Meeting *the* Scientific Needs *of* Ecological RISK Assessment *in* a Regulatory Context

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Three strategies could move both science and regulation forward.

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During the past decade, the field of ecological risk assessment has progressed considerably. Advances have come from such international bodies as the Organisation for Economic Co-operation and Development (OECD), the World Health Organisation (WHO), the European and Mediterranean Plant Protection Organisation (EPPO), and the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (*1*–*8*). Risk assessments have played a critical role in the development of various regulations within the European Commission (EC) as well as in other parts of the world, including the United States, Canada, and Japan (*9*–*17*). But scientists and regulators are faced with three significant challenges: streamlining the risk-assessment process, quantifying risks in a spatially explicit manner, and acquiring the correct kind of environmental data to enable regulatory programs to effectively focus on future environmental protection activities.

Increasing efficiency, cost-effectiveness, and focus

Risk assessment is a tiered process distinguished by levels of increasing complexity, beginning with the preliminary categorization step, followed by a refined or screening assessment, and progressing to the full, comprehensive risk assessment (*4*, *18*, *19*). For each tier, a minimum level of information is required. For example, OECD has established an international program—called the Screening Information Data Sets (SIDS)—for surveying high-production-volume chemicals (HPV) for potential effects. SIDS include the basic information needed to perform a preliminary assessment of a chemical's potential risk (*20*).

Applying the current risk-assessment paradigm and meeting the associated data-generation requirements, combined with the increased need to evaluate the potential effects posed by thousands of industrial chemicals, are big challenges for the chemical industry, national and international regulatory

agencies, and associated stakeholders (*19*, *21*, *22*). To address these challenges, several initiatives have been implemented that focus on the lack of publicly available data on the hazardous properties of chemicals and on the need for greater efficiency in decision making, while enhancing the quality of the risk assessment and the management of chemicals. Some of these initiatives are voluntary, such as the U.S. HPV Challenge Program (*23*) and the Human and Environmental Risk Assessment project for detergent ingredients (*24*); some are regulatory (e.g., the EU Existing Substances Regulation REF EEC No. 793/93; *9*, *11*); and some are of a more global nature, such as the OECD Existing Chemicals Programme (*20*). As a result of these initiatives and the subsequent reversal of the burden of proof, the EC has proposed new legislation on chemicals, including a law called Registration, Evaluation, Authorisation, and Restrictions of Chemicals (REACH; *25*–*27*).

Governmental agencies, the regulated community, and stakeholders also face the challenges of generating and interpreting data for risk assessments in a cost-effective and efficient manner.

The lack of publicly available chemical safety information for industrial chemicals is not a new problem. In 1984, the U.S. National Research Council estimated that only 22% of U.S. HPV chemicals had "minimal" toxicity data available. In 1990, a detailed analysis of chemical control in the EU showed a similar lack of information on use and toxicity (*28*). Analyses by the European Chemicals Bureau (*11*) and the U.S. EPA found that only 14% of EU HPV chemicals had data at the level of the base set (Directive 67/548/EEC, Annex VIIA); 65% had less than the base set; and 21% had no data at all (*29*, *30*).

In EPA's HPV Challenge Program, significant amounts of previously unpublished data were submitted by industry sponsors for 1257 chemicals, and where this was not the case, a high percentage of the missing data was estimated by using quantitative structure–activity relationships (QSARs) and read-across methods (*31*). QSARs/read-across methods are a promising approach that combines experimental information on the toxicity of chemicals with grouping of chemicals based on chemical structure and mode of toxic action. Of the human health data needed in the HPV Challenge Program, 50% was readily available, 44% was estimated, and only 6% was tested (in fact, 88% of the missing data was estimated using QSARs and read across). For the environmental data, 58% was available, 35% was estimated, and only 7% needed testing (in fact, 83% of the missing data was estimated).

Governmental agencies, the regulated community, and stakeholders also face the challenges of generating and interpreting data for risk assessments in a cost-effective and efficient manner for regulatory programs that require submission of defined studies (e.g., pesticide registration programs). Although test requirements can result in data for a wide array of end points, in many cases only a subset of the in vivo data forms the basis for the final risk assessment. This outcome is consistent with basic dose–response principles and the fact that a compound's range of estimated exposure concentrations is typically relevant for a small number of potential toxicity endpoints and their effect thresholds.

