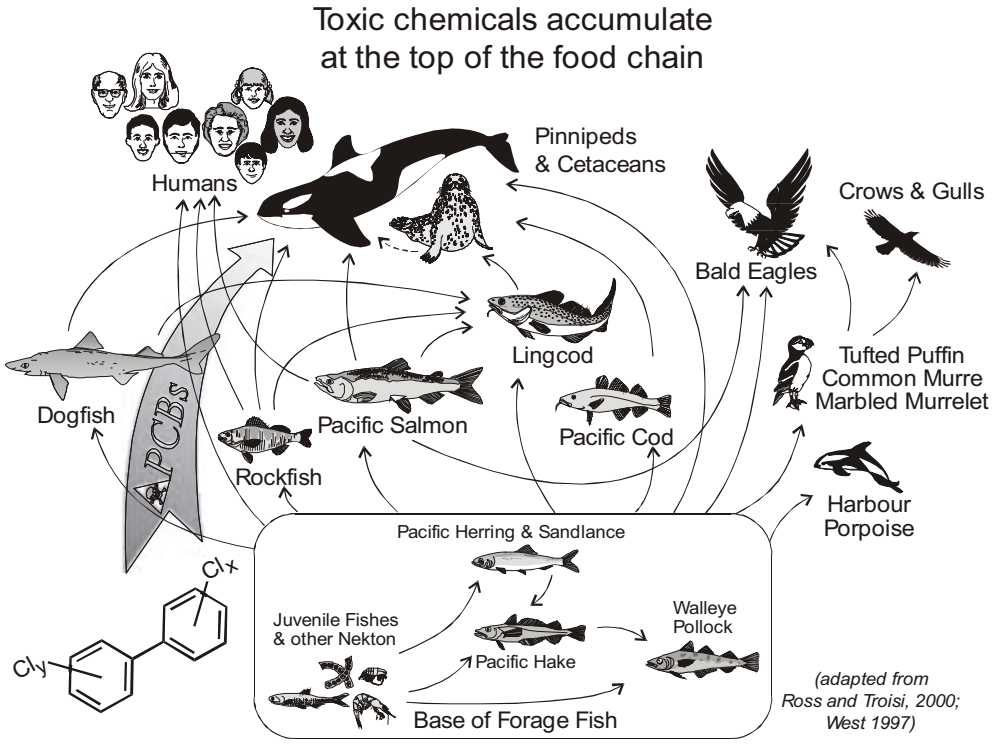

Figure 2*: Aquatic food chains are vulnerable to contamination by POPs and their "dioxin-like" components as a result of the lipophilic characteristics of these chemicals and their resistance to breakdown. Organisms occupying high trophic levels are often exposed to high concentrations of such chemicals as a result of biomagnification.*

Assessment questions

This case study will examine the shared exposure to complex mixtures of POPs and the common "dioxin-like" effects of POP components in both humans and wildlife by addressing:

- the nature of global environmental contamination by POPs and the "dioxin-like" components therein;
- the bioaccumulation of POPs and the "dioxin-like" compounds in aquatic food chain;
- the exposure of high trophic level wildlife and certain human consumer groups to elevated concentrations of POPs, and "dioxin-like" compounds in particular;
- the dioxin-related effects, or the risk of effects, in highly exposed human and wildlife populations or cohorts (the "human-wildlife connection");
- the risk of adverse health effects in the general human public as a result of exposure to "background levels" of "dioxin-like" compounds;
- means of reducing environmental contamination by POPs and the risk of adverse health effects in humans and high trophic level wildlife;
- the availability of robust scientific information which is useful to managers and regulators.

Assessment endpoints

"Target" organisms can be selected on the basis of trophic level, utility or value as an ecological indicator, ease of study, and/or relevance to both human and wildlife health. Some of the better studied wildlife include the fish-eating birds and pinnipeds (seals), for which much data is available. "Endpoints" for assessment include measures of exposure (chemical contaminant patterns in predator vs prey; in different high trophic level species), as well as measures of effect (e.g. immunotoxicity, reproductive impairment), which are based on known or putative mechanisms of action (e.g. Aryl hydrocarbon receptor, *Ah*R, in the case of dioxin-like compounds; see Figure 3). Identification of possible "non-dioxin" like effects (e.g. estrogen-disrupting effects via estrogen receptor or *ER*) or effects which may be due to both *Ah*R mediated and "non-dioxin" like mechanisms (e.g. disruption of vitamin A and thyroid hormone physiology) should be examined in order to evaluate the relative importance of "dioxin-like" and "non-dioxin" like effects in exposed organisms.

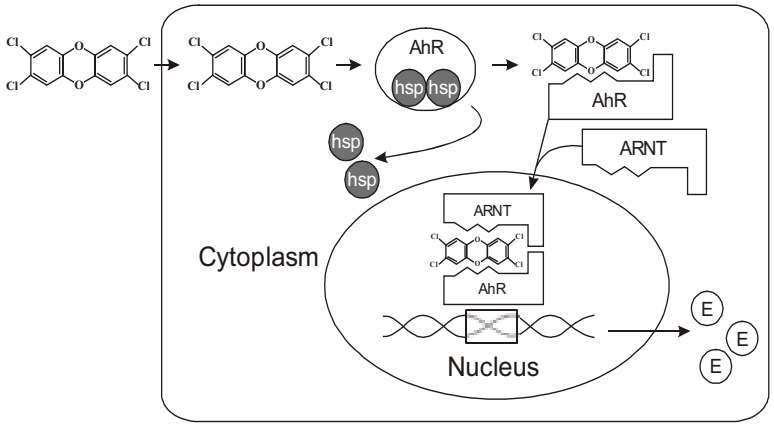

Figure 3: *The Aryl hydrocarbon receptor (AhR) found in all vertebrates studied to date binds 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) with high affinity relative to other "dioxin-like" compounds. The binding of "dioxin-like" chemicals to the AhR is considered the initial step in the toxic effects observed in mammals. The potency of "dioxin-like" compounds relative to 2,3,7,8-TCDD, and the conserved nature of the AhR among species, provide a basis for the Toxic Equivalency Factor (TEF) approach and integrating human and ecological risk assessment. AhR: Aryl hydrocarbon receptor; hsp: heat shock protein; ARNT: AhR nuclear translocator; E: enzyme production.*

Among the vertebrates, many physiological systems remain highly conserved, enabling extrapolation from e.g. laboratory rat to human; cormorant or seal to human; laboratory rat to seal. The conserved nature of these systems increases our level of confidence in extrapolating from one species to another, and in this case study strongly supports an integration of human and ecological risk assessment.

Conceptual models

1- *Global environment:* Evidence indicating the importance of atmospheric distribution and deposition of POPs into bodies of water, even at remote sites such as the Arctic, the Antarctic, and the mid Pacific Ocean, necessitates a basic understanding of POPs and "dioxin-like" compounds in the context of the global environment.

2- *Ecosystem approach:* An ecosystem-based approach should form the basis for the integrated risk assessment, characterizing movement, transport and fate processes, as well as compartmentalization in the environment.
3- *Food chain basis:* An emphasis on food chains (freshwater, marine, terrestrial) is integral to the process, since most POPs bioaccumulate in the food chain.
4- *Target organisms and sentinel species:* The use of wildlife as sentinels of environmental contamination and indicators of human health risks associated with low level exposure to "dioxin-like" POPs is particularly relevant. Laboratory animal studies will help document mechanisms of action under more controlled circumstances.

Analysis plan

1- *Transport and fate literature:* Review of transport and fate models for POPs, with an emphasis on sources, atmospheric transport, food chain biomagnification, watershed studies in freshwater systems, soil-air and sediment-water exchange (ongoing source) and air-plant and water-sediment exchange (sink).
2- *Toxicokinetic literature:* Review of toxicokinetic models in wildlife and humans to assess route of intake and elimination, half-life of POPs in organisms, and temporal models to characterize past and future trends in biota.
3- *Toxicological literature:* Literature review of toxicological information from laboratory animal studies, wildlife toxicology studies, human health studies.

2.6 Summary

Common routes of dioxin-like POP exposure and effects observed in wildlife in the environment, humans and domestic animals accidentally exposed, and the general public strongly support an integrated risk assessment approach. The conserved basis of vertebrate physiology (e.g. AhR, endocrine regulation), and common dioxin-related reproductive, immunological, and neurological effects observed, enable interspecies extrapolation and form a basis for an integrated risk assessment.

3. Characterization of Exposure

POPs and their "dioxin-like" components represent ubiquitous and often unintentional global environmental pollutants. Their introduction into the environment through various processes (leakage, discharge, combustion, incineration, agricultural application) and their physicochemical properties have led to a contamination of aquatic food chains in particular. Their presence as complex mixtures in the food of wildlife and humans (i.e. prey, cattle, fish, crops and forest ecosystems) ensures a broad exposure on a global basis.

3.1 Sources and emissions

Production: Manufacture, distribution and application (closed vs open) of industrial compounds; formation of unintentional by-products through low temperature combustion and

herbicide production; use of elemental chlorine in bleaching process used by pulp and paper mills; natural sources (e.g. forest fires, volcanoes); and continued cycling of persistent chemicals in the environment.

Formulation: Different products and product formulations (e.g. for PCBs: *Aroclor® 1242, 1254, 1260* in North America; *Clophen®* in Europe; *Sovol®* in Russia where production capacity only recently ceased). Pattern changes in the environment as a function of intra-compound (i.e. congener-specific) differences in chemical characteristics, abiotic or biotic degradation, and metabolic elimination by different organisms in the food chain.

Use: Estimates of quantities produced intentionally or unintentionally, and released into the environment should be itemized. Point sources vs diffuse sources should be evaluated in the context of a mass-balance approach to environmental distribution.

3.2 Distribution pathways

Documenting the initial production and formulation, distribution, use and disposal of deliberately manufactured POPs is an important prerequisite to understanding sources, pathways and fate in the environment. The subsequent importance of soils and sediments as ongoing sources (former agricultural application areas; contaminated landfill, industrial and harbour sites) reflect the persistence of many contaminants (Hermanson and Hites, 1989; Jantunen et al., 2000). Exchange among different environmental compartments on regional and global scales represents a critical component of characterizing the cycling of POPs once released into the environment (Hornbuckle et al., 1994; Swackhamer et al., 1998; Macdonald et al., 2000). Additionally, understanding the processes, both natural and anthropogenic, which produce some of the other POPs (e.g. dioxins and furans), produces a foundation for understanding how these chemicals may enter the natural environment. Such information, when coupled with the chemical characteristics of the POPs in question, and the nature of environmental processes affecting their movement, provide the baseline needed for risk assessment purposes. Given the "ubiquitous" distribution of many POPs, this work on distribution pathways is clearly relevant to both humans and wildlife.

3.3 Transport and fate models

1- *Global distribution:* Atmospheric distribution is known to be an important part of the distribution of POPs in the global environment. Global models have been developed to describe the influence of the physicochemical characteristics of POPs in their atmospheric distribution to remote, colder polar regions of the world (Wania and Mackay, 1995; Wania and Mackay, 2001). Transport and fate models used may include formalized approaches such as the Quantitative Water Air Sediment Interaction (QWASI) fugacity model developed for Lake Ontario (Mackay, 1989) and mass-balance studies of certain basins and watersheds (e.g. Great Lakes) (Eisenreich et al., 1981; Hornbuckle et al., 1994; Hoff et al., 1996). System-wide reviews of data have provided detailed overviews of contamination of the

Arctic. These include both abiotic as well as food chain-based assessments (Muir et al., 1992; Muir et al., 1999), and transect-based studies of contaminants in marine waters and air samples (Iwata et al., 1993), and comprehensive international assessments (CACAR, 1997; AMAP, 1998).

2- *Environmental compartmentalization:* Predictive estimates for biomagnification in the food chain may be generated from the physico-chemical characteristics of different compounds, such as the octanol-water coefficient (K_{ow}) (Shaw and Connell, 1984; Oliver and Niimi, 1988; Hawker and Connell, 1988). For example, "dioxin-like" PCBs with a log Kow of >4.0 are particularly bioaccumulative and largely persistent in food chains.

3- *Metabolic degradation:* The metabolic capacity of organisms to selectively attack certain compounds, leading to either detoxification and elimination or to the formation of toxic metabolites must be assessed. This has been carefully examined in the case of PCBs, where congeners with adjacent unsubstituted pairs of C positions on the phenyl rings are more prone to metabolic attack and removal through the production of soluble metabolites (e.g. hydroxy-PCBs) (Boon et al., 1997). The relative ability of organisms (e.g. marine mammals) to remove certain types of PCBs may allow for a degree of risk assessment by characterizing the persistent vs the less persistent compounds, as well as the inferred induction of detoxifying enzymes in the liver (Boon et al., 1994; Kannan et al., 1995). Conversely, the formation of hydroxy-PCB and other POP metabolites ("reactive intermediates") following enzymatic processes in mammals, may play an important role in the disruption of certain endocrine processes (Brouwer et al., 1998; Sandau et al., 2000). Documenting pattern changes as a consequence of these metabolic processes at each level of the food chain represents an important element in characterizing the exposure of humans and wildlife as it relates to transport and fate.

4- *Degradation processes:* Both abiotic and biological processes have been identified that can lead to the slow degradation of POPs and "dioxin-like" compounds (Abramowicz, 1995), although considerable variation exists between different chemicals and under different conditions. Sedimentation represents a mechanism by which the biological availability of contaminants in food chains may be reduced (i.e. sediments as a "sink"), even though little or no degradation may take place. Despite such processes, the persistence of many of the POPs and "dioxin-like" components in the environment remains a characteristic of these chemical classes, and represents a reason for an integrated risk assessment.

3.4 External and internal exposure models

Integrated human and ecological risk assessment must be sufficiently flexible to be applicable to a wide range of circumstances and target species. Using external and internal exposure models from better understood species may be the most effective approach in many cases, but attention should be given to the ecological circumstances for the species or case in question. Position in the food chain, feeding habits, migratory routes, metabolic considerations,

phylogenetic relationships and life histories are but some of considerations which may affect exposure models (Hickie et al., 1999). In the case of POPs, high trophic level organisms are vulnerable to accumulating high concentrations of POPs, but considerable variation exists among species. For example, cetaceans appear to be able to metabolically eliminate many dioxin-like PCBs, PCDDs and PCDFs, but are prone to accumulating the non-dioxin-like (or "globular") PCBs (Tanabe et al., 1988; Kannan et al., 1989).

3.5 Measures of exposure-related parameters

Environmental transport and fate models are relevant to both humans and wildlife, although dietary exposure will vary as a function of diet (i.e. position in the food chain, species consumed, quantities consumed). Measures of exposure are routinely documented for contaminant concentrations in study subjects (human or wildlife): 1) tissue concentrations, measured on a lipid weight basis, provides a means of evaluating both a measure of accumulated exposure that can be related to effects or risk of effects; 2) tissue concentrations, measured on a wet weight basis, provide a means of assessing intakes by predators or humans (i.e. when contaminant concentrations are measured in prey or foodstuffs consumed), but also provide a basis of estimating body burden (when contaminants are measured in any organism); and 3) daily intake (e.g. ng/kg body weight/day). The first two measures are taken routinely in studies of both humans and wildlife, while the third requires detailed knowledge of dietary intakes, something that is often lacking for wildlife. Toxicokinetic models allow the body burden and daily intake to be interconverted. Expressing contaminant data in terms of body burden or tissue concentration is advantageous because these measures incorporate toxicokinetic considerations and therefore allow interspecies comparisons.

3.6 Analytical tools

Chemical contaminant analysis will be dependent on a dedicated chemical analysis laboratory, preferably with high resolution mass spectrometry capabilities sufficient to generate congener-specific data for "dioxin-like" PCBs, PCDDs and PCDFs. Aroclor-based estimates of total PCBs and low-resolution congener-specific approaches to PCB analysis will provide only a limited capacity to evaluate pattern changes through the food chain, metabolic removal, biomagnification, and the risks associated with different types of contaminants. In addition, such methods will be unable to distinguish between "dioxin-like" and "non dioxin-like" components of these chemicals. Interlaboratory calibration exercises are carried out routinely, and certified reference materials are used.

Since "dioxin-like" chemicals have been identified, in part, by their ability to bind to a common receptor protein found in many vertebrates (i.e. the *Ah*R), bioassays using this receptor offer an alternative means of quantifying "dioxin-like" contaminants in environmental samples which have toxicological relevance. Existing assays include the Chemical-activated luciferase gene expression (CALUX) assay for total TEQ (Murk et al., 1996) and the H4IIE assay (Kennedy et al., 1992). Such mechanistically-based assays provide a cost-effective and

integrated screen for determining contaminant concentrations, which can be followed by more costly and comprehensive chemical analyses. Additional, rapid screening techniques including immunoassays and chemical screens are under development.

3.7 Summary

The global distribution of "dioxin-like" POPs, coupled with their persistence in the environment and in biota, highlight the need for integration of human and ecological risk assessments. Exposure of both humans and wildlife through the consumption of contaminated foods represents a shared feature within an integrated risk assessment. Chemically- and biologically-based analytical and toxicological methods exist which can be applied equally to studies of both humans and wildlife.

4. Characterization of Effects

4.1 Reported effects and modes of action

Many of the effects of the toxic POPs were first identified in fish-eating wildlife, but precise mechanisms of action and chemicals involved were subsequently elucidated in carefully-controlled experimental designs in laboratory animals. *In vitro* and *in vivo* (Silkworth et al., 1986) receptor-based assays have strengthened the understanding of mechanism of action of POPs including the dioxin-like compounds.

The Toxic Equivalency Factor (TEF) approach allows a "ranking" of the toxic risks of the PCBs, PCDDs and PCDFs, as well as the different congeners within each group, relative to 2,3,7,8-TCDD (Safe, 1992; Birnbaum, 1999). Using internationally-derived TEFs (Van den Berg et al., 1998), coupled with information from mechanistic laboratory animal experiments (Vos et al., 1978; Ross et al., 1997), Ross et al. (Ross et al., 1995) ascribed the immunotoxicity observed in captive harbour seals fed Baltic Sea herring to the "dioxin-like" effects of PCBs. Evidence is accumulating that implicates PCBs and dioxin-like TEQs in neurotoxic and developmental effects in human infants exposed through mother's milk (Koopman-Esseboom et al., 1994; Seegal, 1996; Schantz et al., 1996; Patandin et al., 1999). An assessment of the relative risks presented by the different classes of chemicals is not always easy, but the TEF approach allows us to deal with one important toxic subset within a complex mixture and help to simplify the ranking of chemicals of concern.

4.2 Biomarkers and indicators

Common mechanisms of action identified across taxa for "dioxin-like" toxicities have led to the development of biomarkers of exposure and effect in both humans and wildlife. Several biomarkers have been used routinely for the dioxin-like contaminants, largely based on their affinity for the *Ah*R and consequent induction of the cytochrome P4501A enzyme system. While study animals have often been sacrificed in order to collect the liver samples necessary for such

studies, liver biopsies taken under general anesthesia, and skin and blood samples, have been used successfully as a minimally-invasive means of obtaining reliable dioxin-related enzyme induction information from certain mammalian species (Fossi, 1994; Bandiera et al., 1997). Results from biomarker studies of fish, birds and amphibians also provide information on the effects of dioxin-like POPs (Kennedy et al., 1992; Hahn and Stegeman, 1994; Stegeman and Livingstone, 1998).

The immune system is an organ system that is particularly vulnerable to "dioxin-like" toxicity, with observations of thymus atrophy and reduced T-lymphocyte function representing patterns of effects considered "typical" of dioxin exposure at low levels in both laboratory animals and wildlife (Vos et al., 1978; Grasman et al., 1996; Ross et al., 1996b). However, while the immune system represents a sensitive target for many POPs, no biomarkers exist for assessing immune function. This necessitates a more applied research strategy which incorporates the "relative" functionality of many immunological endpoints.

Another strategy has been to assess non-immunological biomarkers to shed light on toxic injury to an organism and provide a measure against which immunological insults can be compared. Biomarkers have been used in wildlife studies where the mechanistic link to particular classes of chemicals within the complex mixture are less certain. For example, the disruption of vitamin A physiology observed in seals and fish-eating birds can be due to both "dioxin-like" and "non-dioxin-like" effects as a result of exposure to PCBs, PCDDs and PCDFs (Brouwer et al., 1986; Brouwer et al., 1989b; Simms and Ross, 2001). Concurrent alterations in vitamin A and immune function endpoints have been noted in studies of wildlife exposed to POPs (De Swart et al., 1994).

4.3 Exposure-response modelling

All humans and wildlife are exposed to complex dietary mixtures of POPs and related contaminants. However, certain groups (species, populations, cohorts or age groups) may be more exposed than others, enabling an assessment of adverse health effects based on differential exposures. Such approaches have been used in assessing the effects of POPs in human cohorts (e.g. nursing infants, subsistence-oriented humans) (Dewailly et al., 2000; Weisglas-Kuperus et al., 2000). In addition, semi-field studies in which two groups of animals are fed different diets have provided useful information on the effects of complex mixtures (e.g. (De Swart et al., 1994; De Swart et al., 1996; Ross et al., 1996a)).

4.4 Extrapolations

Studies carried out to date suggest that many aspects of physiology are conserved among species, providing a basis for inter-species extrapolations. For example, the AhR has been identified in numerous organisms including fish, amphibians, reptiles, birds and mammals (Hahn, 1998). As a consequence, the risk of dioxin-associated toxicity to different species may be estimated, and AhR-mediated effects observed in one species can form a basis for assessing

risk in other species where constraints would otherwise preclude assessment (e.g. humans, endangered Monk seals, or large whales). Extrapolation from studies of highly exposed human groups (occupational or subsistence groups) to the general public will provide a link vital to this risk assessment. However, caution is required when extrapolating: although different species often exhibit similar patterns of effects (i.e. mechanisms of action) as a result of the conserved nature of many physiological systems, inter-species differences in sensitivities do exist.

4.5 Direct and indirect effects

Dioxin-like chemicals are well known to bind with high, but varying, affinities to the *Ah*R in vertebrates, which in turn, triggers a cascade of enzyme induction responses, immunotoxicity, oxidative stress, cytokine production, hormonal and growth factor perturbations and a number of other less well documented effects (Birnbaum, 1994). Indirect toxic effects may include the formation of reactive, water-soluble intermediates from the more metabolizable compounds following metabolic attack by the mixed function oxidase system (e.g. CYP P4501A). A significant challenge to scientists and risk assessors is to delineate mechanistic, cause-and-effect relationships in humans and wildlife, something that will require data support from carefully controlled laboratory experiments using laboratory animals (*in vivo*) and/or bioassays (*in vitro*).

Additional indirect effects of contamination of organisms in the environment may arise in certain cases. For example, even though crabs exposed to pulp mill-associated dioxins and furans may not suffer from toxic effects, a resulting fishery closure could have negative socio-economic effects for dependent human fishers and communities.

Acute human exposures are infrequent and often poorly documented, but several incidences of poisoning have occurred after accidental mixing of PCB/PCDD/PCDF and edible oil products or animal feeds. Symptoms have included weight loss, chloracne and immunotoxicity (Nakanishi et al., 1985; Takayama et al., 1991). Altered sex ratio in offspring has also been documented (Mocarelli et al., 1996). Chronic exposure to low or moderate levels represents a more insidious health risk to high trophic level organisms and humans, principally because of the persistence and ubiquity of POPs in the global environment.

4.6 Summary

The common mechanism of action of “dioxin-like” compounds (i.e. via the AhR) leads to a similar hazard identification process across vertebrate species. The development of the Toxic Equivalency Factor (TEF) approach has demonstrated the utility of an integrated approach to evaluating the potential effects of particular “dioxin-like” compounds in complex mixtures on both humans and wildlife.

5. Risk Characterization

5.1 Combining exposure and effects

In humans, the World Health Organization (WHO) has set a Tolerable Daily Intake (TDI) of 1-4 pg TEQ/kg/day based on knowledge gained largely from laboratory animal studies and epidemiological investigations. Much work remains to be done on the links between exposure, burden and effects, although laboratory animal models (e.g. rodents, cows, fish, non-human primates, and birds) provide a basis for a mechanistic understanding in this area. Such work clearly requires a critical and multidisciplinary approach to evaluation, extrapolation and

understanding mechanism of action in a dose-dependent manner. Human risk assessments typically consider "adjustment factors" to allow for i) differences in sensitivity among humans (i.e. some humans are more sensitive than others); ii) variability among species (i.e. humans are "more sensitive" than laboratory animals); and iii) differences between acute and chronic exposures (effects may be more pronounced in a chronic exposure regime). In this manner, data from laboratory animal-based studies and/or human studies may be combined in order to describe "risk" even in the absence of direct evidence in humans.

In the case of wildlife, both "real world" and captive dosing studies have enabled scientists to document the adverse effects of POPs, although ethical and logistical constraints are increasingly requiring studies to be non-invasive. Exposure regimes for wildlife studies can be divided as follows: i) captive experiments relating dose-related single chemicals exposures to effects; ii) captive experiments with realistic dietary exposures (i.e. fish from areas of differing degrees of contamination fed to top predator) vs effects; and iii) studies of free-ranging wildlife that are exposed to varying degrees of contamination vs effects.

5.2 Determining causation

A mechanistic understanding of contaminant exposure and toxic effect is lacking for many species. In some cases, this is due to the challenges associated with working with a particular species. In other cases, the complexity of the mixtures of POPs and other chemical stressors to which humans and wildlife are exposed renders it virtually impossible to tease out a particular chemical responsible for an effect. Most research which has identified chemicals of concern, and the nature of their toxicity, has relied upon laboratory animals, including rodents. A reliance on the conserved nature of many organ, endocrine and immune systems, as well as certain processes (e.g. reproduction, circulation and development), provides a basis for comparison between laboratory (surrogate) study animal and the organism in question. Establishing a mechanistic basis for a particular chemical and its related toxic effects in a laboratory setting provides an initial a foundation for extrapolation and interpretation when working with humans or wildlife that are either difficult to work with or are exposed to complex POP mixtures.

5.3 Combining lines of evidence

Inherent technical, logistical, ethical and legal challenges associated with carrying out conclusive or mechanistic research in certain species (including humans, cetaceans and endangered wildlife) underscore the need to combine lines of evidence. These difficulties may include: non-availability of specialized reagents needed for clinical or toxicological research (e.g. cell surface markers for immunology) for all species; size of the species in question (e.g. many whale species); working with human subjects, where considerable constraints exist in carrying out research; and working with endangered species, where legal statutes limit any form of invasive sampling and access to populations. Both human and wildlife toxicology groups partially overcome such obstacles by relying on laboratory animal models and in vitro assays. Ultimately, a combination of lines of evidence best serves the managers responsible for implementing regulations (Ross et al., 2000b).

5.4 Uncertainty

While mechanism of action may be highly conserved among species, differences in sensitivity for various responses can exist, necessitating a critical examination of assumptions, observed or predicted effects, exposure and metabolic variables, and biological or ecological differences. “Biomarkers” of exposure and effect have been useful in identifying toxic effects in different organisms. For example, circulating thyroid hormone levels have been found to be affected by exposure to PCBs in laboratory animals, seals and nursing human infants (Koopman-Esseboom et al., 1994; Brouwer et al., 1998), providing a means for interspecies comparison of adverse effects. In such instances, the “risk” of other undocumented toxic effects may be predicted with greater confidence than had the risk assessment been based solely on “exposure” variables (e.g. concentrations of POPs in diet; intake rates).

5.5 Presentation of results

A central context for an integrated human and ecological risk assessment will be a “weight of evidence” approach which allows for data, or summaries of data, to be incorporated from studies of different species, under varying degrees of control. A number of examples can be used for “dioxin-like” compounds. For examples, a “weight of evidence” model designed for use in marine mammals (Ross, 2000) could be adapted for use in an integrated human and ecological risk assessment (see Figure 4).

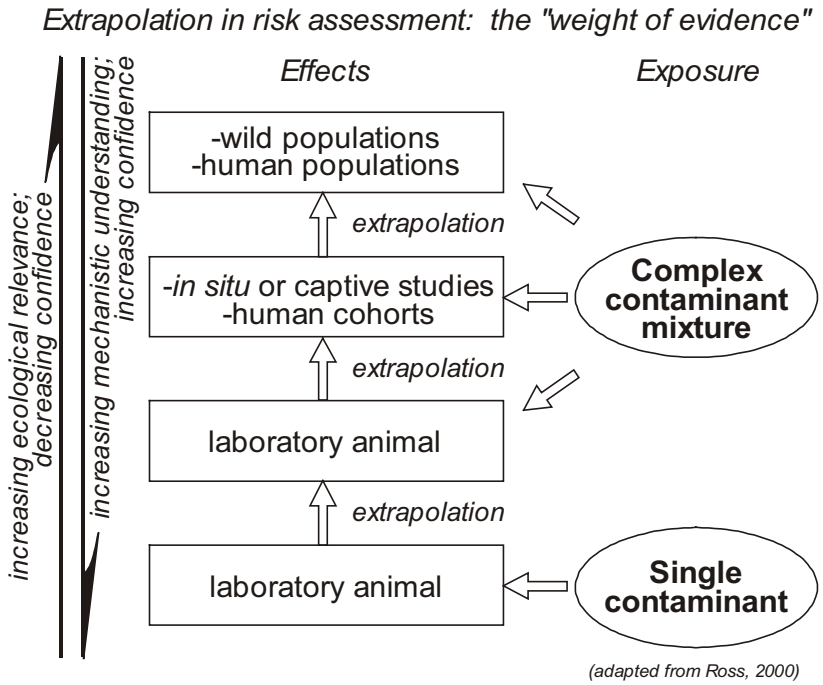

Figure 4: *Given the challenges inherent in establishing cause-and-effect in humans or specific wildlife species exposed to complex mixtures of "dioxin-like" compounds, a "weight of evidence" gathered from different experimental approaches would be beneficial to an integrated risk assessment model. Contributing to this scheme are the extensive in vitro and molecular studies which provide further insight into the mechanism of action of POPs and additional means of assessing inter-species differences in sensitivity (Jensen and Hahn, 2001; Kim and Hahn, 2001).*

5.6 Summary

A major advantage of an integrated approach to risk assessment is the ability to gain mechanistic understanding that provides a link between exposure and effect based on multiple lines of evidence. In the case of human health, it is difficult to directly demonstrate a conclusive link between exposure and effect. In this case, knowledge gained from laboratory animal and wildlife studies, and epidemiological investigations, has led to the concept of tolerable daily intake as one measure of characterizing risks associated with exposure.

6. Risk Management and Stakeholder Participation

A comprehensive evaluation of contaminant levels in different parts of the marine food chain, with an emphasis on the high trophic level consumers, provides a mechanism for education and outreach that should be easily recognizable by the public: many humans share the top of the food chain with fish-eating marine mammals, and can therefore be exposed to relatively high levels of persistent and fat-soluble toxic chemicals.

6.1 Summary

There is a need for commonality when describing human health and ecological risks in an integrated manner. The common routes of contaminant exposure and shared effects in humans and wildlife provide a background for communicating these issues to the public and to managers.

7. Risk Communication

Several aspects of risk management bear mention, including the management of chemical production, transport, application and disposal; remediation efforts related to cleaning up sites of contamination (old disposal sites, industrial areas, sediments); and human behaviour where food selection can influence the degree to which consumers are exposed to "dioxin-like" compounds and other POPs.

Given the persistence and global distribution of such chemicals, though, it is inevitable that exposure of humans and wildlife will continue for some time. In the interim, risk reduction strategies could be developed which involve education, consumption guidelines, and community outreach programmes, each of which incorporate the concepts of stakeholder groups, socio-cultural values, and conservation strategies. For example, the Inuit from the Canadian Arctic are exposed to high levels of "dioxin-like" POPs through the consumption of "country foods", exceeding the ADI by up to ten times (Kuhnlein et al., 1995). These foods are an important part of their cultural heritage, so that encouraging a switch to non-traditional "western" foods may be counter-productive. However, the elimination of beluga whale skin and blubber alone was estimated to reduce dietary exposure by approximately 50% because of the high degree of contamination of these particular lipid-rich products (Dewailly et al., 1996). While changing the subsistence-orientation of such peoples may have undesirable socio-cultural effects, such findings emphasize the need for continued regulatory vigilance on a global scale.

Other human groups that consume fish have been targetted for risk communication. While consumption advisories for fish from the heavily industrialized Great Lakes region of North America are common, an advisory exists even at the remote Lake Laberge in the Yukon Territory in northern Canada. High POP concentrations in fish there appear to be due to an influx of atmospheric pollutants and altered trophodynamic structure (AMAP, 1998).

While subsistence-oriented humans and fish-eating wildlife are particularly prone to accumulating high levels of these contaminants, certain lifestages are more vulnerable than others (Birnbaum, 1994; Birnbaum, 1995). Nursing infants, for example, have been found to be exposed to high levels of contaminants through mother's milk, coinciding with a sensitive time for growth and development (Dewailly et al., 1993a; Dewailly et al., 1993b; Koopman-Esseboom et al., 1994). The same has been observed in high trophic level wildlife (Addison and Brodie, 1987; Gilbertson et al., 1991; Fry, 1995; Nisbet et al., 1996; Simms et al., 2000). Particular care to reduce animal fat consumption by females from birth to post-reproductive age represents one important element of risk management in the case of humans.

Options to reduce the risk of exposure to "dioxin-like" compounds by humans and wildlife include the destruction of existing stockpiles of PCBs and related compounds (e.g. >800°C incineration); changes to the manufacturing and combustion processes that lead to the formation of such compounds (e.g. dioxins and furans as by-products of pesticide and herbicide manufacture, as by-products of the pulp bleaching process, or as by-products of low temperature combustion); and the remediation of contaminated sites. Given the extent that atmospheric processes result in the global distribution of POPs, coordinated efforts among industrialized and developing nations would be beneficial (e.g. UNEP Convention on elimination of 12 priority POPs; UN-Economic Commission for Europe work toward remediation of contaminated sites). The design and manufacture of new chemicals could also be carried out in such a manner so as to avoid the creation of new chemicals with "dioxin-like" properties (e.g. persistent; fat-soluble; endocrine modulators; *Ah*R active).

7.1 Summary

The persistence, and in some cases continued production (deliberate or inadvertent), of "dioxin-like" compounds, coupled with their risk to both humans and biota, necessitate an integrated approach to managing aspects of POP production, waste, remediation and exposure. Both humans and wildlife are exposed to complex mixtures of POPs and their "dioxin-like" components, and continued international regulatory diligence is required for effective multispecies risk management. While fisheries closures and consumption advisories can be implemented by health authorities in certain cases, risk communication with stakeholders represents an important challenge.

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B. Ultraviolet radiation effects on amphibians, coral, humans, and oceanic primary productivity

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Abstract:

Ultraviolet radiation (UVR) is a naturally occurring stressor to most forms of life. The sole relevant source of this stressor is the sun. The earth's stratospheric ozone layer reduces the amount of UVR that reaches the earth's surface. The potential for depletion of this ozone layer due to human activities and the subsequent increase in UVR at the earth's surface is a global environmental concern for both humans and ecosystems. An integrated risk assessment provides efficiency in data gathering, analysis and reporting by enabling risk assessors to use the combined knowledge from many disciplines to evaluate overall risk. This report describes the steps and example information that could be used for an integrated risk assessment but is not an actual risk assessment with all its associated calculations and conclusions. It is intended to be used as an example to stimulate discussion on the applicability of an integrated risk assessment process to a non-chemical stressor.

1. Background

There are very few ecosystems on the Earth that are unaffected by the daily incidence of ultraviolet radiation (UVR). There are fewer still that have not been shaped by exposure to UVR during the evolution of their biological components. Recent changes in UVR exposure at both the global and local level have, however, renewed concern regarding the potentially damaging effects of this ubiquitous stressor. Ozone depletion (Madronich et al., 1995; Kerr and McElroy, 1993), is the primary cause of changes in the dose of UVR received by aquatic and terrestrial species, including humans. Ozone depletion is the thinning (or eradication in the case of the polar ozone holes) of the UVR blocking ozone layer. This is caused by a host of chemicals, most notably chlorofluorocarbons (CFCs). While the 1987 Montreal Protocol and subsequent amendments have limited the production of these ozone-destroying chemicals, recovery of the protective ozone layer is expected to take several more decades (UNEP, 1998).

Although ozone depletion is the primary cause of altered UVR at the Earth's surface, other factors are also changing our contemporary environment. Global climate change, particularly global warming, and acidification both decrease the amount of dissolved organic carbon (DOC) which in turn increases UVR penetration into aquatic ecosystems (Schindler et al., 1996). Dissolved organic carbon is the primary mechanism for limiting UVR penetration into the water column (protecting aquatic organisms and establishing the lower limit of the photic zone); water itself has no UVR absorptive capacity. Climate warming primarily influences UVR penetration by decreasing the total amount of DOC, which is produced in terrestrial systems and then transported to aquatic systems. Climate warming can also act on DOC like acidification does, directly decreasing the amount of DOC already in the water body.

The overall effect of these changes is increased UV irradiance in both terrestrial and aquatic ecosystems. These changes in the relative amount of UVR reaching various habitats may be affecting ecosystems and human health, but research is only beginning to assess and quantify these effects. Humans, amphibians, coral, polar planktonic species, and crop plants are perhaps the five most widely studied biotic groups up to this point regarding UVR effects. Ozone depletion and other forms of global change that can influence UVR exposure are predicted to continue for several decades, if not longer. In addition, ecosystems impacted by increased UVR may take even longer to recover. It therefore is important to begin a comprehensive assessment of the risk of this stressor to living systems.

When considering UVR risks, it is important and unavoidable to note the other side of our long evolution with UVR, namely that organisms require sunlight. Vascular plants, algae and a whole host of organisms that contain autotrophic endosymbionts require light to fix carbon during photosynthesis. Sunlight is required for most vision systems. Exothermic organisms require the radiative heat of sunlight to maintain metabolic processes for cellular growth, development and reproduction. Vitamin D synthesis also requires full spectrum solar radiation. Conversely, it is important to note

that DNA, the genetic roadmap upon which all life relies, is damaged by UVR exposure. Through a number of adaptations (pigment, protective compounds, repair mechanisms, morphology, etc.) biota can exist with UVR exposure. There is a limit, however, to the amount of protection which can be provided and the amount of UVR against which adaptation can protect. Skin cancers are a classic example of the impact of UVR induced DNA damage.