Risk assessors need information to address the assessment uncertainties across chemical classes to determine adverse effects and outcomes of concern, but the magnitude of the data gaps precludes the use of a traditional toxicity-testing approach. The long-term solution to these challenges will not be to generate more hazard data more quickly but rather to determine which specific effects data, groups of chemicals, and exposures are essential for assessment and appropriate management of the risks.

For chemicals that lack toxicological and exposure data, the researcher's challenge is to create ways to efficiently and credibly predict toxic potency and exposure levels. These predictions would help assessors make reasonable decisions about whether empirical studies are required to further refine a risk assessment. In the context of regulatory programs, where data generation is required to make regulatory decisions, the challenge is to move in a scientifically credible and transparent manner from a paradigm that requires extensive hazard testing to one in which a hypothesis- and risk-driven approach can be used to identify the most relevant in vivo information (*32*–*34*).

Combes et al. recently articulated this idea of predictive modeling and intelligent testing, writing that "additional testing should only be required where essential information is missing, rather than testing to cover all data gaps according to a generalized, checklist approach" (*32*). This perspective also addresses responsible use of animals in in vivo testing (*32*, *33*).

If one assumes all chemicals on "a list" do not need to be tested, and for those that do, not all can be tested for all possible endpoints at once, then the following questions must be addressed: Which chemicals should be tested? And of these, which should be tested first? For what endpoints? On the basis of what rationale?

Components of an intelligent testing strategy include the use of exposure information (*27*, *34*), thresholds of toxicological concern (TTCs) (*35*, *36*), QSARs, read-across methods, and in vitro testing methodologies. TTC is an exposure threshold value for chemicals, below which no significant risk is expected.

For example, in de Wolf et al.'s analysis of environmental toxicological databases (acute and chron-

ic end points) and substance hazard assessments, lowest numbers and 95th percentile values were derived with data stratification based on mode of action (MOA 1, inert chemicals; MOA 2, less-inert chemicals; MOA 3, reactive chemicals; and MOA 4, specifically acting chemicals) (*36*). The authors derived TTC values by multiplying these values by appropriate application factors (10, 100, or 1000). The derived values for MOA 1–3 were ~0.1 μg/L.

Combined with simple or more refined exposure scenarios, these TTC values can form the basis of an intelligent testing approach in a tiered risk-assessment scheme. Figure 1 shows how this testing scheme can help to set data-generation priorities and to refine or reduce animal use.

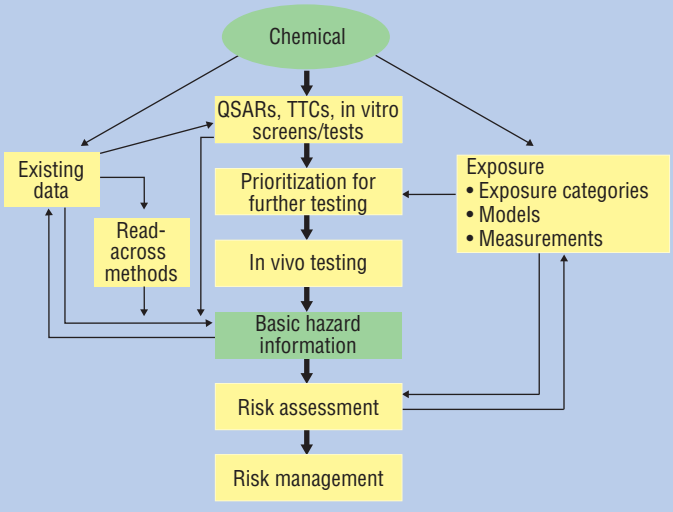
Over the past 25 years, many OECD member countries have established QSAR tools to provide exposure and effects inputs in ranking and prioritization schemes for in vivo screening and testing programs (*37*–*44*). Because of today's computing capabilities, thousands of chemicals can be processed readily in near real time to estimate properties associated with 3-D structures. As a result, it is now possible to rapidly predict ecotoxicological potential for end points associated with chemical reactivity (e.g., covalent binding to nucleophilic sites in DNA, RNA, or critical proteins), redox-cycling, and oxidative stress, as well as for noncovalent interactions with membrane and protein receptors. New developments in molecular technologies hold considerable promise to enhance exposure and effect characterizations; these technologies could optimize test methods and testing strategies. With the establishment of increasingly diagnostic cellular and biochemical end points derived from well-characterized in vitro systems, defined and consistent toxicological responses can also now be generated. Development and validation of this capability are essential to formulating QSARs as well as standardized assay methods for empirically evaluating chemicals of concern. In the coming years, the advent of "omic" technologies could dramatically increase the synergy between QSAR and in vitro assay methods (*41*, *42*).