This case study illustrates the advantages of the integrated approach to risk assessment because it capitalizes on the commonalities in stressor source, exposure pathways, and at least some of the mechanisms of effect to enhance the coherence, efficiency, and quality of an assessment of risks from a physical stressor such as UVR. Further, the selection of assessment endpoints emphasizes the interdependence of ecological and human health risks, as effected by the multiple cascading effects possible from exposure to increased levels of UVR. It also demonstrates the importance of considering how environmental regulation can influence the risks of a naturally occurring (albeit artificially modified) stressor.

2. Problem Formulation

2.1 Impetus for the Assessment

Ultraviolet radiation is a ubiquitous stressor that may be impacting human and ecological systems on a global scale. It has been implicated in observed shifts in polar plankton community composition, local and global declines in amphibian population abundance and diversity, coral bleaching syndrome, and an increasing incidence of human skin cancer and other diseases. For example, excesses in human cataracts are estimated to peak at approximately 25 cases per million population under the UVR scenario associated with successful application of the 1997 Montreal amendments to the Montreal Protocol (reported in UNEP, 1998). Similarly, excess skin cancers are estimated to peak at around 100 per million (reported in UNEP, 1998). While quantitative data are limited, failure to understand the risks of changes in UVR has potentially far-reaching implications for the current state of life on this planet. Ecosystems may not be lost but they may be changed from what they are now. Human condition may not change dramatically as a sole result of UVR enhancement but human well-being will no doubt be influenced by the seemingly necessary changes in life style mandated by increased UVR. How the direct and indirect effects of a changing UVR regime influence ecosystem integrity and the health and status of human populations are areas of necessary exploration and assessment. The result of such an assessment should help to identify the extent of need for mitigation actions in both regulatory and personal behavior modification senses.

2.2 Assessment Questions

Put simply, the general question faced by regulatory agencies, public health organizations, and other stakeholder groups is:

> What are the risks to humans and nonhuman biota to the changes in exposure to UV radiation predicted over the next 50 years?

With the myriad defense and repair mechanisms that have evolved through time, there will likely be some populations and species that are better prepared to cope with enhanced UVR exposure. It must be kept in mind that UVR, unlike most traditionally considered environmental stressors, originates from a natural source: the sun. It is, however, enhanced by anthropogenic habitat and climatic alterations, such as ozone depletion, surface water warming, and water acidification.

Additional confounders to answering this question are the established interactive effects between UVR and xenobiotic chemicals (polycyclic aromatic hydrocarbons, pesticides, metals, pharmaceuticals), both in terms of photo-enhanced toxicity and photosensitization. While these factors increase the complexity of the assessment of risk from changes in UV radiation, they also increase the importance of assessing those risks in the context of multiple stressors (chemical pollution, nutrient enrichment and eutrophication, lake acidification) and seemingly unrelated regulatory actions (e.g., promulgation of water quality criteria).

Some additional assessment questions that may be specific to one or more assessment endpoints are:

> What is the relative change in dose at a given location due to all physical factors that influence exposure?
>
> What affects (both direct and indirect) does increased UVR have on specific biological receptors of concern?
>
> How do the interactions between UVR and xenobiotics modify the risk of UVR alone?
>
> Which biological effects are sensitive indicators of risks to broader systems that might serve as sentinels or early warning indicators of UVR risk?

2.3 Assessment Endpoints

Several issues shape the selection of endpoints in this stressor-driven assessment. They include observation of increased damage in important biotic systems that is linked plausibly to changes in UVR, as well as suspicion of increased likelihood of exposure (and subsequent effect) to elevated levels of UVR due to characteristics of the receptor. Although the risks of increases in UVR could be realized across a broad spectrum of living systems, this integrated risk assessment case study focuses on the following four (broadly defined) assessment endpoints. These endpoints are particularly good candidates due to the research already complete and data available.

1. Increased incidence of photo-damage related diseases in humans and wildlife, including skin cancer, ocular damage, immune suppression, and enhanced photosensitivity, that influence health and well being.

2. Disruption and lose of coral reef communities due to coral bleaching/disease, coral mortality, changes in reef persistence and formation dynamics, and cascading reef community interactions.

3. Declines in amphibian populations and lose of amphibian diversity locally and globally, due to increased mutation load, immune system suppression, photo-enhanced toxicity, and other mechanisms.

4. Decreases in oceanic primary productivity that result from impacts on photosynthesis and other UVR-induced damage, and the cascading effects on oceanic plankton community structure and function.

2.4 Conceptual Model

Figure 1 conceptualizes the relationships between the source of UV radiation (the Sun), exposure pathways, and effects on both humans and wildlife to be included in the integrated risk assessment of UVR. The conceptual model communicates hypothesized commonalities in exposure pathways, suggesting efficiencies in data collection, modeling efforts, and characterization of expected direct effects. It further describes suspected linkages among assessment endpoints (sometimes through intermediate biological components) that help to identify potential indirect effects resulting from changes in UVR. This integrated conceptual model helps to define the exposure and effects characterization activities described in subsequent sections. Relationships hypothesized in the model are further described in those sections.

2.5 Analysis Plan

The analysis plan for this assessment takes advantage of commonalities in source and exposure pathways, as well as similarities in some of the mechanisms of action of

UVR damage in all species. The following primary steps would be followed to assess risks to all assessment endpoints:

- Predict changes in levels of UVR impacting earth's surface based on modeling efforts and trends analysis (sources and emissions). Acknowledge uncertainty in future trends projections.

- Estimate local dosimetry based on near-field influences and site-dependent characteristics using data from surface monitoring networks; evaluate exposure confounders for media specific to each of the four assessment endpoints (e.g., water quality), developing relationships between UVR intensity spectra and environmental modulators.

- Translate exposure to expected effect based on action spectra for effect endpoints. Some spectra may be generic for all taxa (e.g., DNA damage); others may be specific for particular assessment endpoints (e.g., photo-inhibition of photosynthesis). Some relevant action spectra exist in the literature; others may need to be developed.

- Cascade direct effects through species interactions and food web dynamics to secondary, indirect effects (relevant only to coral reef and oceanic productivity assessment endpoints) using ecological models.

- Evaluate mitigating results of homeostasis (including repair mechanisms) and adaptation/acclimation on predicted effects using understanding gained through past experimental evidence, natural "experiments" (e.g., the Australian situation described later), and analogy.

- Explore the potential for ecosystems to recover from UVR impacts as the ozone layer and UVR levels return to near-normal conditions.

2.6 Summary

Commonalities in stressor source, exposure pathways, and mechanisms of damage and repair facilitate development of analogous assessment endpoints and holistic conceptual model(s). These conceptual models communicate the direct and indirect pathways of the primary (UVR) and secondary (e.g., loss of food source) stressors to relevant biotic components, taking advantage of the full level of current understanding of UVR physics and exposure issues. Although the UVR action spectrum may be dependent on the specific assessment endpoint, knowing the nature and mechanisms of effect in humans informs our conceptualization of possible direct effects of UVR on amphibians, coral, and phytoplankton, and probably vice versa. Problem Formulation has identified common data needs to evaluate risks from the direct effects of UVR on a variety of receptor organisms and target systems. The integrated assessment benefits substantially from the resource efficiencies gained through use of common models and

flux measurements (networks) in predicting outcomes, and the enhanced insights to possible effects to receptor organisms gained through analogy to other species.

3. Characterization of Exposure

3.1 Sources and Emissions

The only environmentally relevant source of UVR is the Sun. Irradiance from this source is expected to remain fairly constant relative to the temporal scale of this assessment, although significant modification of the amount of UVR reaching Earth's surface are projected as a result of decreased concentrations of ozone in the stratosphere (see below).

3.2 Distribution Pathways

The amount of UVR reaching specific receptors is affected by a number of processes and conditions, including ozone depletion, global change (particularly increased sea surface temperature and altered cloud cover), aquatic acidification (by alteration of concentration of dissolved organic matter), and changing nutrient profiles all can influence the amount of UVR reaching specific receptors.

Specific factors that will influence exposure to receptors include:

- location of the receptor on Earth's surface, because the angle of the sun and altitude both influence the intensity and wavelength spectrum of the radiation
- thickness of the Stratospheric ozone layer as influenced by natural distribution phenomenon and global changes (depletion, hole formation)
- natural habitat protection (e.g., shade, water depth)
- physiological/morphological adaptations or characteristics of receptor organisms (e.g., pigmentation, fur/feather)
- behavioral adaptations of receptor organisms (including use of screens and block by humans and changes in activity patterns by all organisms)
- water quality and clarity

As a result of current efforts to control ozone-destroying chemicals, the maximum ozone depletion and accompanying UVR increase is expected to occur within the next decade (UNEP, 1998). The rate of ozone recovery is difficult to predict, however, due to complicated interactions with changes in the atmosphere such as the expected increase in greenhouse gases. Madronich et al. (1998) estimated that if the various Montreal Protocol controls are met, UVR would be expected to return to normal levels by the middle of this century. These estimates also assume changes in UVR are solely influenced by changes in ozone and that ozone changes are the direct result of halocarbon inputs. Deviations from adherence to the protocols and uncertainties in our understanding of atmospheric chemistry could impact these predictions significantly.

3.3 Transport and Fate Models

Transport (except in the form of radiance) and fate models are not applicable to this stressor.

3.4 External and Internal Exposure Models

Estimates of actual exposure experienced by receptors would be made using existing models of radiance, ozone layer protective effects, and light transmission and penetration through the lower atmosphere and into local habitats and setting. Models of global change and trends analysis based on monitoring data from surface networks would be used to project plausible UVR change scenarios relevant to the temporal bounds of the assessment. "Local" modifications of intensity spectra would be made as appropriate to receptor habitat (e.g., depth in water column) using appropriate models, empirical relationships, and estimated exposure at the molecular level estimated.

Similar considerations are needed for secondary stressors (xenobiotics) and other confounders. Secondary stressors of concern include polycyclic aromatic hydrocarbons, or PAHs (Arfsten et al., 1996; Fernandez and l'Haridon, 1994; Huang et al., 1993), pesticides (Zaga et al., 1998), and metals (Rossman, 1981). Interactions between these stressors and UVR have been found in both marine and freshwater systems, in plants and animals. Effects may only be seen in the combined exposure of UVR and these compounds when exposure to ambient levels of the chemical are insufficient to cause effects. Additional confounders include environmental changes such as acid rain (Wright and Schindler, 1995) and global climate change, especially altered sea surface and lake temperature (Leavitt et al., 1997; Morris and Hargreaves, 1997; Vodacek et al., 1997; Siegel and Michaels, 1996; Schindler et al., 1996).

3.5 Measures of Exposure Related Parameters

The important step in assessing the current and predicted risk of enhanced UVR is to have reliable and comparable dosimetry. This needs to be done on both global and local scales. Global/regional monitoring systems are currently being employed and expanded in North America and Europe, as well as at several global hot spots. Examples of such systems in the United States include networks run by the U.S. Environmental Protection Agency and the Department of Agriculture. On a local level, individual experiment and field monitoring needs to include full spectrum, calibrated dosimetry. Additionally water quality parameters (DOC concentration, turbidity, reactive chemical concentrations) also need to be monitored during research evaluating UVR effects on aquatic ecosystems.

3.6 Analytical Tools

While there still is some debate regarding the best instrumentation at both the local and the global scale, every effort should be made to provide such data so that results

are comparable. Models will be used to extrapolate broad-based monitoring data to dose. Because biological damage and effects are functions of both wavelength frequency and intensity, UVR exposure would be quantified as frequency spectra. Modifiers and other confounders would be quantified as appropriate to those factors.

3.7 Summary

The source of UV radiation and many of the exposure pathways are identical for both human and ecological assessments, allowing common information on UVR intensity obtained from monitoring networks and tools to be used as the initial measure of exposure. Models and methods for estimating or measuring dose can also be shared. The benefits of an integrated approach thus include cost efficiencies and minimization of data collection needs.

4. Characterization of Effects

4.1 Reported effects and modes of action

The range of effects of UVR on humans includes skin cancer, immunosuppression, and ocular damage (de Gruijl and Van der Leun, 1993; Noonan and De Fabo, 1993; Zigman, 1993). Enhanced photosensitivity also has been reported in conjunction with use of some pharmaceuticals. Reported direct effects on amphibians include developmental damage, mortality, and possible immunocompromise (Carey, 2000; Blaustein et al., 1997; Worrest and Kimeldorf, 1976; Cummins et al., 1999). UVR has been implicated as a factor in coral bleaching but the mechanism is unknown (Fitt and Warner, 1995; Gleason and Wellington, 1993; Lesser et al., 1990). Enhanced UVR also has been reported to decrease photosynthetic rate of marine algae. Many of these effects are predicated on DNA damage although the mechanisms are mostly speculative. The role of behavioral, morphological and physiological protections increase the variability in these responses among species, populations and individuals.

In the case of humans, cumulative life-long dose seems to play a role in susceptibility, with early life exposure having the most impact, yet effects often are not seen until later in life (WHO, 1995). Early life-stages of other organisms are also likely to be the most sensitive (Longstreth et al., 1998). Frogs, for example, are more sensitive in the early larval stages than as adults (Hansen, 1998).

Another important aspect of UVR effects, due to the evolutionary time frame of exposure, is the variability of effects among populations. Some populations are simply better adapted to higher levels of UVR. In humans, the most obvious example includes the observation that human populations which have historically existed in areas near the equator, where UVR is naturally more intense, have greater concentrations of melanophores and melanin in their skin. The effectiveness of this phenology as protection is demonstrated in the adverse impacts of UVR on individuals from higher latitudes when they immigrate to equatorial regions. For example, Australians of British

extraction suffer a higher rate of skin cancer compared to their aboriginal neighbors (Green and Williams, 1993). In coral, such variation is seen between shallow and deep-water populations of the same species (Gleason, 1993; Siebeck, 1981, 1988). Variability has also been seen in amphibian populations, with high elevation populations often being better adapted to high UVR intensity (Hansen, 1998). Phenologic variation among populations will influence the degree to which effects are experienced even at similar exposure levels.

4.2 Biomarkers and Indicators

DNA is often referred to as one of, if not the, most sensitive targets of UV-B (a limited range of the UVR spectrum) damage (Setlow, 1997), with exposure resulting in mutations or cell death (Mitchell and Karentz, 1993). DNA lesions can be linked directly to UV-B radiation (Buma et al., 1997; Malloy et al., 1997). Lesions produced by UV-B include pyrimidine dimers and (6-4) photoproducts. Biomarkers of DNA damage might be both useful indicators of exposure to UVR and predictors of biological effect. Commonalities among species in causal pathways leading from DNA damage to biological effect could increase the efficiency of data collection and use in the integrated risk assessment.

4.3 Exposure-Response Modeling

UV radiation is composed of a band of wavelengths with varying influence of environmental factors on exposure and effects. As a result, measures of biological responses to UVR need to be based on exposure to specific wavelengths, i.e., action spectra. The response of DNA to UVR has been quantified by its action spectra for damage (Setlow, 1974). Other endpoints have also been quantified with their action spectra, including erythemal response (McKinlay and Diffey, 1987) and plant damage (Rundel, 1983). Characterization of direct effects of UVR on the assessment endpoints would rely on action spectra as the description of exposure-response relationships. Action spectra may be transportable across assessment endpoints if the mechanisms of effect are similar.

4.4 Extrapolation

Because data on the effects of UVR will always be limited, the ability to extrapolate existing data to other organisms, systems, and situations is a necessary activity of the integrated risk assessment. Many uncertainties result from our inadequate knowledge of the factors influencing the accuracy of such extrapolation. Extrapolations of effects between tested and untested species (e.g., mice and humans, frogs, and salamanders) can be aided by the knowledge of common mechanisms and action spectra. These data can assist in estimating responses of sensitive populations as well as understanding the influence of changes in behavior patterns on exposure. Extrapolations from individuals to populations require models of population responses that incorporate

measures of survival, fecundity, productivity, and other factors that influence population dynamics. These models are often unavailable. Our ability to extrapolate to ecosystems from individual species responses must be based on an understanding of the interactions among biotic and abiotic components, and depend on models of ecosystem structure and function at a variety of spatial scales.

4.5 Direct and indirect effects

As was mentioned earlier, UVR can impact biological systems on a number of levels in ways that are not limited to the direct effects on the exposed individuals themselves. In addition to DNA and cellular damage, morphological changes induced by UVR exposure can affect trophic dynamics (Zellmer, 2000). In the case of a coral reef ecosystem, UVR effects can occur at a number of trophic levels. The heart of the coral reef ecosystem is the coral/zooxanthellae symbiosis. Both species in the symbiotic relationship may be affected independently by UVR and by the resultant adverse reaction of the other. For example, changes in dinoflagellate pigmentation can alter the protection afforded to the coral, and changes in coral cell condition may alter the suitability of the environment in which their endosymbionts live. As coral rely on zooxanthellae to some extent for energy production through photosynthesis, any alteration in zooxanthellae condition or location could adversely effect coral condition. Additionally, other coral reef inhabitants, including algae (macro- and micro-), invertebrates, and fish, all can be affected directly by UVR exposure and indirectly by changes in coral condition. The cascading effects of poor coral condition can include a shift in dominance in the reef community to algal species that changes nutrient profiles and habitat suitability for other reef inhabitants.

The effects of UVR on oceanic primary production could also extend beyond the direct effects on phytoplankton. The biomass production of nearly every fisheries is limited by food supply (Cushing, 1982; Nixon, 1988). An UVR-induced decrease in primary production could cascade through the food web to affect larval fish that feed on phytoplankton or, more often, on zooplankton whose abundance is tied to primary production. These effects include reduced growth rates of larval stages of fish and invertebrates. In turn, reduced growth rates can increase larval mortality rates through intense size-specific predation and survival. An extended larval stage also increases the probability that currents will transport the larvae to an unsuitable habitat. Changes in oceanic productivity likely would have indirect effects on humans and other consumers through impacts on food supplies.

However, the specific mechanisms by which UVR effects cascade through the food web are likely to vary in different portions of the ocean. Biologically damaging UV-B appears to be limited to approximately the top 10-15% of the euphotic zone in ocean waters (Behrenfeld et al., 1995). Hardy et al. (1996) concluded that the most pronounced inhibitory effect on oceanic primary productivity would occur in the sub-Antarctic (40-50 degrees south) and not in the Antarctic or the tropics. Measurable decreases in phytoplankton-specific growth rates and biomass from UVR are also most

likely to occur in nutrient-rich areas of the ocean. In other areas, nutrient limitation rather than UVR may well be the limiting factor (Behrenfeld et al., 1994).

4.6 Summary

Several endpoints have common mechanisms of effect and similar biomarkers of effect, a situation that promotes characterization efficiencies by permitting extrapolation of effects across species. An extrapolation approach to developing action spectra models (wavelength specific exposure-response models) may be possible depending on the similarity in mechanisms and exposure pathways. Recognition of linkages among components of the integrated conceptual model enhances understanding of the indirect effects of UVR exposure that can influence risks to the assessment endpoints in (sometimes) unexpected ways. Similarly, information about potential effects to some assessment endpoints may suggest previously unexpected effects to other endpoints for which information is lacking.

5. Risk Characterization

5.1 Combining Exposure and Effects

As described in section 2, the assessment question being addressed is "what are the risks to humans and nonhuman biota to changes in exposure to UV radiation over the next 50 years?". To evaluate these risks requires projection(s) of specific stratospheric ozone depletion scenarios and the resultant increases in UV radiation projected to reach the earth's surfaces. Profiles of UVR exposure at various points on the earth can be coupled with exposure-response relationships for individual assessment endpoints to estimate expected direct effects on humans and ecological systems. When combined with modeled estimates of indirect effects resulting from ecosystem interactions and linkages among assessment endpoints, the exposure profiles and exposure-response relationships provide holistic, integrated estimates of risk to the assessment endpoints.

5.2 Determining Causation

Establishing causation between UVR and apparent effects on assessment endpoints depends upon two primary types of information: correlative (associative) and mechanistic. Correlative relationships are associations of changes in human or ecosystem condition with broad measures of variation in UV radiation. These associations might include, for example, incidence of skin cancer and cataracts as a function of latitude and longitude, or effects on plankton productivity as a function of water quality and behavioral patterns. Mechanistic relationships provide understanding of the causal linkages between exposure and the direct and indirect effects on specific receptors. Mechanistic relationships often are deduced experimentally by manipulating UVR wavelengths in the laboratory (using artificial lights or specific wavelength filters) or in limited field manipulations (using specific wavelength filters of natural sunlight). Conclusions regarding causation are strengthened as similarities in associative and

mechanistic relationships increase among the various pathways described in the integrated conceptual model.

5.3 Combining Lines of Evidence

Conclusions about the risks of UVR, and confidence in those conclusions, can also be strengthened by accumulating evidence that verifies and quantifies the relationships hypothesized in the integrated conceptual model. Evidence of biologically meaningful changes in UVR (as modeled by exposure scenarios) derives from the aforementioned monitoring network data and observations of stratospheric ozone depletion. The evidence of effects of UVR on assessment endpoints includes a combination of direct experimental determinations of UVR action spectra relevant to the assessment endpoints coupled with associative descriptions relating differences in UVR intensity with direct biological effects as observed in natural manipulations of UVR. The weight of evidence supporting risk conclusions increases as the information about expected effects across assessment endpoints converges onto a common picture. Thus, evidence of effects of increased UVR on amphibians, when combined with evidence of analogous effects on humans, helps to define and strengthens confidence in the risk characterization.

5.4 Uncertainties

The primary uncertainties in the assessment reflect those associated with future UVR changes and the specific adaptations individuals and organisms use that influence dose and effect. Estimating the future risk of UVR depends in part on predictions of future ozone levels as part of overall global change. There also is limited quantitative data on the relationship between environmental variables and UVR transmittance/penetration in specific systems (particularly aquatic). Because UVR is a naturally occurring stressor, numerous adaptations, behaviors and repair mechanisms exist. Predicting risk to individuals and populations generally includes only a subset of these adaptations. Additional uncertainties in understanding and predicting effects on humans and ecological systems include: (1) confirming the mechanism of effects on a broad spectrum of organisms and endpoints; (2) extrapolating the effects from tested to untested species; (3) understanding the significance of predicted effects to populations and system functions; and (4) the inadequacy of our knowledge of the global nature of interactions impacting large-scale ecological systems.

5.5 Presentation of results

Results of the integrated risk assessment of changes in UVR would be presented as a coherent package that presents risks to endpoints in connected fashion based on a common scenario for UVR intensity and distribution. Results would be communicated as probabilities of direct effects on individual humans (increases in cancer rates and ocular damage) in the context of human welfare, well being, and social systems coupled with probabilities of extinction and projected losses of biodiversity and productivity of aquatic

ecosystems. The relationships between loss of ecosystem productivity to quality of human condition will be described to the extent possible.

5.6 Summary

The risk characterization would use future UV radiation scenarios, action spectra and other exposure-response relationships to characterize direct effects, and ecological models to characterize indirect effects on assessment endpoints. Understanding of the relative risks among assessment endpoints is enhanced by using exposure scenarios, models, and data shared in common, and by drawing analogies among mechanisms of effect when possible. Causation would be determined through evaluation of a combination of correlative and mechanistic relationships linking UVR to biological effect, with risk conclusions being further defined and strengthen as multiple lines of evidence about those relationships converge. The overall confidence in risk conclusions would be enhanced as similarities among risk estimates for individual assessment endpoints emerge.

6. Risk Communication

To date, communication of risks of UVR has focused primarily on those to human health. Some regions of the world are establishing and communicating policy to respond to elevated UVR levels and human sensitivity. Many federal governments, including the US, have adopted the UVR Index (developed by the World Health Organization, World Meteorological Organization, United Nations Environmental Program and the International Commission on Non-Ionizing Radiation Protection) to explain daily dose and risk to the public. Many countries are also offering standardized guidelines on use of sunscreens and acceptable daily UVR exposure. For example, the Australian Radiation Protection and Nuclear Safety Agency monitors UVR levels, assesses effects, and offers "personal protection strategies." In 1996, Australia started to standardize UVR protection rating of clothing, and several countries (including Australia, the UK, Germany, France, and the US) have developed such standards for sunglasses. Further, various governmental (US EPA SunWise School Program, Australian Radiation Protection and Nuclear Safety Agency, and others) and non-governmental (national Cancer Societies, World Health Organization, United Nations Ozone Sectretariat, and others) groups have developed aggressive public health communication efforts about risks and personal protection approaches. Because of this attention to public health, and despite implications that UVR may be a contributor to observed impacts in selected ecological systems such as coral reef communities, phytoplankton communities, and amphibian populations, public perception of UVR risks has been shaped largely by human health effects.

To support a more holistic understanding of UVR risks, and thereby facilitate more effective risk management (including personal choice) decisions, coherent messages should be developed about risks to all assessment endpoints. Such messages should explain the current knowledge of UVR effects, including expected impacts on

sensitive ecosystems as well as projected changes in human disease incident attributable to UVR exposure. Although continued emphasis on health effects may be needed in certain venues (for example, public health programs) to promote effective personal protection, communication of risks to regulatory agencies and international governance bodies needs to be consistent and integrated with respect to all assessment endpoints. Coherent expression of the risks of changing UVR will help these groups establish priorities for risk management action.

6.1 Summary

An emphasis on communicating risks of UVR exposure to human health, although necessary to facilitate effective choices about personal protection, has under-represented possible adverse effects on ecological systems. The resulting lack of appreciation of ecological risks can hinder identification of risk management priorities. An integrated approach to risk communication would provide consistent, coherent, and simultaneous expressions of risks to all assessment endpoints, thereby facilitating selection among potential mitigation efforts that minimize risk to humans and non-humans alike, and promoting understand of why various risk management actions are taken.

7. Risk Management and Stakeholders

Due to the global nature of UVR exposure and the causes of UVR enhancement, effective risk management and stakeholder involvement will require creative solutions. Although the integrated risk assessment can provide improved understanding of the likely adverse effects that would be experienced by all assessment endpoints under various exposure scenarios, the decisions made by the regulatory community and the public should be integrative as well to be effective in mitigating risk.

The Montreal Protocol, along with its subsequent amendments (see UN Ozone Secretariat for details), currently sets down control limits on known causes of ozone depletion. It will be at least a decade before their effectiveness can be assessed with respect to reduced UVR exposure. In the interim, the public health community will need to continue programs to encourage human behavioral changes to minimize exposure. The most aggressive these have been in Australia, but many other countries (including the United States) are increasing public awareness both through government agencies and non-government organizations, such as national cancer societies. Additionally, there may be need for enhanced regulatory approaches for evaluating and rating protection, such as creating testing and guidelines to standardize SPF and sunscreen ingredients, sunglasses, and clothing. As mentioned above, a group of international organizations have created the UV Index for informing the public about UVR exposure effects and personal exposure decision making.

In contrast, facilitated behavioral adjustments and personal protection strategies are not possible or feasible for non-human receptors. Protection of stratospheric ozone

layer seemingly is the principle option for minimizing risks to ecosystems. Ideally, management decisions directed towards source reduction (that is, minimization of ozone stratospheric depletion through control of ozone-depleting substances) would consider the potential for both direct and indirect effects on ecological systems and direct effects on humans simultaneously. In evaluating relationships between source reduction and risk, attention should be paid to alterations in UVR penetration due to changing sea surface temperature, DOC content, and acidification, and to introduction of photoreactive anthropogenic contaminants in sensitive ecosystems.

In addition to direct and indirect effects of increased UVR on ecosystems and ecological processes, risk management decisions should consider the impact of ecosystem degradation on human well-being. Potential indirect ecological impacts with respect to humans include: changes in food production (availability and success of crops and fisheries), forest health (crucial in limiting the effects of greenhouse gases), and other ecosystem services (decreased oxygen production by phytoplankton, loss of recreational resources). Loss or degradation of any of these ecosystem functions likely would be detrimental to humans and other assessment endpoints, as well as difficult to correct once they are altered. The connections between ecological and human well-being are, perhaps, among the strongest arguments for integrated assessment and management of UVR risks.

7.1 Summary

Risk management informed by more holistic understanding of risks of changing UVR to humans and ecological systems will result in management and personal decisions that are most effective in optimizing risk mitigation strategies. Integrated risk assessment characterizes the adverse effects of enhanced UVR on all assessment endpoints in a consistent and coherent manner, allowing relative risks among assessment endpoints to be compared and understood, and the tradeoffs inherent in various risk management options to be transparent and recognized. Integrated risk assessment also facilitates a deeper understanding of the dependence of human well-being on ecological functions and services, thereby aiding in the identification of management approaches that optimize risk reduction from both human health and ecological perspectives, and avoiding unintended consequences.

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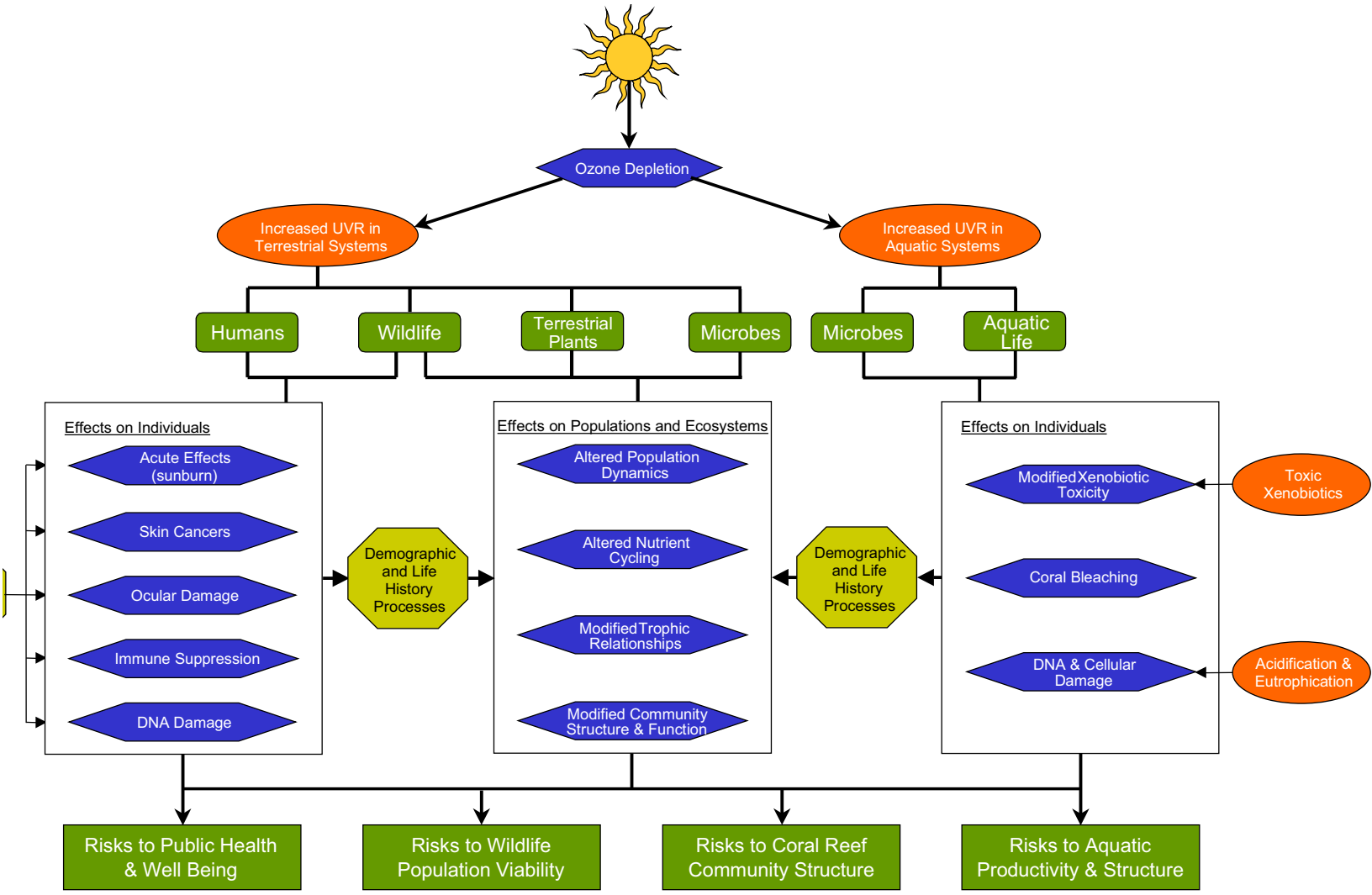
Figure 1. Conceptual model of risk of UV to humans and ecosystems (modified from U.S. EPA, 1998)



C. Tributyltin and triphenyltin compounds

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Abstract:

Tributyltin and triphenyltin (TBT and TPT) are biocides that have been used to prevent fouling of boats, to preserve wood, kill molluscs, and for other purposes. Due to observed effects on oysters and snails, their use in boat paints has been banned in many nations. However, use on ships and some uses other than as antifouling paints continue. These uses, the relative persistence of these compounds, their tendency to bioaccumulate, and their toxicity cause lingering concerns about risks to humans and nonhuman organisms. This paper outlines an integrated assessment of TBT and TPT. Based on prior human health and ecological assessments, it suggests that an integrated assessment that recognized common pathways of transport, fate and exposure, and on common modes of action would be more efficient and complete than additional independent assessments. In addition, the presentation of risks in an integrated manner could lead to better decisions by defining the various benefits of any management action.

1. Background

Tributyltin (TBT) and triphenyltin (TPT) compounds are used widely for various purposes owing to their strong biocidal activity toward a range of aquatic organisms such as bacteria, fungi, algae, molluscs, and crustaceans. Some examples of their use have been as antifouling paints for boats and cooling towers to prevent adhesion of aquatic organisms, as wood preservatives, as slimicides in industrial processes, as molluscicides to prevent schistosomiasis, and, in the case of TPT, as a fungicide. However, the finding that TBT was damaging oyster production in France in the 1970s made people recognize the negative aspects of use of these compounds in the aquatic environment (Alzieu 1981). More recently, the discovery that TBT and TPT at very low concentrations (1 ng/L in water) causes "imposex," the induction of a penis in females of certain snails, suggested that TBT and TPT are endocrine disruptors (IPCS, 1999 a & b).

TBT and TPT were chosen as a case study of integrated assessment for two reasons. First, their use as antifoulants was restricted in many nations based solely on risks to nonhuman organisms. Hence, these compounds make an unusual case for integration in that the ecological risks have dominated recent regulatory actions. Second, the possibility that there may have been significant risks to humans has remained unresolved. Many reports show that marine mammals and human fish eaters have accumulated these compounds in their bodies. This exposure and the various adverse effects observed in laboratory animals, raise concerns of risks to humans and other vertebrates as well as invertebrates. The potential for bioaccumulation and the complex toxicity profiles of these compounds suggest that a holistic approach to assessment is needed.

This case study is limited to tributyltin and triphenyltin compounds and their metabolites. One metabolite, dibutyltin is also used in as a stabilizer for polyvinyl chloride polymers, and is suspected to be more toxic in some ways than tributyltin. Some other organotins, such as trimethyltin (TMT) or triethyltin (TET) compounds are known to cause principally neurotoxic effects. However they are not covered in this case study, because their use patterns and toxicity profiles differ greatly from TBT and TPT.

2. Problem Formulation

2.1 Impetus for the assessment

Concerns for TBT and TPT arose from observations of deformities and reproductive failure in oysters, and certain gastropods. These observations combined with complex toxicity profile in rodents and aquatic organisms raised concern not only for effects on molluscs, but also for the possibility of effects caused from unknown, but common background mechanisms. Observations of immune suppression and developmental and reproductive toxicity in rodents at low levels of exposure (around or less than 1 mg/kg body weight) give some support on this concern.

Nonhuman organisms can serve as sentinels for certain effects that have not been identified in humans. Opportunistic infections and mortalities of some marine mammals appear to be related to immune suppression possibly caused by exposure to multiple agents, such as organotin compounds and polychlorinated biphenyls (PCBs). Some human populations who eat a lot of fish also accumulate organotin compounds and PCBs.

2.2 Assessment questions

Environment managers in various nations have asked whether the organotin compounds posed risks to human health or environmental quality that might justify further restricting their use. Evidence shows that current partial restrictions in many countries are not effective in preventing high local pollution in some inland seas and bays where contaminants are poorly dispersed or in preventing dispersal to remote areas (Champ, 2000). This assessment question encompasses the potential restriction of global uses of TBT and TPT in antifouling paints and other uses, as well as further national or local restrictions. The question must address the global consequences of local use due to movement of treated vessels and long-range transport of the compounds.

While the issue is not addressed in this assessment due to lack of evidence, it should be noted that the release of dibutyltin compounds from polyvinyl chloride polymers, and from consumer products, as a metabolite from TBT, may also pose a risk to human health and the environment.

2.3 Assessment endpoints

The regulation of TBT was based on the observation of deformities and imposex in molluscs. Hence, the frequency of deformities must be an endpoint in any new assessment.

Reproductive effects of TBT and TPT observed both in rodents and some aquatic organisms make reduced fecundity and developmental abnormalities another potential endpoint for both humans and nonhuman organisms.

Finally, organotin compounds exhibit immunotoxic effects, making increased frequency of disease an important endpoint for both humans and nonhuman organisms.

If risks of any of these organism-level effects are estimated to be significant for nonhuman organisms, risks to higher-level endpoints should be estimated. Depending on the species and situation, these could include population production or abundance, community composition, or ecosystem production.

2.4 Conceptual models

A conceptual model of sources, fate, exposure and effects of organotins is shown in Fig.1. Sources include treatment of vessels and other marine structures with organotin antifoulants and treatment of waters with organotins to suppress molluscs. In water, the

compounds may partition to suspended solids and deposit in sediments. In addition, sediments may be contaminated by paint and paint chips from hull-maintenance operations. Organisms may be directly exposed to organotins in water and sediment. Organotins may also be bioconcentrated and then bioaccumulated through aquatic food webs. Humans may experience health effects or socioeconomic effects due to loss of livelihood and cultural practices.

The conceptual model illustrates the potential utility of integration in risk assessment. In this case, humans, seabirds and marine mammals share similar exposure scenarios, through common sources, environmental fate of chemicals and media of intake, leading to high body burdens. In addition, the effects on nonhuman organisms have consequences for humans such as the losses experienced by oyster farmers and workers.

Other potential sources of exposure, such as polyvinyl chloride tubing in waterworks or consumer products, are not dealt in this paper.

2.5 Analysis plan

An analysis plan for an assessment of the need for further regulation of organotin compounds should go beyond the focus on local effects of antifoulants on highly sensitive molluscs. It should consider the regional and global consequences of all uses and releases of organotins. It should also consider the risks from specific mechanisms of toxic action on the full range of exposed species.