As depicted in Figure 2, toxicity pathways define discrete events across a continuum of biological organization—from the proximal or initial alteration caused by a xenobiotic interacting with a biological molecule (e.g., enzyme or hormone) through the cascade of biochemical, physiological, organism-, and population-level responses associated with adverse outcomes. While studies at lower levels of biological organization are used to determine mechanisms or modes of toxic action for xenobiotics, interpretation of the relevant toxicological events for risk-management decisions is typically associated with adverse responses observed at higher levels of biological organization. Knowledge of the common initiating events across chemical classes will facilitate the development of QSARs and read-across methods that predict the toxicological potential of untested chemicals. A greater understanding of the subsequent events in a toxicity pathway provides the means for development of empirical, diagnostic in vitro tests that predict with greater confidence whether a chemical can interact with a biological molecule of concern

FIGURE 1

Efficient risk assessment

Combining use and exposure information and effects information obtained from quantitative structure–activity relationships (QSARs), read-across methods, thresholds of toxicological concern (TTCs), and in vitro tests prior to in vivo testing is a more rapid, efficient, and cost-effective way to perform risk assessment of chemicals.



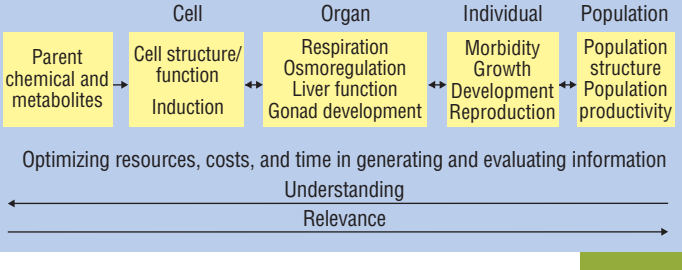
to cause a resultant molecular, subcellular, or cellular response. If such responses are observed, then further empirical evaluation with in vivo assays can be focused on the end point of concern. The elucidation of toxicity pathways will support a risk-assessment paradigm based on the use of rapid and relatively inexpensive in silico and in vitro techniques to form and focus risk-based hypotheses for identifying when and for what end point in vivo data are required. As a result, resources, costs, and time can be optimized for those chemicals and end points most likely to be of concern.

The scientific advances needed to meet these challenges will require further investment in computational chemistry; systems biology; molecular, cellular, and biochemical toxicology; and exposure modeling (*45*). The full potential of scientific advances in risk assessment will only be realized if these disciplines are integrated in a concerted and systematic fashion.

FIGURE 2

Toxicity pathways

Linking toxicological responses across levels of biological organization would help prioritize risk-based assessment questions and associated data and information needs.



Spatially quantifying risks

Streamlining the risk-assessment process provides a foundation for a rigorous ranking, prioritization, and risk-based-screening approach that can effectively discriminate among substances of varying concerns. A stepwise or tiered approach to risk assessment is intended to incorporate the most efficient use of resources by facilitating credible decisions at the earliest possible stage, while maintaining ample margins of safety to protect the environment. With the tiered approach, scientific expertise, laboratory capabilities, test organisms, time, and costs can be allocated to the highest-priority compounds. Applying realistic worst-case application factors or safety factors at the initial prioritization, ranking, or screening phases of the risk assessment will help risk assessors to eliminate those substances that are not of concern.

The second challenge is to advance the scientific means to refine and characterize ecological risk projections in higher-tier risk assessments at biological, spatial, and temporal scales under consideration in risk management decisions.

Exposure analysis. The scientific gaps that significantly limit the assessment of environmental exposure are in the areas of exposure modeling and monitoring. In principle, any validated exposure model can be used to estimate exposure levels. However, before applying these models, risk assessors need information about the physicochemical properties, the fate (e.g., biodegradation and sorption), production, use (including use in products), and emission of the chemicals involved (*18*, *19*, *21*, *27*). Yet, even validated models are not perfect. They are only a mathematical approximation of the processes that affect environmental fate. Inherent temporal and spatial variability prevents them from being a 100% accurate representation of the real processes.

Increased realism in the exposure evaluation will allow stakeholders to eliminate a higher number of substances that are of no concern.

Simple, conservative, and generic exposure models may be appropriate for the early tiers in the chemical priority-setting and risk-assessment processes but inappropriate for site-specific risk assessment.

In order to increase efficiency, assessors should use generic or evaluative environments, with standard properties, to decrease complexity inherent in real environments to model exposures, for example, EUSES (*46*) and E-FAST (*47*). The predicted steady-state exposure concentrations for such generic scenarios often form the basis for an initial integration with the chemical effect data. If a concern is identified with the use of these generic exposure models, more representative data and/or model formulations for the environmental compartment of concern or the specific site of concern can be used to further refine the exposure. This approach may require more refined and more reliable data on the chemical's use, release, and emission. Data on a substance's environmental fate and specific information on the environmental compartment of concern (e.g., specific tributary, watershed, or food web) as well as the site of concern (e.g., plant emission as a point source) may also be needed. Examples include Geography-referenced Regional Exposure Assessment Tools for European Rivers (GREAT-ER) or route-type modeling approaches in which required environmental information is obtained from geography-linked databases (*48*). To store and access the majority of these data in a user-friendly format, geographic information systems (GIS) are used. These GIS-based exposure models such as GREAT-ER provide a distribution map of a chemical's predicted environmental concentration, including temporal variability and seasonality. GIS also allows the risk manager to zoom in to the chemical, compartment, and area of concern (see Figure 3).

To further increase the realism and efficiency of the exposure assessment in the early stages of the risk assessment, higher-tier GIS-based exposure should be used to further verify and refine generic environments (*49*). Increased realism in the exposure evaluation will allow stakeholders to eliminate a higher number of substances that are of no concern. This approach can further reduce the need for specific input data and hazard information for substances that have exposure levels of no concern. Alternatively, chemical concentrations in relevant environmental compartments or sample specific biota of interest can be measured. This approach is possible only when appropriate measurement techniques are available that detect the stressor or the response to the stressor (e.g., analytical, ecotoxicogenomics, bio-indicator). In practice, however, laboratory and field data are used to provide parameters for the models, whereas monitoring data are used to evaluate the model predictions. Discrepancies between the results of models and monitoring should be investigated to evaluate how well model assumptions and monitoring designs represent the "real-world scenario" of regulatory interests.