Environmental sources, fate and distribution of organotin compounds must be assessed quantitatively. This requires inventorying current and historic uses, measuring the compound in environmental compartments, estimating transformation rates and partitioning parameters, and using them to generate models of human and environmental exposure. Such models are required for both local and global scales.

Additional studies should be performed to elucidate the mechanisms of toxicity behind the toxicity profile in laboratory mammals and other organisms. The implications for toxic mechanisms of the commonalities and differences in human and nonhuman organisms, especially difference in metabolism, must be taken into account. Because organotins have been found to bioaccumulate in marine organisms, it will also be important to determine how they interact (i.e., in an additive, synergistic or inhibitory manner) with other bioaccumulated marine contaminants such as mercury, PCBs and chlorinated dioxins.

3. Characterisation of Exposure

3.1 Sources and emissions

Organotin compounds are still used as antifouling agents in many developed countries for boats over 25 m in length and on all boats in developing countries where no regulations exist. Their principal use has been in anti-fouling paints, from which they are released directly to the environment by leaching during use or in paint sandblasted from hulls during maintenance.

Organotin compounds are also used as fungicides or molluscicides in some countries, either applied directly or used to treat wood for piers and other materials.

3.2 Transport and fate models

The most important common route of exposure for humans and nonhuman mammals is consumption of contaminated seafood. In addition, aquatic organisms are directly exposed to contaminants in water and sediment. Our knowledge of exposure to organotins is largely based on analyses of waters and tissues of various organisms at local, regional and global scales. However, the release, distribution, and fate of organotins from various sources have not been modeled like the persistent organochlorine compounds, although the major sources and distribution by global processes is fairly clear now.

Environmental concentrations of TBT and TPT vary depending upon how, when and where compounds are used. Up to 1.58 μg/l (sea water) and 7.1 μg/l (fresh water) of TBT, and nearly 200 ng/l of TPT (Table 1) were detected in some bay areas or marinas with many boats treated with organotin-based antifouling-paints (IPCS, 1999 a & b).

Concentrations of TBT and TPT went down to 16.4 ng/L (TBT) and 1.8 ng/L (TPT) in 1993 in Tokyo bay area (Fig.2) after a 1991 ban on use of these compounds (National Committee for CICAD, 1997). However TBT concentrations appeared not to decrease further probably because boats from countries where regulations are not tight sail in the area. Similarly, aqueous TBT concentrations in Sarah Creek, Virginia, have shown little change in the 1990s after a steep decline in the late 1980s (Hall et al. 2000). This was attributed to mobilization of TBT from sediments.

TBT and TPT are sparingly soluble in water and easily adsorbed to particulate matter in the aquatic environment. Hence they are accumulated in sediment where they are relatively persistent and are taken up by the benthic organisms such as clams. TBT and TPT are accumulated in fish and other aquatic organisms with bioconcentration factors of 10^2-10^4 (Table 1). In a global survey of organotin pollution using livers of squids, Yamada et al (1997) found high levels in coastal waters of Japan and France.

These transport and fate properties are reflected in the results of a mathematical simulation of TBT in a large freshwater lake by Traas et al (1996). They predicted that, following restriction of TBT use, aqueous concentrations would decrease rapidly, but concentrations in sediment and biota would decrease slowly.

3.3 Dose due to seafood consumption

The average intake of TBT by humans from seafood may be estimated from standard market-basket surveys. A survey conducted yearly in Japan by ca. ten local research stations estimated that the average Japanese TPT and TBT intakes in 1997 were 2.7 μg/day/ person and 2.3 μg/day/person (as chloride), respectively (Fig. 3). Keithly et al (1999) estimated TBT intake

from analyses of five to nine seafood species purchased from markets in eight cities in Asia, Australia, Europe and the USA. Based on national diets and geometric means of seafood contamination from Keithly et al. (1999), TBT doses can be estimated to range from 0.18 (United Kingdom) to 2.6 (Korea) μg/day/ person. Another study, which analyzed seafood purchased in the U.S., gave similar results (Cardwell et al. 1999a).

3.4 Internal exposure

Body burdens of organotins are highly variable, due to differences in external exposure and metabolism. The highest observed levels are in dolphins, which lack metabolic capability and accumulate high levels of organotins in their body through food chains (Iwata et al., 1997; Lee, 1996). Levels are generally lower in invertebrates and in fishes. Although data are sparse, body burdens are high enough to suggest that there could be some risk to humans and certain marine mammals (Table 1).

Body burdens of TBT in the livers of Japanese males (taken from four people by autopsy in 1997/1998) were estimated to be 84 ng/g (Table 1; Takahashi et al, 1999 a & b). Interestingly, the relatively concentrations of butyltin compounds in liver and kidney is similar to those of methyl mercury. This suggests that their distributions are less dependent on their affinity to lipid than other persistent organic pollutants such as PCBs and DDT (Tanabe et al, 1981).

TBT and TPT also accumulate in livers and kidneys of nonhuman mammals. More than 10 g/g of butyltin ions, on a wet weight basis, were detected in the livers of dolphins collected in the semi-closed Seto Inland Sea, Japan, in 1985 (Iwata et al., 1997) and in the Gulf coast of the USA in 1989 (Kannan et al., 1997). They have also been found in the blubber and adrenal glands of coastal whales (Iwata et al., 1995), in the hair of sea lions and the feathers of common cormorants (Kim et al., 1996, Guruge et al., 1996). The lack of key metabolic enzymes in some cetaceans accounts for the differences observed in human and cetacean body burdens.

3.5 Analytical tools

Integrated assessment should be based on consistent and reliable sampling, preparation and chemical analysis techniques. In addition, common statistical designs and common approaches to estimating spatial and temporal variance are needed to allow global integration of human and ecological exposure estimation and modeling. This is an important area for international and interdisciplinary harmonization.

4. Characterization of Effects

4.1 Reported effects and mode of action

The extreme toxicity of TBT to molluscs and its peculiar and highly specific effects have raised concerns about toxic effects on humans and other organisms. Although toxicological profiles of organotin compounds are complex in both aquatic organisms and laboratory mammals, integration of knowledge of the diverse effects of organotin compounds in various

organisms will shed light to possible common mechanism of some effects in humans and nonhuman organisms. Recent reports support this notion as described below.

(1) Effects on aquatic organisms:

Toxicological profiles from conventional toxicity testing of aquatic organisms with TBT and TPT are presented in Tables 2A-D. The effects levels are low, but not remarkable for a biocide. The range of acutely lethal concentrations across species (700x), is also not particularly wide. However, some of the intraspecies variances in sensitivity are quite large. In particular, acute LC_{50} values in larvae and adults of the Pacific oyster *Crassostrea gigas* are 1.6 and 1800 μg/l for TBT while chronic larval mortality occurs at 0.05 μg/l and shell deformities occur at 0.02 μg/l (IPCS 1990, EPA 1997).. The effect of TBT that has made it remarkable is imposex in gastropods, which occurs at as little as one ng/l and affects at least 150 species (deFur et al. 1999). That effects level is less than a tenth of those observed in standard chronic toxicity tests (Table 2B). While imposex appears to be a result of perturbation of estrogen formation, the mechanism of action is still not clear (Oberdorster and Cheek, 2001). Symptoms of TBT toxicity in fish include thymus reduction, decrease in numbers of lymphocytes, and inhibition of gonad development (IPCS, 1999b). These symptoms suggest that studies on mechanism of action or field studies may reveal reproductive or other effects at lower concentrations than those reported from the subchronic tests of fishes conducted to date.

(2) Effects on laboratory mammals:

TPT and TBT produce various health effects in laboratory mammals, including effects on the immune system, such as decreases in immunoglobulin concentrations, lymphopenia, and thymus or splenic atrophy in rats and mice, reproductive/developmental effects (LOAELs: lowest-observed-adverse-effect-levels are mostly in the 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 with TPT (IPCS, 1999a, Table 2). Similar effects at similar concentrations were seen for TBT with a NOAEL (no-observed-adverse-effect-level) of 25 g/kg bw/day (IPCS, 1999b).

(3) Integration in multiple endpoints and multiple agents linked to action mechanism

Common endpoints, such as immunotoxicity found in both aquatic organisms and laboratory mammals appear to share common mechanisms of action. For example, immunotoxic action of organotins could partly be caused by cytoskelton modification in addition to perturbation of thymocyte Ca^{2+} homeostasis which may be linked to apoptosis of thymus cells caused at **5** μM level by TBT or DBT (Chow & Orrenius, 1994).

Proliferative responses of peripheral blood mononuclear cells of human and dolphins to coplanar PCBs and TBT were assayed after stimulation with different concentrations of mitogens (Nakata et al., 1998). Mitogen responses were inhibited at concentrations of 30 nM and 300 nM of TBT, in humans and marine mammals, respectively, whereas PCBs did not markedly affect the response at concentrations tested (2.7 pM -34 nM) in human cells.

Potentiation of ethoxyresorufin-o-deethylase (EROD) activity and cytotoxicity detected in rat hepatoma cells as a consequence of co-exposure to PCB and TBT is of considerable toxicological significance, given their co-accumulation in a variety of aquatic organisms (Kannan, et al, 1998).

In the case of reproductive effects, imposex in the gastropods was suggested to be related to inhibition of CYP (P450)1A1-dependent aromatase which catalyzes aromatization of androgen to estrogen (Bettin et al., 1996). However, it may also result from inhibition of other steroid-synthesizing enzymes or to direct effects on the neurohormonal system (Oberdorster and Cheek, 2001). The most sensitive reproductive effect in rats is implantation failure in early stage of pregnancy (Ema et al., 1997), which is not yet known to be related to the mechanisms suggested above.

TPT at micromolar concentrations induced calcium overload in rat pheochromocytoma cells, which caused internucleosomal DNA cleavage typical of apoptotic cell death (Viviani et al., 1995). As Ca^{2+} is involved in signal transduction in regulating various cellular activities, it could be possible that perturbation of Ca^{2+} homeostasis at the cellular level can cause a variety of effects at various concentrations depending on different critical concentrations of organotin compounds at the target organs.

Inhibition of ion transport, oxidative phosphorylation in mitochondria and cell membrane damage are suggested as other causes of organotin toxicity (Fent, 1996).

4.2 Biomarkers and indicators

Where appropriate populations of gastropods occur, the presence of masculinized female snails (imposex) may be used as a bioindicator of the presence of toxicologically significant levels of organotin compounds (Davies et al. 1987). Biochemical biomarkers of organotin exposure or effects may be developed, as mechanisms of action become better understood.

4.3 Direct and indirect effects

The deformities of oysters had economic effects on oyster farmers in France, which are likely to have had social and psychological sequella. Those effects and the observation of imposex in snails led to the restriction of TBT on small recreational and commercial craft. Those restrictions have associated costs due to the substitution of other antifouling paints, greater operating costs, and more frequent maintenance. If it is determined that organotins in seafood are significantly affecting humans and wildlife, indirect effects could result from restrictions of seafood consumption and from further restrictions on antifouling paints.

5. Risk Characterization

Risk is a function of the magnitude of exposure and the toxicity of the compounds. Risks to aquatic organisms have been characterized on the basis of aqueous concentrations. Risks to humans and piscivorous wildlife have been estimated based on concentrations in seafood and body burdens.

5.1 Combining exposure and effects: aquatic biota

Cardwell et al. (1999b) assessed risks from TBT to populations of aquatic organisms in the U.S. by comparing the distributions of acute and chronic effects benchmarks to the distributions of concentrations measured in seven harbors. They found that 25% of species in marinas were likely to experience death or decrements in growth or reproduction prior to 1989. However, by 1996, 6% of species in the sampled marinas experienced those risks. Hall et al. (2000) assessed risks from TBT to the aquatic ecosystem of the Chesapeake Bay by comparing the distributions of acute and chronic effects benchmarks to the distributions of concentrations measured at various localities in the Bay. Significant risks of chronic effects were found in several locations.

The authors of both of these assessments limited themselves to standard toxicity data and standard risk characterization methods, which are derived from methods for calculating water quality criteria. Because this practice excluded imposex and shell deformities, the assessments did not include the very effects that led to the restrictions on use of TBT. Cardwell et al. (1999b) dismissed these effects as biomarkers, which had no population-level consequences. As a result, thresholds for significant risks in the assessments (5 and 10 ng/L) were above the 1ng/L threshold for imposex (Hall et al. 2000, Cardwell et al. 1999). One might argue that the fact that imposex and shell deformities prompted a specific act of the U.S. Congress and similar responses in other countries is sufficient grounds for including those effects as endpoints. Further, the severe economic effects of oyster deformities on oyster fishermen suggest that nonstandard effects may be significant. Further, imposex does have consequences for reproduction, which have not been demonstrated in standard tests. Hence, risks to aquatic organisms are greater if the specific adverse effects of TBT are included in the assessment.

These risk characterizations focused on TBT release from boats. They did not explicitly consider other uses of TBT or other organotins. For example, the use of TBT as a molluscide to control schistosomiasis has resulted in severe effects on fish (Seinen et al. 1981). Because some fish are as sensitive as snails, such effects are to be expected (Seinen et al. 1981).

5.2 Combining exposure and effects: humans and piscivorous wildlife

Daily intake values of TPT and TBT for Japanese can be compared with the acceptable daily intake (ADI) of the World Health Organization (0.5 μg /kg bw/day) which corresponds to 25 μg /day for a Japanese person of 50 kg bw, and a guidance value evaluated by the Final Review Board of the IPCS for the CICAD on tributyltin oxide (TBTO) (0.3 μg /kg bw/day)

which corresponds to 15 μg /day per a Japanese person of 50 kg bw, to be 33.4% and 10.8%, respectively (when combined sums up to 44.2%). Since TBT and TPT exert similar toxicities to humans and organisms in the environment, combined risk from coexposure to TPT and TBT must be taken into account considering their use patterns and amount of use (IPCS, 1990; Sekizawa, 1998).

Cardwell et al. (1999) and Keithly et al. (1999) performed similar risk characterizations for people consuming fish in the North America, Asia, Australia and Europe. Using a 70 kg body weight, they found that geometric mean daily intakes of TBT were 0.9% (United Kingdom) to 12% (Korea) of the 0.3 μg TBT/kg/day tolerable dose. They analyzed a relatively small number of mostly pelagic species, which are less polluted because they live in the open ocean. In contrast, the Japanese study included various food items purchased from markets in various cities and composite foods prepared according to average food intake of recent years to estimate mean intake of various locations in the country. Since several organisms such as squids and dolphins from coastal waters of France, USA and Japan were shown to be similarly contaminated with TBT and TPT, it is probable that the apparent difference in the results between Keithly et al (1999) and the Japanese survey are primarily due to the seafood items analyzed. TBT levels causing inhibition in this study are close to those found in the marine mammals inhabiting coastal waters in Japan and North America that some populations of coastal cetaceans may be at risk of immunotoxicity.

Because of their exclusively piscivorous diet, many birds and mammals are more at risk than humans from dietary exposure to organotins. Some marine mammals, such as Dall's porpoise are devoid of CYP enzymes, which can break down TBT and DBT to MBT, and current levels of organotin body-burden are high enough to cause immune deficiency in those animals increasing their susceptibility to opportunistic infections (Tanabe, 1998; Nakata et al, 1998). In addition, organotin compounds are shown to elicit synergistic effects with PCB (Rice & Rozwell, 1998), which occur at high levels in piscivorous birds and mammals all over the world. However, these risks have not been quantified.

5.3 What is integrated?

The use of a common toxicity data set and common data on organotin concentrations in seafood to assess risks to humans and wildlife is an obvious form or integration. Such an assessment has not been performed, but the human risks are high enough to suggest a significant risk to piscivorous wildlife, particularly in ports and harbors. The 100% fish diet of these organisms and the fact that their sensitivity may be greater than laboratory mammals is cause for concern. Birds are commonly more sensitive than mammals.

The inclusion of imposex in molluscs as an endpoint effect may constitute a more subtle form of integration. While ecological risk assessors excluded this effect as not ecologically appropriate, the public and law makers appear to have made an analogy to humans and determined that development of male genitals in a female organism is adverse. That is, nonscientists performed an integration of health concerns and observed ecological effects that

bypassed conventional ecological criteria for declaring an effect to be adverse. Similarly, the deformities in oysters became endpoints in regulatory assessments both because of an implicit analogy to human deformity and because of the socioeconomic significance.

Mechanistic toxicology is another potential area for integration. The rather unusual and specific effects of organotins in molluscs suggests that a mechanistic understanding of the effects of organotins might reveal the potential for effects that are not detected in conventional mammalian or ecological toxicology.

The immunotoxic effects of organotins highlight the need for improved methods in risk assessment for that mode of action. Currently it is not feasible to predict the health consequences of a change in immune function or structure or to determine whether observed epidemics or epizootics were enhanced by immunotoxic chemicals. An integrated approach to this problem should be fruitful and efficient.

5.4 Determining causation

The concern for risks to aquatic biota from TBT originated with observations of effects on molluscs. The cause of these effects were determined by associating the effects spatially and temporally with the use of antifouling paints, by demonstrating effects in controlled laboratory exposures, and by demonstrating that effects in the field were associated with body burdens of TBT similar to those in affected organisms in the laboratory. Similarly, mortality of fish was associated with the use of TBT as a molluscicide and subsequent laboratory studies confirmed that TBT was a sufficient cause for those effects (Seinen et al. 1981). Some effects on piscivorous wildlife have been observed which, from circumstantial evidences, can be related to exposures to pollutants including organotins. A similar approach to determining causation, based on the weighing of laboratory and field derived data, should be employed when such effects are suspected.

5.5 Uncertainty and variability

Conventional ecological toxicology, and the risk assessments that rely on it, are uncertain due to the limited number of species and responses that are measured. This is illustrated by the observance of imposex and shell deformities in field populations, but not in standard tests. This suggests that other effects may be missed.

The immunotoxicity of organotins poses uncertain risks. Given current knowledge, it is not possible to predict the effects of a particular change in immune system structure or function. It is also not possible to confidently associate epidemics or epizootics with contamination by organotins or any other immunotoxic chemical.

Market basket studies in Japan show that there was about a two-fold variation in intake estimates between the national average value and that of local governments in the 1990-1993 period (Tsuda et al., 1995). Since there will be people who eat much more seafood than average,

variability in intake will contribute to variability in risks among populations, and this uncertainty in risks must be taken into consideration in protecting different populations (Sekizawa, 1998).

5.6 Presentation of results

The results of an integrated assessment of health and ecological risks should be presented in a consistent manner. That is, similar graphical, tabular and textual presentations should be used so that the current risks and consequences of action for humans and ecological receptors are clear and readily compared or combined.

6. Risk Communication

The history of TBT regulation constitutes a useful case study in risk communication. Early regulations of TPT and TBT as pesticides, in occupational settings, or in use for consumer products were based on human observations and animal studies. However, the use of TBT as antifoulants for boats and fishing nets was restricted based on demonstrated effects on nonhuman organisms without any indication that humans were at risk from this source. The affected species were invertebrates and therefore neither similar to humans nor aesthetically appealing. The public acceptance of regulatory action seems to suggest that humans are defining their interests broadly and are likely to see consequences for themselves in even the lowliest organisms, particularly if the effects are vivid. This suggests that risk communication for all chemicals should present health and ecological risks in an integrated fashion. If risk assessors do not explain the relationships in a coherent fashion, the public is likely to make its own inferences. For example, if the effects of TBT on sexual development of molluscs do not imply analogous effects in humans, those differences must be elucidated and clearly communicated.