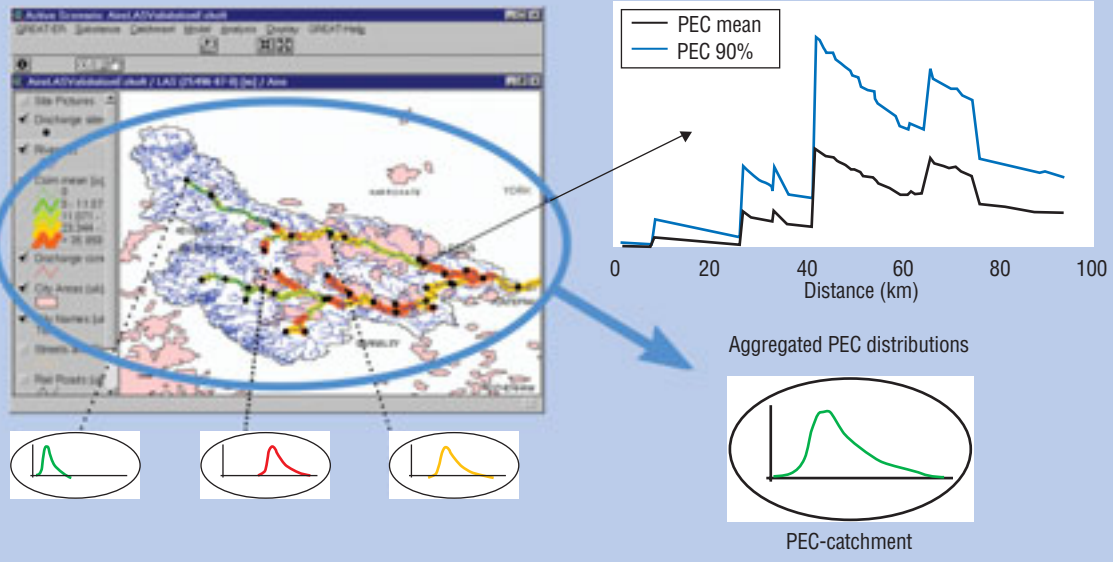
Reliable, high-quality monitoring data, if they are available, can help risk assessors to derive realistic exposure estimates in conjunction with model predictions. Monitoring data may therefore be used to verify the exposure model, improve default emission assumptions, and define the relevant exposure level for risk assessment. The selection of monitoring sites and the design of future monitoring programs should be optimized through consultations to meet the multiple objectives of various stakeholders; these objectives include water-quality assessment and comprehensive exposure and risk assessment.

Effects analysis. The stepwise or tiered approach to hazard assessment was first described more than 20 years ago and has been adopted within regulatory schemes around the globe (*18*, *21*, *50*, *51*). The tiered testing approach was envisioned to proceed

FIGURE 3

GREAT-ER modeling output for the Aire catchment (U.K.)

The output enables the risk assessor to capture the spatial variability of exposure concentrations for a detergent surfactant. PEC means predicted environmental concentration.



from acute and chronic bioassays to microcosm and mesocosm testing to provide more realistic and refined effects assessments by addressing higher levels of biological organization. Early tier- or screening-level assessments were designed to infer effects at higher levels of biological organization. More extensive data generation was typically associated with programs required to make safety findings and/or credible risk–benefit decisions. The need to better understand relationships between toxicological processes and responses at higher levels of biological organization is also fundamental to advancing the means to interpret and communicate the ecological significance of predicted toxic effects for those regulatory programs where testing requirements are limited.

For both data-rich and data-poor situations, the fundamental challenge to current effects analyses centers on answering the "so what?" question when characterizing risk. For example, what can happen to a population of fish if the predicted environmental concentration exceeds an LC50 derived from an acute toxicity test or a QSAR estimate? What are the potential consequences to a fish population if x% has y level of reproductive impairment at a given exposure level? How long can it take for the population of fish to be affected? Will these population effects happen in certain places? Which places? Some places more than others?

A number of international organizations are pursuing ways to answer these "so what?" questions. For example, in EPA's Office of Pesticide Programs (*52*) and in the EU (*53*), ongoing efforts focus on the development of probabilistic techniques to estimate the risk of pesticide exposures to aquatic life and wildlife. The immediate efforts are designed to move risk assessments of effects at the individuals-level beyond single-point deterministic assessment approaches to relate an estimated environmental concentration to a specific adverse effect (e.g., an LC50 or no-observed adverse-effect level [NOAEL]). Probabilistic techniques help answer the "so what?" questions by estimating the magnitude and extent of mortality rates, growth rates, fecundity, and other effects for varying exposure scenarios. This approach more fully uses available information (e.g., dose–response data, when available) and provides risk managers with a better understanding of the potential effects associated with a chemical stressor.

With the continued use of deterministic risk assessments, such as measured or QSAR-predicted LC50s, or with probabilistic techniques to characterize risk of mortality or reproductive fitness at the individual level, additional questions remain. For example, to what degree do changes in survival or reproductive performance translate to changes in populations and communities? To what degree are these mortality or reproductive effects—and for that matter, population and community effects—expected to be significant at the field, watershed, or regional scale?

Regulatory decision making for environmental effects may require information at biological, temporal, and spatial scales that are typically not addressed with current techniques. For example, environmental management evaluations, especially those that are required to evaluate the costs and benefits of a decision, operate at spatial scales that can encompass eco-regions, watersheds, or the critical habitat ranges of species. Clearly, environmental management decisions concerning potential chemical effects require science and tools to provide spatially explicit estimates of chemical exposure, population responses, and potential risk to aquatic life and wildlife.

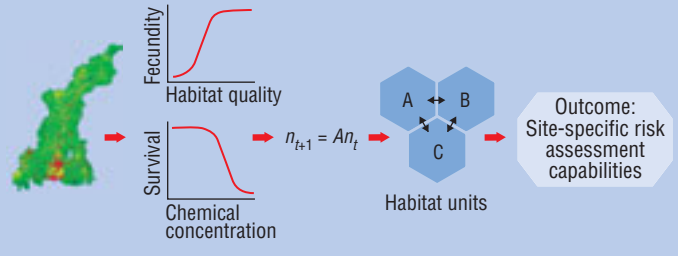
Aquatic life and wildlife populations, as well as the associated community structure and function that provide habitat for forage and reproduction, are po-

tentially impacted by many stressors related to human activity, including habitat alteration, introduced species, and chemical use. The magnitude and extent of population responses and the sustainability of a population to changes in the landscape are functions of the interactive and cumulative effects of the associated stressors. Populations and stressors are distributed heterogeneously within the landscape. Understanding relationships between spatial and temporal patterns of stressor exposures and the spatial and temporal distribution of populations is a major facet to estimating or interpreting the severity of population responses.

FIGURE 4

Conceptual model of spatially explicit population-based risk assessments

Linking databases for species-specific toxicity, demographics, life history, and habitat quality requirements to models that can estimate missing values from existing information will provide the means for projecting population responses for specified species in defined locations. The first of four steps in the GIS-based risk-assessment modeling process is a landscape characterization that requires spatial and temporal characterization of the chemical stressors exposure as well as the spatial and temporal characterization of habitat quantity and quality. Results from Step 1 feed into Step 2, which is quantification of the chemical dose–response relationships and the habitat–response relationships. The response variables in Step 2 are spatially explicit demographic rates of individuals within a population. These demographic rates then permit estimates of population growth rates, population extinction rates, or other appropriate population-level end points through the use of population models in Step 3. Finally, in Step 4, the population dynamics derived from Step 3 are placed back into the landscape to estimate habitat-specific population sources and sinks. This cumulative analysis permits estimates of aquatic-life and wildlife risks at the population level from chemical exposure, habitat changes, and other forms of landscape perturbations.



The development of spatially explicit population estimates requires techniques for generating quantitative chemical exposure–response relationships and habitat–response relationships at the individual level. Such capabilities must be tailored to address applications that range from general, broad screening-level assessments to realistic and situation-specific assessments. Approaches for extrapolating toxicological data across species also need improvement. Models appropriate for these applications must generate outputs describing population growth rates or other appropriate population-level end points as functions of stressor relationships to fecundity, life-stage-specific survival, and related demographic rates. Finally, if these relationships can be projected in the context of generic/representative or actual spatial and temporal characterizations of stressors and populations in a landscape, it may be possible to assess effects due to chemical exposure in the context of habitat modification.

Creating the means to answer these "so what?" questions through GIS will be contingent on developing interactive information-management systems that link databases for species-specific toxicity, demographics, life history, and habitat quality requirements. These knowledge bases, linked to models that can estimate missing values from existing information, will provide ways to project population responses for specified species in defined locations (Figure 4). This conceptual approach can apply to a wide range of risk-assessment applications. For applications with limited measured or predicted toxicological data and generic representations of appropriate landscape scenarios, assessors can explore bounding conditions and assumptions. Simple but insightful "what if?" analyses can help characterize and communicate potential risks. In cases where the species' toxicological, population demography, and associated landscape information is increasingly resolved and rich, more explicit risk assessments are possible. Obviously, all risk assessments will have limited or missing data in one or more facets of an analysis. This modeling construct, however, helps assessors to evaluate the uncertainties and assess the extent to which generation of additional, specific data can make a material difference in the risk estimate.