More generally, a holistic approach to risk communication is imperative to effective risk management. It should facilitate environmental decision making by providing a consistent and coherent set of human and ecological risk estimates to help identify priorities in action. Communication of the results in a consistent and integrated manner to risk managers and stakeholders will support their understanding of assessment results and the impacts of possible management actions.

7. Risk Management

Existing environmental controls of organotin compounds as antifoulants are based mostly on incidental findings of localized effects on molluscs, particularly reproductive failure and deformity of snails and oysters. Following the lead of France, most developed countries banned or restricted the use of organotin compounds on for small boats (typically those less than 25 m in length). Their use on larger boats was continued due to the large economic benefits. TBT concentrations in Tokyo bay appeared not to decrease further after complete ban of use in Japan in 1990, probably because boats from countries where regulations are not such tight sail in the area. In many developing countries organotins are not regulated. Although monitoring has shown that local organotin levels have greatly declined as a result of regulation, unregulated

boats travel all over the world and release organotin compounds. In addition, organotin-containing paint is released during ship scraping and repainting.

In this context, regional and global scale pollution by both TBT and TPT need to be taken into account. For example, local management actions restricting use of organotin antifouling paint are less effective if boats from areas permitting such paint utilize the same area. In addition, the processes of global hydrological and meteorological circulation, which have distributed organochlorine chemicals, may also result in surprising distributions of organotins.

In addition to their use in anti-fouling paints, organotin compounds are used as fungicides and molluscicides (the use was prohibited rather early in Japan). They also occur in plastic products, some of which contaminate foods as reported by Takahashi et al. (1999b) who detected elution of dibutyltin during oven baking from cooking sheets used to wrap baked cakes. This implies that, for every application, the amount of use of organotin compounds, which may potentially contaminate the environment and food, needs to be surveyed and examined for counter measures to be effective.

The toxicity of organotins, their persistence, and their continued use make them chemicals of concern. The possibilities of combined effects of different organotins, their global distribution and novel specific toxic effects; suggest the need for integrated research and risk assessment. Without globally integrated assessments followed by appropriate counter measures, risk to humans and other organisms may not be sufficiently diminished.

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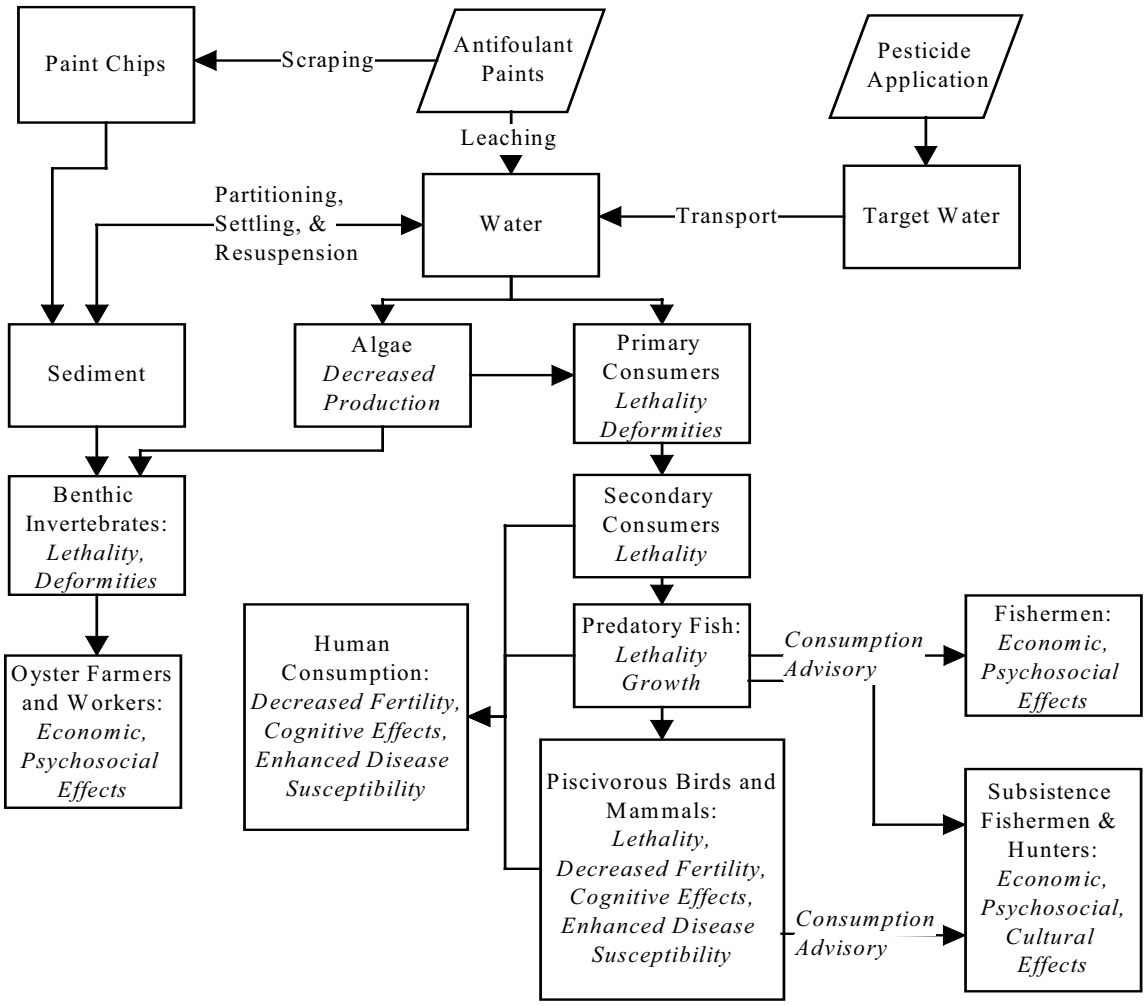

Fig.1 A conceptual model for exposure and effects of humans and marine mammals to tributyltin and triphenyltin compounds

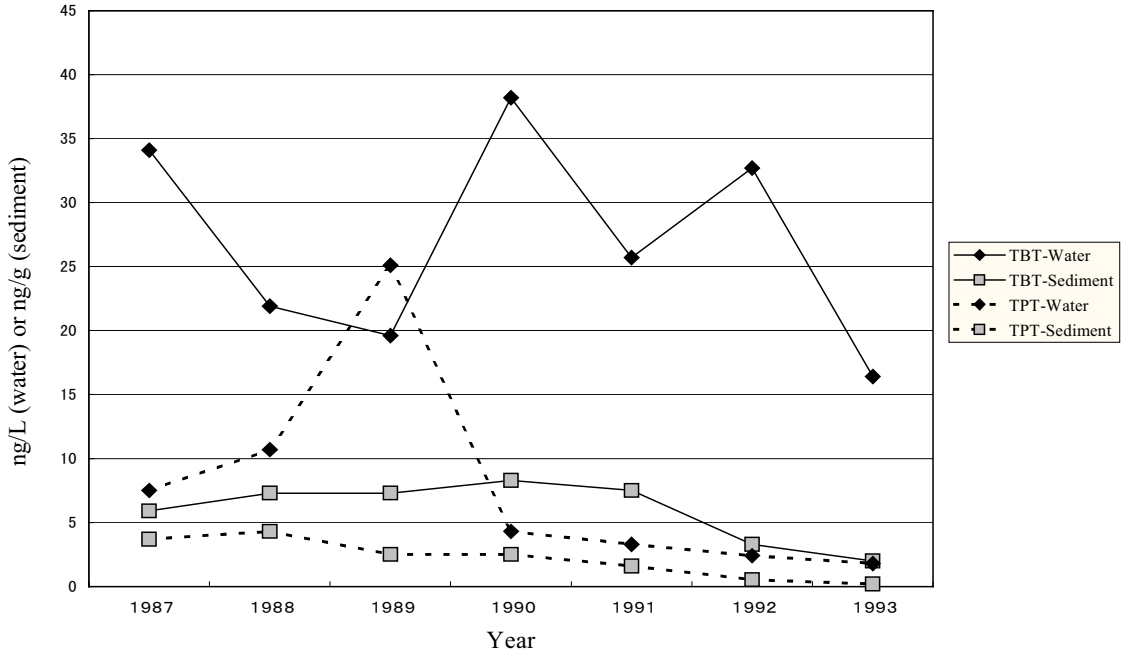

Fig. 2 TBT and TPT concentrations in Tokyo bay area
(National Committee for CICAD)

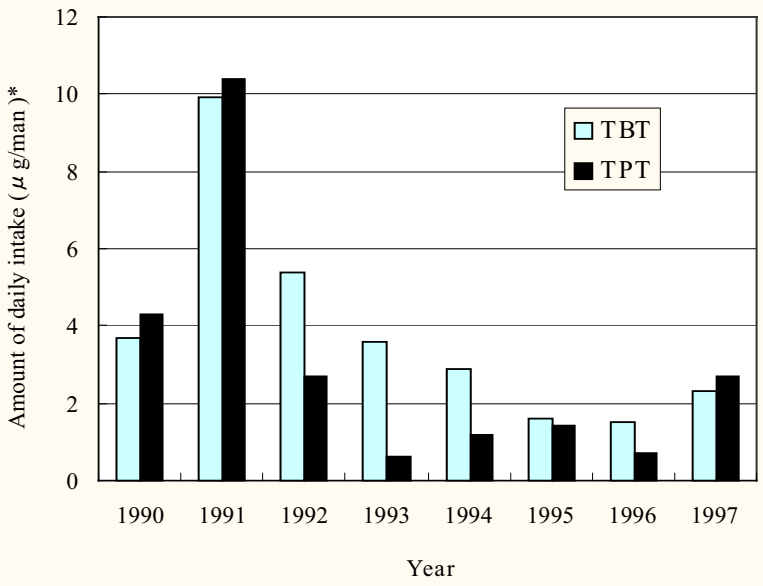

Fig. 3. Estimation of daily intake of TBT and TPT in Japan by the market basket method.

* as triphenyltin chloride or tributyltin chloride

Table 1 Environmental fate, exposure and body burden of humans and organisms in the environment with TBT and TPT
(prepared from IPCS, 1999 a & b and EPA 1997)

	TBT	TPT
Concentrations in the surface water	up to 7.1 μg/l (fresh water area); up to 1.58 μg/l (sea water area)	nearly 200 ng/l (bays & marinas)
Bio-concentration factor	100 - 30,000 in bacteria & algae, 2,000 - 180,427 in molluscs, 24- 1976 in whole fish	32,500 in intestinal sac of a fresh water snail, 7000 in Pacific oyster 257- 4100 in whole fish
Average daily intake (market basket survey)	2.3 μg/day/person (as chloride) in Japan in 1997	2.7 μg/day/person (as chloride) in Japan in 1997
Body burden in liver	84 ng total butyltin compounds/g wet weight - of which 79% were DBT for humans; up to 11,340 ng/g wet weight for dolphins	

Table 2A Concentrations of tributyltin compounds lethal to aquatic organisms (data from IPCS, 1999a, EPA 1997 and Hall et al. 2000)

Taxon (number of tested species)	Criterion	Effective Concentrations (g/l)
Echinoderms (1)	96 h LC_{50}	0.42
Saltwater rotifer (1)	24 h LC_{50}	300
Freshwater rotifer (1)	24 h LC_{50}	19
Freshwater hydrozoans (3)	96 h LC_{50}	1.1 - 1.8
Saltwater molluscs (6)	48-96 h LC_{50}	0.71 - 1800
Freshwater molluscs (4)	24-96 h LC_{50}	12 - 110
Saltwater crustaceans (18)	24-96 h LC_{50}	0.42 - >15
Freshwater insects (3)	24-96 h LC_{50}	3.3 - 16
Saltwater annelids (2)	96 hr LC_{50}	2.0 - 6.8
Freshwater annelids (1)	96 hr LC_{50}	5.4
Saltwater amphioxus (1)	96 hr LC_{50}	<10
Saltwater fishes (9)	48-96 hr LC_{50}	1.5 - 17
Freshwater fishes (5)	96 hr LC_{50}	1.3 - 7.2

Table 2B Chronic or subchronic sublethal toxicity of tributyltin compounds to aquatic organisms (data from IPCS, 1999a, EPA 1997, and Hall et al. 2000)

Organism	Criterion	Effective Concentration (g/l)[1]
Freshwater algae (3 species)	IC_{50} (primary production)	10 - 15
Saltwater algae (5 species)	IC_{50} (primary production)	0.92 - 320
Acartia tonsa (Copepod)	6 day	0.014
Euryptemora affinis (Copepod)	13day Life Cycle test	<0.088 & 0.15
Acanthomysis scuppta (Mysid)	63 day Life Cycle test	0.13
Daphnia magna	21day Life Cycle test	0.14 & 0.25 (2 tests)
Mytilus edulis (Mussel)	33 day CV	0.017
Crassostrea gigas (Pacific oyster)*	Chronic larval mortality Shell thickening	0.05 0.02
Nucella lapillus (Atlantic dogwinkle)*	2 year Life Cycle tests	0.002 (imposex and sterility)
Rainbow trout fingerlings	110 day subchronic	0.2 (histopathology & 20% growth reduction
Pimephales promelas (fathead minnow)	33 day CV, Early Life Stage test	0.26

* marine and estuarine species

[1] Effective concentrations, except where noted, are chronic values (CVs) which are the geometric means of No Observed Effect Concentrations (NOECs) and Lowest Observed Adverse Effects Concentrations (LOECs).

Table 2C. Acute toxicity of triphenyltin compounds to aquatic organisms (modified from IPCS, 1999a)

Organism	Criterion	Levels and/or Note
Debaryomyces hansenii (yeast)	Minimal Inhibitory Concentration	5 μg/ml
Ankisrodesmus (fresh-water alga)	4hr IC_{50} for primary productivity	10 μg/l, static condition, at 20C
Skeletonema costatum: major component of fouling slime*	EC_{50} for carbon fixation, and LC_{50}	0.92 μg/l, and 13.8 μg/l
Daphnia magna (water flea)	48 h LC_{50}	10 μg/l
Nitrocra spinipes (harpacticoid copepod)	96 hr LC_{50}	8 μg/l
Eight fish species	96 hr LC_{50}	*Pimephales promelas* (fathead minnow) most sensitive species, 7.1 μg/l
Pagrus major (red sea bream)*	48-hr LC_{50}	12.6 μg/l

* marine and estuarine species

Table 2D Chronic/subchronic toxicity of triphenyltin compounds to aquatic organisms (modified from IPCS, 1999a)

Organism	Criterion	Levels and/or Note
Natural community of fresh water algae	50% reduction of reproduction and primary production	2 μg/l, Indigenous algae more sensitive than pure cultures
Daphnia magna	21days No-Observed-Effect Concentration	0.1 μg/l
Lymnae stagnalis: a fresh water sludge snail	9 days LC_{100}, or deficiencies in growth, mobility, and embryo development after 5 weeks exposure	10 μg/l for LC_{100}, and 2 μg/l for deficiencies
Thais clavigera (Japanese rock shell)*	Imposex: RPL (relative penis length) in female	RPL significantly increased with injection of 0.1 μg TPT/g wet tissue and culture for 30 days, or at 1 ng/l in water.
Pimephales promelas (fathead minnow)	30-day LC_{50}, NOEC, and LOEC (Lowest-Observed-Effect Concentration)	1.5, 0.15, and 0.23 μg/l, respectively

* marine and estuarine species

Table 3 Health effects of triphenyltin compounds (modified from IPCS, 1990a & b)

Type of test	Organisms (route of exposure, duration of test)	Results/remarks
Single exposure	Rat (oral)	LD_{50} 160 mg/kg
Short term	Dog (oral, 52 weeks)	NOAEL: 0.21 mg/kg bw/day, based on relative liver weight decrease at effect levels;
	Rat (dermal, 29 days)	NOAEL: 10 mg/kg bw/day, based on erythema, mortality, lymphocyte decrease at effect levels,
	Rat(inhalation, 4-weeks)	NOAEL: 0.014 mg/m^3 based on IgM (an immuno-globulin species) increase at effect levels
Long-term	Mouse (feeding, 80 weeks)	NOAEL: 0.85-1.36 mg/kg bw/day, based on decreased body weight at effect levels;
Genotoxicity	In vivo/In vitro	Mostly negative
Reproduction	Rat (feeding, two generation)	NOAEL: 0.4 mg/kg bw/day, based on decreased litter size, pup weight, relative spleen/thymus weight in weanlings at effect levels
Teratogenicity	Rabbit (gavage, day 6 to day 18 of gestation)	NOAEL for maternal toxicity: 0.1 mg/kg based on decreased body weight gain
Immunotoxicity *	Rat (feeding, two years)	Immunosuppresive. LOAEL: 0.3 mg/kg bw/day, based on reduced immunoglobulin levels and reduction in white blood cell count
Neurotoxicity	Rat (gavage, 6 weeks)	Toxic at 0.36 mg/kg bw/day in maze learning test

* With tributyltin oxide, when weanling rats fed orally up to 4.5 months, NOAEL was 0.025 mg/kg bw/day, based on the depression of IgE titres and impairment of clearance of injected *Trichinella spiralis* at effect levels

D. Organophosphorous pesticides in the environment

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Abstract:

This study was chosen as an example of integrated risk assessment because organophosphorous esters (OPs) share exposure characteristics for different species, inc luding human beings and because a common mechanism of action can be identified. The "Framework for the integration of health and ecological risk assessment" is being tested against a deterministic integrated environmental health risk assessment for OPs used in a typical farming community. It is argued that the integrated approach helps both the risk manager and the risk assessor in formulating a more holistic approach towards the risk of the use of OP-esters. It avoids conclusions based on incomplete assessments or on separate assessments. The database available can be expanded and results can be expressed in a more coherent manner. In the integrated exposure assessment of OPs, the risk assessments for human beings and the environment share many communalities with regards to sources and emissions, distribution routes and exposure scenarios. The site of action of OPs, acetylcholinesterase, has been established in a vast array of species, including humans. It follows that in the integrated approach the effects assessment for various species will show communalities in reported effects and standard setting approaches. In the risk characterisation, a common set of evidence, common criteria, and common interpretations of those criteria are used to determine the cause of human and ecological effects that co-occur or are apparently associated with exposure to OPs. Results of health and ecological risk assessments are presented in a common format that facilitates comparison of results. It avoids acceptable risk conclusions with regard to the environment, which are unacceptable with regard to human risk and vice versa. Risk managers will be prompted to a more balanced judgement and understanding and acceptance of risk reduction measures will be facilitated.

1. Background

This study was chosen as an example of integrated risk assessment for two reasons: first because organophosphorous esters (OPs) share exposure characteristics for different species, including human beings, such as sources, emissions, distribution and pathways of exposure, and secondly because a common mechanism of action can be identified. Similarities in exposure and effect provide a means of evaluation and comparison across species. Additionally, other types of integration such as cumulative and aggregated exposure can be considered for OPs. Aggregate and cumulative exposure to OPs is relevant in integrated approaches since both humans and environmental species can be exposed through various, not seldom common pathways of exposure to OPs, which are believed to share a common mechanism of action.

The US-NRC (NRC, 1993) performed a risk assessment for children exposed through residues in food to 5 commonly used organophosphates (OPs:acephate, chlorpyrifos, dimethoate, disulfoton, ethion) and used actual data on their presence on eight foods and three juices to explore the development of methods for assessing exposure to multiple chemicals. Recently the US-EPA (2001) released a preliminary OP cumulative risk assessment for 24 OPs incorporating exposure of humans via food, drinking water and residential/non-occupational pathways

In this case study information package the possibility is explored to include other routes of human exposure (direct exposure, exposure via the environment) and exposure of aquatic, terrestrial and wildlife species. The analysis includes the use of both monitoring and modelling results. The aim therefore is to explore:

1. The integration of risk assessments for man and the environment (integrated and aggregated exposure)
2. The integration of risk assessments of several OPs together (cumulative exposure).

2. Problem Formulation

2.1 Impetus for the assessment

Organophosphorous pesticides (OPs) are widely used pesticides and are believed to act through a common mechanism of action. There are ample reasons for integrating research and risk assessments for the OPs. OP exposure pathways overlap for many wildlife species and humans. For example, the spraying of crops with OPs can cause pesticide drift to nearby communities. Similarly, pesticide run-off into water bodies can cause harmful effects on aquatic species, terrestrial species that forage around water bodies, and humans that reside or recreate in the vicinity. OP contamination of well water can harm humans, long after the adverse impact of spraying on wildlife has occurred. In many instances it may be possible to use wildlife species as sentinels of the imminent or impending risks of OPs to human health. In addition, the site of action of OPs (acetylcholinesterase) has been well established in a vast array of species, including humans. Moreover, cholinergic receptors, which are stimulated indirectly by cholinesterase inhibition, are found throughout most taxonomic groups of animals.

The risk manager may have been made aware of the fact that, although exposure to a single compound may not exceed the level considered to be without acceptable risk for either humans or environmental species, concurrent exposures to numerous OP-compounds could exceed a safe level because of increased ChE inhibition. Moreover, absence of a probable risk for one species, e.g. man, does not automatically imply absence of a probable risk for other species.

These considerations will prompt the risk manager to formulate a question to risk assessors advocating an integrated approach and, if needed, a risk reduction strategy benefiting all organisms.

2.2 Assessment questions

The risk manager will work out the basic questions to be addressed together with the risk assessor. In this particular case the question may look like this:
Given the considerations above (see under 'Impetus for the assessment'), present a deterministic, integrated environmental health risk assessment for a group of commonly used OPs in a typical farming community. This local scale assessment should consider the risk for humans, wildlife and other environmental species resulting from both direct and indirect exposure at and following application of OPs. The assessment should include both short-term and long-term risks. Poisoning is not considered in this case information package. Integration is not always needed: the risk manager finally decides on the issues of concern in the problem formulation stage.

2.3 Assessment endpoints

Coherence in endpoints used to assess health and ecological risk can be specified for this case to pertain to acetylcholinesterase inhibition and differences in susceptibility in man, wildlife, aquatic species and terrestrial species as a result of exposure via dietary and non-dietary sources. Cholinesterases as the site of action of OPs have been identified in a vast array of species, including humans, but not in plants and microorganisms. Cholinergic receptors, which are stimulated indirectly by cholinesterase inhibition, are found throughout most taxonomic groups of animals. Though acetylcholinesterase inhibition in itself is not an adverse effect, studies have been performed in different species to investigate the relation between toxicity and cholinesterase inhibition.

2.4 Conceptual models

The conceptual model involves sources and pathways of exposure of:

1. Environmental organisms and applicators directly exposed after spraying/granulate treatment; this route includes exposure of water- and sediment organisms, and perhaps by-standers, via spray drift.
2. Environmental/domesticated organisms and humans indirectly exposed via
   ?? (residues in) food derived from crops on which the pesticide is applied directly

?? crops, ambient air, and soil in non-target areas
?? indoor air/surfaces during and following use of OPs in sprays/foggers/etc. and perhaps via medication and personal care products (head lice treatment, via contaminated lanolin). This route obviously only is applicable to man and domesticated animals.

The conceptual model for the local problem may be put in a wider context of a regional or watershed approach.

2.5 Analysis plan

An integrated approach offers substantial opportunities for more efficient data gathering activities. This case offers the following opportunities:

1. Sharing of data on emissions,
2. Sharing of distribution, fate and exposure models and the parameter values and distributions needed for these models,
3. Sharing of data on concentrations in environmental media and food
4. Sharing of analytical activities to obtain the data mentioned above
5. Sharing of toxicokinetic and physiologically-base pharmacokinetic models
6. Sharing of dose-response models for ChE-inhibition
7. Sharing of analytical activities to obtain information on dose-response and variability across and within species.

2.6 Summary

An integrated approach already offers advantages in the problem formulation stage:

1. It helps both the risk manager and the risk assessor in formulating a more holistic approach towards the risk of the use of OP-esters. It avoids conclusions based on incomplete assessments or on separate assessments using unnecessarily different assumptions, parameter values, distribution and fate models and exposure scenarios.
2. It helps in identifying opportunities in increasing the database available for both the human and the environmental risk assessment risk (increased efficiency/resource-effective)
3. It helps to identify a coherent expression of the results across species in terms of exposure (common pathways), adverse effects (in relation to ChE-inhibition), dose response and eventually the risks.

3. Characterisation of Exposure

3.1 Sources and emissions

In an integrated approach it is useful to consider the whole life cycle of OPs and all possible sources. This inventory will allow a well-founded selection of sources and relevant life

cycle stages with potentially significant emissions. The expertise required here is the same for both the human and the environmental RA.

Potentially, emissions of OPs can occur at production, formulation, use and disposal. For convenience, we will leave out production, formulation and disposal in our example, assuming these processes occur outside the geographic area of interest. Specifically, the exposure assessment concentrates on sources and emissions following use of OPs as pesticides and biocides. Sources with possible emissions to the environment or direct exposure can be identified at spraying or application of granulates in agriculture, use in dips in animal husbandry, use as a biocide and use in medications (NRC, 1993). Biocidal uses include use in indoor sprays and foggers and in flee control products for pets. OPs are used medicinally in head lice treatment products. Residues of OPs may be present in lanolin originating for sheep treated in dips.

3.2 Distribution pathways

See Figure 1 below.

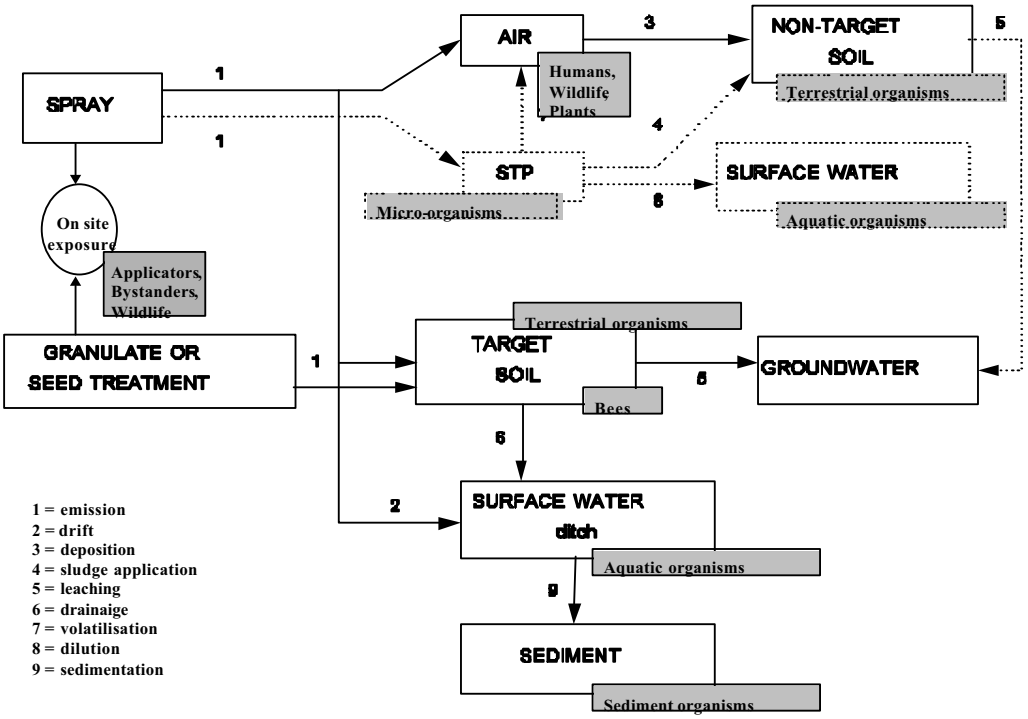

Fig. 1: Distribution routes for agricultural pesticides. Grey boxes contain the receptor organisms; dotted lines and boxes are used if the only release is via the Sewage Treatment Plant (STP)

Figure 1 shows distribution towards the environmental media ambient air, soil, surface water, groundwater, sediment, and soil.

Communalities: see section 3.4 ‘External and internal exposure models’

3.3 Transport and fate models

Data needed are measured concentrations in the environmental compartments or input for distribution models to estimate environmental concentrations. The latter requires physico-chemical properties, partition coefficients, degradation rates, deposition rates, and environmental characteristics (Van Leeuwen and Hermens, 1995). General local distribution screening model specific for agricultural and non-agricultural pesticides are available (e.g. RIVM et al., 1999).

3.4 External and internal exposure models

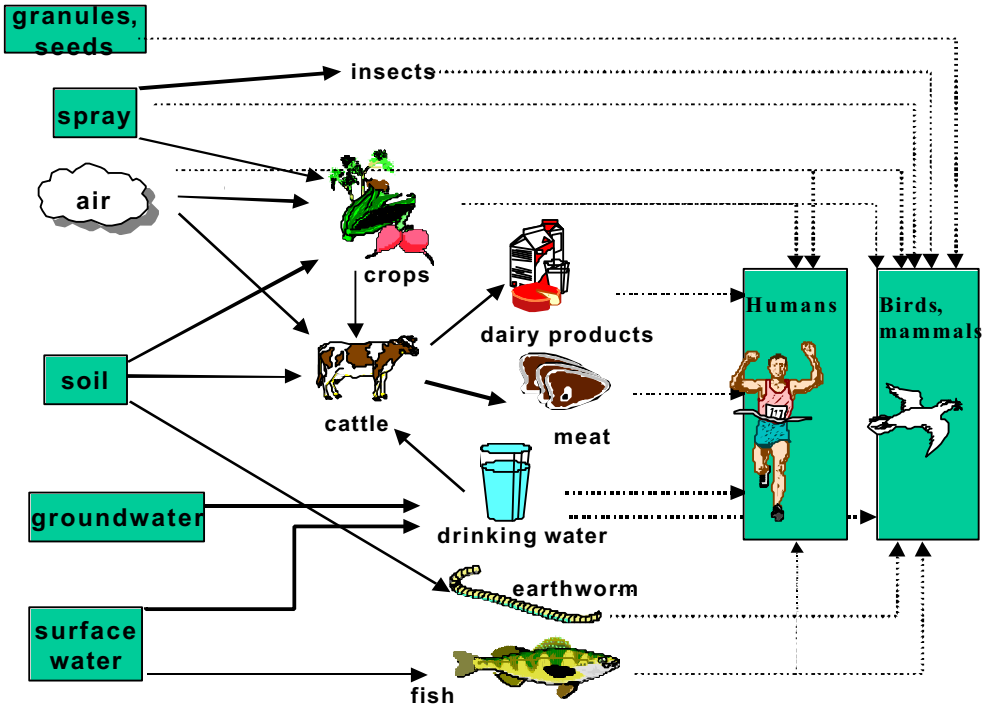

Fig. 2: Schematic representation of possible routes of environmental exposure of humans and wildlife

Examples of common distribution and exposure routes, sharing common transport models, fate models and monitoring data:

- ?? Direct exposure of applicators, by-standers and wildlife and invertebrates to OPs in spray drift;
- ?? The route from OPs spray application towards surface water leading to exposure of aquatic organisms and, through drinking water and food, of human beings, birds and mammals;
- ?? The route from OPs application towards non-target soil leading to exposure of terrestrial organisms and, through crops and drinking water prepared from groundwater, of human beings, birds and mammals;

Figure 2 shows possible routes of environmental exposure of humans and wildlife Further communalities can be found in the estimation of aggregate exposure

of human beings, wildlife and birds through food (oral), drinking water (oral) and air (inhalation, dermal). Cumulative exposure to several OPs together is an issue relevant to both human beings and wildlife.

Direct exposure estimation need quantification of the potential exposure in the form of concentrations in the exposure media that may contact the human body. Quantification may follow from exposure data. Otherwise, simple models may be applied to obtain a reasonable worst case prediction of the exposure. This modelling involves quantification of the contact with the exposure media containing the substance by defining exposure routes and exposure patterns, including contact durations, contact frequencies and site of contact. Both a chronic exposure measure and an acute exposure measure may be needed, depending on the expected effects and exposure patterns. Consumer exposure models are available and may be modified to be applicable to wildlife as well (Van Veen, 1996; Van Veen 1997; Pandian et al., 1997; EC, 1997). Local screening models for the estimation of environmental exposure of man and other organisms to pesticides are also available (e.g. RIVM et al., 1999). This estimation involves bioaccumulation and biotransformation models (Van Leeuwen and Hermens, 1995). Aggregate exposure assessment methodology is specifically addressed by ILSI (1998). There is little experience with cumulative exposure methodology. With respect to OPs, a cumulative risk assessment has been published by NRC (1993) and recently by the US-EPA (US-EPA, 2001).

Most risk assessments dealing with OPs rely upon the administered dose or the external dose because of insufficient understanding of how to estimate the internal dose and the relation between the internal dose and effects. In some cases, however, PBPK models may be available and may be used for a risk assessment based on the internal dose for human beings or wildlife (Paustenbach, 2000).

3.5 Measures of exposure related parameters

Examples of not-receptor-specific parameters with common values and units are:

- Emission rates: e.g. the fraction of the amount of OPs applied in kg per ha, emitted to air and water at spraying;
- Concentrations in environmental media: e.g. Predicted Environmental Concentrations (PECs) in air, soil and surface water;
- Biotic and abiotic degradation/disappearance rates in environmental media: e.g. the rate of biodegradation in soil and surface water, the rate of hydrolysis and photodegradation, the rate of volatilisation, resuspension, and sedimentation;
- Characteristics of environmental compartments: e.g. the fraction organic carbon in soil and sediment, temperature, rainfall, dilution rates, water flows etc.;
- Partition coefficients: e.g. the octanol-water partition coefficient and the air-water partition coefficient.

3.6 Analytical tools

Integrated exposure assessment requires the application of the same quantitative methods such as methods for sensitivity and uncertainty analysis. Monitoring of environmental media, drinking water and food (target and non-target crops) is relevant both for the human and the environmental risk assessment of OPs. Monitoring strategies for OPs should, however, consider the spatial and time scales relevant for common exposure routes e.g. consider the need for local, short-term concentrations in surface water as medium of exposure for fish, mammals and birds just after spraying and the need for long-term averages at a larger spatial scale to estimate the exposure of birds, mammals and human beings (following treatment) away from the application area.

3.7 Summary

In an integrated exposure assessment of OPs, the risk assessments for human beings and the environment share many communalities with regards to sources and emissions, distribution routes and exposure scenarios. Taking these into account will be an efficient way to deal with the risks to all organisms, including humans. Monitoring efforts can be more cost-effective.

4. Characterisation of Effects

4.1 Reported effects and modes of action

Organophosphates (OPs) are widely used pesticides that are applied primarily to crops for the control of agricultural pests, as well as in and around residences and offices for the control of urban pests. OPs are also one of the two major classes of cholinesterase-inhibiting pesticide. The main mode of action of the OPs is inhibition of acetylcholinesterase, the enzyme that terminates the action of acetylcholine neurotransmitter, which is released by nerve stimulation, on postsynaptic cholinergic receptors in the nervous system. OPs produce an irreversible inhibition of acetylcholinesterase, in contrast to the carbamates (the second major class) that produce a reversible inhibition.

Since the principle site of action of OPs is the nervous system, it is not surprising that OPs have produced a variety of toxic effects. These effects have been documented in humans, laboratory animals and several wildlife species (aquatic and terrestrial), due to either accidental or intentional exposures (Ecobichon and Joy, 1994; Mineau, 1991). Acute exposures produce a well-known syndrome of autonomic distress including salivation, lacrimation, urination and defecation (the SLUD syndrome). In addition, acute exposure compromises neuromuscular function, decreases motor activity and body temperature, and alters cardiovascular function.

Extremely high doses produce convulsions and death, due to interference with brain-stem structures involved in respiration.

Acute exposure to some OPs also produces a delayed neuromuscular effect, seen mainly in the extremities, which is irreversible and can lead to paralysis (Johnson, 1975). Organophosphate-induced delayed neuropathy (OPIDN) has been shown in several susceptible species, including birds and humans, although the basis for species differences in sensitivity is unknown at this time.

Repeated exposure to OPs can produce tolerance to the acute effects due mainly to a down-regulation of muscarinic cholinergic receptors in the central nervous system. While the observation of tolerance may indicate a reduced risk of exposure, there may be residual risk factors that are operative. For example, organisms made tolerant to an OP are often more sensitive to the effects of muscarinic blocking agents (e.g., belladonna alkaloids). Furthermore, available evidence indicates many OPs are not interchangeable; tolerance to one OP may either confer tolerance to another, have no effect on the actions of another, or may increase susceptibility to still other OPs (Costa and Murphy, 1983).

Currently, there is much concern over age-related susceptibility to the OPs (NRC, 1993). Evidence in support of this concern comes mainly from studies on laboratory rodents, although there is considerable evidence of developmental toxicity in avian reproduction studies (Mineau et al., 1994).

4.2 Biomarkers and indicators

Since the main mode of action of OPs is inhibition of acetylcholinesterase, enzyme inhibition has been widely used as biomarker of exposure in both human-health and ecotoxicology research. Whether enzyme inhibition can be used as a biomarker of effect, on the other hand, is debatable. One complication for arriving at a consensus is the observation of a threshold for inhibition above which toxic effects are produced. For example, it is widely assumed that toxic effects ensue only when the inhibition exceeds 20% in brain. Reviews of the literature, however, provide little empirical support for such a sweeping generalisation. As a consequence, little concerted effort has so far been made at exposure – response modelling.

Despite the advantages of integrated risk assessments for OP pesticides, some caveats are in order. For example, there are numerous methods used to determine OP-induced cholinesterase inhibition. There are, however, no clear indications at this time on the comparability of the inhibition as determined by the different analytical methodologies. In addition, there are a number of other esterases that OPs inhibit to varying degrees. Some of these esterases are considered sinks for OPs that diminish the inhibition of acetylcholinesterase. Understanding the relative abundance and activity of esterases in general will be necessary in order to make firm predictions of risk in receptor species.

4.3 Exposure-response modelling

Since OPs produce systemic toxicity, involving primarily the nervous system, the Reference Dose (RfD) approach is widely used for OP standard setting (see MacPhail and Glowa, 1999 for details). A RfD is calculated by dividing a no-adverse-observed-effect level (NOAEL) by a series of uncertainty factors (UFs). Similar approaches are being applied to determine no-effect levels for environmental organisms using NOAELs, NOECs (No-Observed-Effect Concentrations), LC50's or EC50's. These approaches generally ignore the shape of the dose-response curve. New approaches make use of species sensitivity distributions in ecotoxicological risk assessments (OECD, 1992). In human risk assessment, benchmark dose

modelling (Slob and Pieters, 1999) and categorical regression (Teuschler et al., 1999) have been proposed. Teuschler et al. (1999) applied categorical regression to OPs.