Assessing ecological condition

Two different perspectives influence the regulatory pressure for advancing eco-epidemiology and diagnostics. The first concerns the need to track and document the environmental outcomes of regulatory decision making to evaluate whether or not environmental management has maintained or improved the ecological condition. The second perspective concerns the need to identify likely causative agents within impaired ecosystems. Proper diagnosis of the chemical and/or nonchemical stressors responsible for impairment is essential to forming a cost-effective and efficient approach to remediation or risk mitigation.

Advanced eco-epidemiology and diagnostic methods could address a wide range of management questions. For example, has the removal of contaminants at a hazardous-waste site led to a change in habitat condition over a time span consistent with current understanding of ecosystem recovery? If so, in what way? How has the reduction of nonpoint-source loading in a watershed changed the status of the fish community? Has the introduction of a new class of lower-risk pesticides maintained or improved the condition of bird populations in the associated agro-ecosystems? Have reductions in emissions of persistent bioaccu-

mulative toxic chemicals resulted in lower wildlife body burdens and improved fitness? The ability to answer these questions in a systematic fashion will help risk assessors inform decision makers if previous regulatory actions need refinement and will help inform priority setting for future environmental protection efforts.

The ability to assess the current condition of the environment and to monitor change in condition over time is needed to quantify environmental outcomes derived from protection and restoration programs. Probability-based survey designs need to be developed to assess ecological condition at local, state or provincial, regional, national, and continental scales so that data can be aggregated in a cost-effective manner (*54–56*). The use of comprehensive and comparable methods also provides the means to compare ecosystem conditions across common spatial scales of regulatory interest. Surveys of environmental conditions are based on ecological indicators, which are measures of biological, chemical, and physical attributes, as well as on exposure indicators, which provide information on land use and stressors. The combination of sound survey designs with ecological and exposure indicators, developed through rigorous evaluation criteria, makes it possible to associate trends in environmental condition with stressors most likely associated with impaired condition.

Establishing unbiased estimates of environmental trends in a scientifically and statistically credible manner can lead to ways to associate ecological condition with land-use activities and stressors. This will help risk managers identify regulatory actions that are meeting performance goals and establish priorities for future risk management activities. The development of sound methods that establish baseline environmental conditions and trends is a universal need that transcends ecosystem types, classes of stressors, and regulatory programs.

In this context, the evolution of survey designs for aquatic and terrestrial ecosystems should enable regulatory authorities to ascertain the role chemical stressors play in the environment compared with habitat alteration, introduced species, and other nonchemical stressors—if there are advances in the direct and indirect measurement of chemical exposure to the environment (e.g., analyses of chemical use patterns or use of remotely sensed land-use surrogates of chemical use/loads). With regard to ecological and exposure indicators, the state of the science is reasonably well established for aquatic systems, whereas significant advances are needed for terrestrial ecosystems and for agro-ecosystems in particular.

Although techniques to assess ecological condition and to identify impaired ecosystems are advancing, establishing diagnostic capabilities to determine cause–effect relationships within impaired systems remains a significant challenge. A diagnostic evaluation should define the primary causes of impairment (chemical or nonchemical) and apportion adverse effects across multiple stressors and their potential interactions. The development of diagnostic techniques is critical for refining the leading causes of impairment in specific ecosystems or classes of similar ecosystems, for determining the extent to which existing remediation programs are effective, and for identifying those situations where further refinements in risk-management activities are required.

In the context of chemical stressors, research to date has established numerous indicators at the molecular, biochemical, and organism level that can serve to establish whether exposure to specific chemicals or classes of chemicals has occurred or is occurring. What continues to be a major gap in the science is effect indicators that establish the extent to which adverse outcomes are occurring or are likely to occur in the future.

The advancement of "omics" could also help to develop these effects indicators. The progress of these molecular and biochemical approaches will undoubtedly extend toxicity identification and evaluation procedures for investigating complex chemical mixtures and provide increasingly efficient and refined techniques to identify when specific compounds are responsible for causing adverse effects (*57–59*).

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