4.4 Extrapolations

Standard-setting for OPs based on adverse effects on human health involve a number of extrapolations. This is because the data used for standard setting ordinarily come from experiments on laboratory organisms (most often rodents) exposed to relatively high doses and for relatively brief durations UFs are ordinarily a factor of 10 and are included to compensate for limits in our understanding of how toxic substances works, which severely compromises our ability to make accurate predictions of risk. One UF is included when the human health standard is set using laboratory animal data. In other words, humans are assumed to be approximately 10 times more sensitive to OPs than are laboratory rodents. Another UF of 10 is included to compensate for individual differences in susceptibility to OPs, implying no more than one to two orders of magnitude difference in the range of sensitivity. Recently, an additional UF has been recommended for inclusion in standard setting in order to protect children from the risk of OPs and other pesticides. It is important to note, however, that despite the widespread use of UFs in regulatory decision-making there is little evidence available for the biological plausibility of UFs. The situation could be remedied by empirical selection of UFs and their magnitude(s). In this regard, an empirical approach has recently been described to selecting an UF for interspecies variation in sensitivity that is based on analysis of avian toxicity data used for pesticide regulation purposes (Mineau et al., 1996). Contrary to standard assumptions Mineau et al. found that smaller species were more sensitive. Extrapolation methods for environmental organisms are also available: see for example EC (1996) and Crommentuijn et al. (2000).

The evolutionary conservation of enzyme and receptor make OPs an ideal candidate for comparative studies on physiology, biochemistry, metabolism and susceptibility to OPs. Such studies may make it possible to establish species-specific toxic equivalency factors (TEFs) for the OPs (NRC, 1993).

4.5 Direct and indirect effects

OPs are indirectly acting agents in that inhibition of acetylcholinesterase causes an accumulation of acetylcholine with subsequent overstimulation of cholinergic receptors. Recent evidence suggests, however, some OPs have direct stimulatory effects on cholinergic receptors at extremely low concentrations (Huff and Abou-Donia, 1995; Ward and Mundy, 1996). Recent evidence also suggests that acetylcholinesterase may serve as a tropic factor that guides development of the nervous system in several species (Bigbee et al., 1999). Disruption of brain development by OPs may explain their developmental toxicity in avian species. Behavioural decrements may result in increased susceptibility to predation, reduced provisioning of the young, and reduced feeding. There may be other indirect effects produced by OPs. For example, some OPs have repellent actions that underlie the avoidance of OP-contaminated food displayed in avian species Bennett (1989). Reduction of forage species can affect growth of other species or, vice versa, the reduction of certain species can lead to excessive growth of forage species (algal bloom following reduction of crustacea). Finally, toxic effects in wildlife may alter

community composition and food-web dynamics leading to further indirect effects of a magnitude and impact on the environment and human beings that is presently unknown. Clearly, only an integrated approach may reveal such interactions.

4.6 Summary

The site of action of OPs, acetylcholinesterase, has been established in a vast array of species, including humans. It follows that in an integrated approach the effects assessment for various species will show communalities in reported effects and standard setting approaches on the basis of no (observed) adverse effect levels. Species-specific toxic equivalency factors (TEFs) have been proposed for OPs.

5. Risk Characterisation

5.1 Combining exposure and effects

The results of the characterisations of exposures to OP compounds and associated effects are combined to estimate the risks to each endpoint. The uncertainties associated with the risks are determined, and summarised for presentation to the risk manager and stakeholders. In this relatively simple case, an exposure estimate is used to estimate the likelihood of adverse effects by comparing the exposure value to a limit value. A common set of evidence, common criteria, and common interpretations of those criteria are used to determine the cause of human and ecological effects that co-occur or are apparently associated with exposure to OPs. A best estimate of risk is derived from 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 are quantitatively weighted and combined evidence from ecological and human health risks is integrated.

5.2 Determining causation

See 5.1

5.3 Combining lines of evidence

See 5.1

5.4 Uncertainty

Through uncertainty analysis, the risks of various stressors is expressed in a common form (e.g., the probability of occurrence of cholinesterase inhibition in humans and in the ecological setting). The integrated assessment starts with a common concept and terminology of uncertainty (e.g., distinguish variance from true uncertainty), and as far as appropriate uses common analytical methods.

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 50^{th} or 99^{th} 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 our example the uncertainty analysis would require the following:

- ?? 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 home-grown, 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;
- ?? Generate a distribution of exposure through simulation.
- ?? Compare this exposure distribution with a fixed value of the Acceptable Daily Intake 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 humans effects assessment.
- ?? A similar approach can be undertaken for environmental species.

5.5 Presentation of results

Results of health and ecological risk assessments are presented in a common format that facilitates comparison of results, i.e., a common presentation of results with an explanation of differences in the magnitude of effects. Similarly, the uncertainties are presented in a common form (e.g., cumulative frequency). This integrated risk characterisation facilitates the task of communicating risks to risk managers and the public. An example of a common risk measure that could be used in this example is the risk characterisation ratio of the exposure estimate (PEC) and the no-effect level for acetyl cholinesterase inhibition (PNEC, ADI, RfD). Alternatively an uncertainty analysis may result in the common risk measure being the probability that the exposure estimate (PEC) exceeds the effects estimate (PNEC, ADI, RfD). If dose-response relations are known, a probability distribution of effects can be obtained and decisions can be taken on the basis of an acceptable level of effects (e.g Klepper et al., 1998, for ecosystems and Slob and Pieters, 1999, for humans). Integration of the results could include an integration of effects over different OPs and over the geographic area of interest, e.g. the farming community in this case.

5.6 Summary

An exposure estimate is used to estimate the likelihood of adverse effects by comparing the exposure value to a limit value. In an integrated approach, a common set of evidence, common criteria, and common interpretations of those criteria are used to determine the cause of human and ecological effects that co-occur or are apparently associated with exposure to OPs. Results of health and ecological risk assessments are presented in a common format that facilitates comparison of results. It avoids acceptable risk conclusions with regard to the environment, which are unacceptable with regard to human risk and vice versa.

6. Risk Manageme nt and Stakeholder Participation

Risk management is the process of deciding what actions should be taken to mitigate or reduce the risk. It involves making decisions concerning actions in response to estimated risks to humans or ecological systems.

Risk managers may be concerned on the potential health effects of occupational and non-occupational exposure to OPs among farmer families in an area known for intensive use of these substances (e.g. Azaroff, 1999; Simcox et al., 1995). Other risk managers may be interested in effects of OPs on wildlife in such an area (e.g. Custer and Mitchell, 1987). In an integrated approach these studies would be combined addressing both issues and making effective use of the available exposure and effects assessment expertise, exposure models, monitoring data and monitoring strategies. The risk managers may be able then to make a balanced judgement on the risks for not only the farmer families, but also their environment on the basis of the estimated risks and the socio-political and economic implications of alternative risk reduction options.

An integrated risk assessment could make clear, which receptors are at risk and which not. Communalities as well as differences will become clear and risk management options can be focussed without neglecting receptors and interactions between them. For example, restrictions on the presence of humans in fields during spraying and for some period thereafter reduce risks to humans, but not ecological receptors. Granular formulations of OPs are less risky to humans than sprays but are more risky to birds, because the latter ingest granules as grit.

6.1 Summary

An integrated approach makes effective use of available resources for estimating risks. It also allows a balanced judgement on the risks to all organisms potentially at risk, showing commonalities as well as differences and interactions.

7. Risk Communication

Risk communication involves risk managers, risk assessors, the general public and stakeholders. Risk questions and answers presented in an integrated way show communalities and differences between the various receptors and will highlight the interaction between risk reduction options for individual receptors. Simple or unnecessary solutions to parts of the

problem are avoided. This will increase understanding of often-complex problems and support coherent decision making which is acceptable to all parties. A ban of a specific OP in spite of the absence of proven risks for professionals or environmental organisms will be more easily explained and accepted when it can be demonstrated that there is an aggregated risk to children exposed via food and via household applications.

7.1 Summary

An integrated approach will increase the likelihood of understanding and acceptance of risk reduction measures in the risk communication stage.

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IV. MEETING REPORT OF THE INTERNATIONAL WORKSHOP ON APPROACHES TO INTEGRATED RISK ASSESSMENT

22-24 APRIL 2001

1. Background

For practical reasons, human health and environmental risk assessment methodologies have generally developed independently. However, with increased recognition of the need to more effectively protect both humans and the environment, an integrated, holistic approach to risk assessment that addresses real life situations of multichemical, multimedia, multiroute, and multispecies exposures is needed. It was recommended that IPCS convene a group of international scientific experts to develop approaches for integrated risk assessment.

In April 1998, IPCS convened an IPCS/OECD/EPA Scoping Meeting on Integrated Approaches to Human Health and Environmental Risk Assessment, in conjunction with a US EPA national symposium on "Extrapolation in Human Health and Ecological Risk Assessment". A number of potential activities/issues related to integrated risk assessment were identified at this scoping meeting. In November 1998, a follow-up planning meeting was convened by IPCS to further identify mechanisms and approaches for integrated risk assessment. That planning meeting agreed on a working definition of integrated risk assessment[1] developed a preliminary generic framework for integrated risk assessment, and proposed that a number of case studies be developed to evaluate the framework. IPCS convened a Framework Sub-Group meeting in July 1999 to review and revise the draft generic framework, and to develop criteria for identification of case studies and guidance for how the case studies would be developed. A meeting to further evaluate possible case study demonstrations of the generic framework was held in November 1999 and four case studies were chosen and their format/content finalized in July 2000. At the July 2000 meeting, plans were made to convene an international workshop to evaluate the framework and demonstrate the benefits of integration using the four case studies. That workshop was convened in Ispra, Italy in April 2001.

2. Goals of the Workshop

The overall goals of the workshop were to promote international understanding and acceptance of integrated risk assessment (IRA). Specific objectives of the meeting were:

1) to demonstrate and communicate the benefits of IRA to the international scientific community;

2) to evaluate a generic framework for IRA using case studies to test its strengths and weaknesses;

3) to identify what integration means with respect to conducting research to develop and support the IRA process;

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[1] Integrated risk assessment is a science-based approach that combines the processes of risk estimation for humans, biota, and natural resources in one assessment.

4) to identify how the IRA paradigm informs the environmental research agenda;

5) to facilitate the implementation and application of the paradigm of integrated risk assessment; and

6) to publish the results of the meeting in peer-reviewed scientific literature.

3. Overview of Generic Framework

Dr Glenn Suter, US EPA, provided an overview of the generic framework:

- Discussion issues: Terminology. Currently, US based terminology is used, but there is a need to incorporate OECD/IPCS harmonization project on terminology.
- Often in EU, the distinction between risk assessment and risk management is unclear. The risk assessor is also risk manager, which leads to differences in approaches.
- In some countries (EU) exposure assessment is already integrated. There still is need to focus more on characterization of effects and dose-response assessments.
- We need a common language, understanding, and harmonized methodologies for effective integration.
- Integration is not always possible; the issue must be defined at the problem formulation stage.

4. Presentation of Case Studies

Four case studies were described to illustrate how an integrated risk assessment could be conducted. Focused on selected stressors in the environment, these were:

- Persistent organic pollutants (POPs) in humans and wildlife (presented by Dr Peter Ross).
- Tributyltin and triphenyltin compounds in humans and wildlife (presented by Dr Jun Sekizawa).
- Organophosphorous compounds in the environment (presented by Dr Theo Vermeire).
- Ultraviolet radiation effects on amphibians, coral, humans, and oceanic primary productivity (presented by Dr Steven Hedtke).

5. Working Group "A" Discussions

Dr Munns provided instructions to workshop participants for the first set of working group deliberations. Participants, organized into four groups, were asked to identify the benefits and obstacles of integrated risk assessment as illustrated in the four case studies by considering the following questions:

- What aspects of human health and ecological risk assessments can be integrated to advantage?
- What are the benefits of integration?
- What are the barriers to integration?
- What do we loose by not integrating?

Additionally, participants were asked to 1) consider how integrated risk assessment can facilitate more timely and responsive regulatory decisions, 2) can help to identify emerging risk issues, and 3) can improve the cost effectiveness of assessments.

Summaries of each of the four Working Group "A" discussions were:

A-1. Persistent organic pollutants

What aspects can be integrated?

- several aspects of ecological and health risk assessments can be integrated
- exposure and effect each can be integrated
- integration goes beyond using "more data" or "packaging existing data"

Benefits

- comprehensive data sets
- reduce uncertainty
- better understanding of mechanism of action
- greater knowledge of environmental chemistry
- reduced cost

Obstacles

- institutional barriers
- scientific/cultural barriers
- differences in terminology/language
- initial cost may be higher

What do we lose?

- base decisions on limited data
- may miss low dose, chronic effects
- may overlook other endpoints (e.g., look for immune problems in Inuits based on observations in seals.
- initial cost may be higher

Predictive risk assessment?

- example - polybrominated diphenyl ethers
- concerns based on knowledge of PCBs, from both environmental media, wildlife, and humans
- global exposures are increasing in some regions
- limited data sets indicate similar mechanisms of action and dose-response relationships
- concluded that current environmental levels may result in potentially adverse effects

A-2. Organotins

What aspects can be integrated?

- sources/transport/pathways of exposure
- mechanisms of action and outcomes

Benefits

- exploit all available data
- improves cross-species extrapolation
- reduces changes of overlooking critical effects
- identification of critical issues
- identifies data gaps
- may serve as "early warnings" for other organisms

Obstacles

- difficult to overcome traditions
- lack of scientific expertise
- ecological and health assessments usually performed by difference experts
- legislative frameworks may be too rigid
- perception that integration is a complex process
- limited availability of data
- inadequate communication of risks

What do we lose?

- do not lose anything, so why not integrate
- critical effects may be overlooked
- integration will eventually result in speedier, more cost-effective regulatory decisions

Research needs

- better data on mechanisms of action
- better tools to use research data

Special issue

- where do economic, psycho-social, and cultural effects fit in?

A-3. Organophosphorous pesticides (OPs)

What aspects can be integrated?

- exposure (similar pathways occur in different species)
- effects acting via similar modes of action; however, caution must be exercised since acetylcholinesterase inhibition will differ for different OPs and different species

Benefits

- better understanding of effects of different levels of acetylcholinesterase inhibition in different species
- more thorough understanding of risks and risk trade-offs
- assist in identifying emerging new risks
- help identify targeted research needs

Obstacles
- institutional/language
- lack of training/decision making experience
- legal mandates
- funding

What do we lose?
- Integration is not always needed. It depends upon issues of concern raised in the problem formulation stage.

A-4. UV radiation

What aspects can be integrated?
- UV exposure assessment is common to both human health and ecological risk assessment
- molecular mechanisms of DNA damage is common to all species; divergence in modes of action result in different endpoints
- can compare different endpoints in different populations

Benefits
- common ground of comparison of data
- opportunity to detect critical pathways across species
- strengthens association of exposure/effects in one species if also observed in other species
- wider use of available data
- improves knowledge on links between molecular events and endpoints

Obstacles
- eco and human health research have different levels of sophistication and uncertainty
- focusing on common causal relationships may lead to oversimplification

What do we lose?
- all the benefits

6. Working Group "B" Discussions

Dr Munns provided instructions to workshop participants for the second set of working group deliberations. Participants, organized into three groups, were asked to identify what is needed to facilitate implementation of integrated risk assessment by considering the following questions:

- What research is needed to conduct integrated risk assessments?
- How will the integrated risk assessment paradigm inform the international research agenda?
- What mechanisms can be employed to facilitate implementation of the paradigm?

Since many of the independent discussions led to similar conclusions and recommendations, the outcomes of all three working groups were combined as:

A. What research is needed to facilitate the implementation of integrated risk assessment?

All the working groups found it difficult and challenging to separate research needs for risk assessment generally from those specific to integrate risk assessment. The following specific needs were identified:

- Exposure assessment and exposure models need to be developed from multiple sources and pathways for both health and wildlife. There needs to be better harmonisation of exposure monitoring and improved environmental and human health surveillance methods as well as access to monitoring data.
- There is a need for improved PB/PK modeling as a tool for combining data sets from different species, and for improving interspecies extrapolation.
- Effects assessment research focusing on common endpoints across phyla/species is needed.
- Effects assessment research focusing on understanding mechanisms of action at the molecular, cellular, organismic and population levels is needed. Examples included: gene array methods for species variance; common biomarkers across species.
- There is a need for improved risk communication methods and common risk measures for both problem formulation and ultimate risk management decisions (also taking into account psychosocial, cultural, and economic factors).
- Develop more effective methods of cost/benefit analysis and demonstrate the benefits of integrated risk assessment.

B. What mechanisms/action can be taken to facilitate the implementation of the IRA paradigm?

- Removal of non-scientific barriers including institutional/political/cultural.
- Removal of language/terminology barriers.
- Communicate to the international/scientific and risk assessment community the advantages of IRA *via* publications, conferences, etc. Scientific advisory committees can also be used to promote integration.
- Promote funding for targeted research of integrated risk assessment.
- Promote integration in educational institutions.
- Publish proceedings of this conference and completed case studies in peer-reviewed scientific literature.
- Develop a "real-life" case study that can be used in a practical situation, demonstrating the advantages of integrated risk assessment.
- Develop a guidance document on conducting integrated risk assessment.
- Develop a website which serves as a clearinghouse for information on integrated risk assessment.

7. Overview of Long-term Research Initiative (LRI)

Dr Rob Taalman, CEFIC, provided an overview of the Long-term Research Initiative (LRI). LRI sponsors global, generic research aimed at improving risk assessment methodologies and is a joint venture of CEFIC, ACC, and JCIA. Examples of activities which will provide better data for use in integrated risk assessment include:

- New test methods for persistence of chemicals in marine and soil environments.
- Conduct tests to determine whether freshwater data can be used as a surrogate for the marine environment.
- Establish database of workplace and consumer exposure.
- Develop an electronic platform with a complete set of risk models for both humans and the environment.
- For developing countries with limited resources, IRA will be a very valuable tool.
- Creation of closer, integrated work among human health and ecological scientists and analysts is needed. More integrated, cooperative work would not alone lead to short-term gains but to a more holistic view in general. A deeper, daily, working integration would greatly increase the chance of serendipitous recognition of problems for which evidence in any one sector is limited, but when all data are considered together, cause for concern may become evident.

8. Next Steps

Based on the recommendations of the Workshop, the following activities were identified to meet the objectives of the integrated risk assessment project:

- Revise generic framework based upon written/oral comments; including issues related to terminology.
- Revise case studies based upon discussions during Working Group "A". Focus should be on benefits, using the format of the case study on OPs as a prototype.
- Publish framework, case studies, and meeting procedures both as an internal WHO document and in the peer-reviewed scientific literature (potential journals include: Human and Experimental Toxicology; Journal of Risk Analysis; and Human and Ecological Risk Assessment).
- Develop an Executive Summary of the Workshop Proceedings and publish widely in journals, newsletters, and at scientific meetings.
- Develop an "integrated risk assessment" on an issue of high political visibility to demonstrate benefits.

9. General Discussions/Concluding Remarks

Dr Kröes and Dr Reiter closed the workshop with the following observations:

- Implementation of integrated risk assessment should be an evolutionary (not a revolutionary) process. Integrated, cooperative work will not only lead to short-term gains but to a more holistic view in general.
- Implementation can occur at three levels: 1) improved scientific data; 2) putting it into practice; and 3) acceptance at governmental levels.