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Critical Review

Integrating emerging science to improve estimates of risk to wildlife from chemical exposure: What are the challenges?

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EDITOR'S NOTE:

This article is part of the special series from the SETAC workshop "Wildlife Risk Assessment in the 21st Century: Integrating Advancements in Ecology, Toxicology, and Conservation." The series presents contributions from a multidisciplinary, multistakeholder team providing examples of applications of emerging science focused on improving processes and estimates of risk for assessments of chemical exposures for terrestrial wildlife. Examples are considered relative to applications within an expanding risk assessment paradigm where improvements are suggested in decision-making and bridging various levels of biological organization.

Abstract

Many jurisdictions require ecological risk assessments for terrestrial wildlife (i.e., terrestrial vertebrates) to assess potential adverse effects from exposure to anthropogenic chemicals. This occurs, for example, at contaminated sites and when new pesticides are proposed, and it occurs for chemicals that are in production and/or proposed for wide-scale use. However, guidance to evaluate such risks has not changed markedly in decades, despite the availability of new scientific tools to do so. In 2019, the Wildlife Toxicology World Interest Group of the Society of Environmental Toxicology and Chemistry (SETAC) initiated a virtual workshop that included a special session coincident with the annual SETAC North America meeting and which focused on the prospect of improving risk assessments for wildlife and improving their use in implementing chemical regulations. Work groups continued the work and investigated the utility of integrating emerging science and novel methods for improving problem formulation (WG1), exposure (WG2), toxicology (WG3), and risk characterization (WG4). Here we provide a summary of that workshop and the follow-up work, the regulations that drive risk assessment, and the key focus areas identified to advance the ability to predict risks of chemicals to wildlife. *Integr Environ Assess Manag* 2024;00:1–13. © 2024 The Authors. *Integrated Environmental Assessment and Management* published by Wiley Periodicals LLC on behalf of Society of Environmental Toxicology & Chemistry (SETAC).

KEYWORDS: Chemical risk assessment; New approach methods; Regulatory framework; Terrestrial vertebrates

INTRODUCTION

For at least the past decade, many scientists, including members of the Society of Environmental Toxicology and Chemistry (SETAC) Wildlife Toxicology Interest Group (WTIG), have expressed disenchantment with the lack of progress in applying new science developed to determine the risks to terrestrial wildlife species from anthropogenic chemical exposure. To address this impasse, the idea of organizing a workshop was conceived, which then led to work groups whose members coalesced in online meetings over time. That process resulted in a series of five reviews, each of which addressed a specific component of the risk-assessment process: problem formulation (Sample et al., 2022), effect assessment (Bean et al., 2023; Rattner et al., 2023), exposure assessment (Morrissey et al., 2023), and risk characterization (Johnson et al., forthcoming). The purpose of the present overview, the sixth article, is to provide the context for the various group recommendations for improving wildlife risk assessment across various regulatory regimes, by describing the perceived problems with current wildlife ecological risk assessment (WERA) practices

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and summarizing prospective advances. This overview focused on regulations from the US, Canada, and the European Union (EU).

All six articles in this series were prepared under the auspices of WTIG, led by a Steering Committee that established four work groups. These work groups were built around the four pillars of risk assessment (Figure 1): problem formulation, exposure assessment, effects assessment (both part of risk analysis), and risk characterization. Following SETAC's tripartite approach, group members from academia, business, and government were involved. Work group members were engaged to represent the jurisdictions, types of wildlife risk assessment, and expertise needed. Although this effort focused mostly on legacy contaminants, industrial chemicals, and current-use pesticides, elements of it can also be applied to emerging contaminants such as pharmaceuticals (including nanomedicines), plastics, nanopesticides and/or fertilizers, biocides, and genetically modified organisms.

Concepts of prospective and retrospective regulatory programs in various jurisdictions

Wildlife risk assessment is conducted for many purposes and under myriad regulations. To organize our thinking around how to apply new and emerging science in risk assessment, we categorized wildlife risk assessment as either predictive or retrospective. Prospective risk assessment includes situations where use of a chemical or product (e.g., pesticides, biocides, new substances) is contemplated. Retrospective risk assessment includes evaluations of risks from exposures that occurred in the past or are ongoing, such as those related to contaminated sites or spills. Prospective risk assessments model exposure and so tend to be

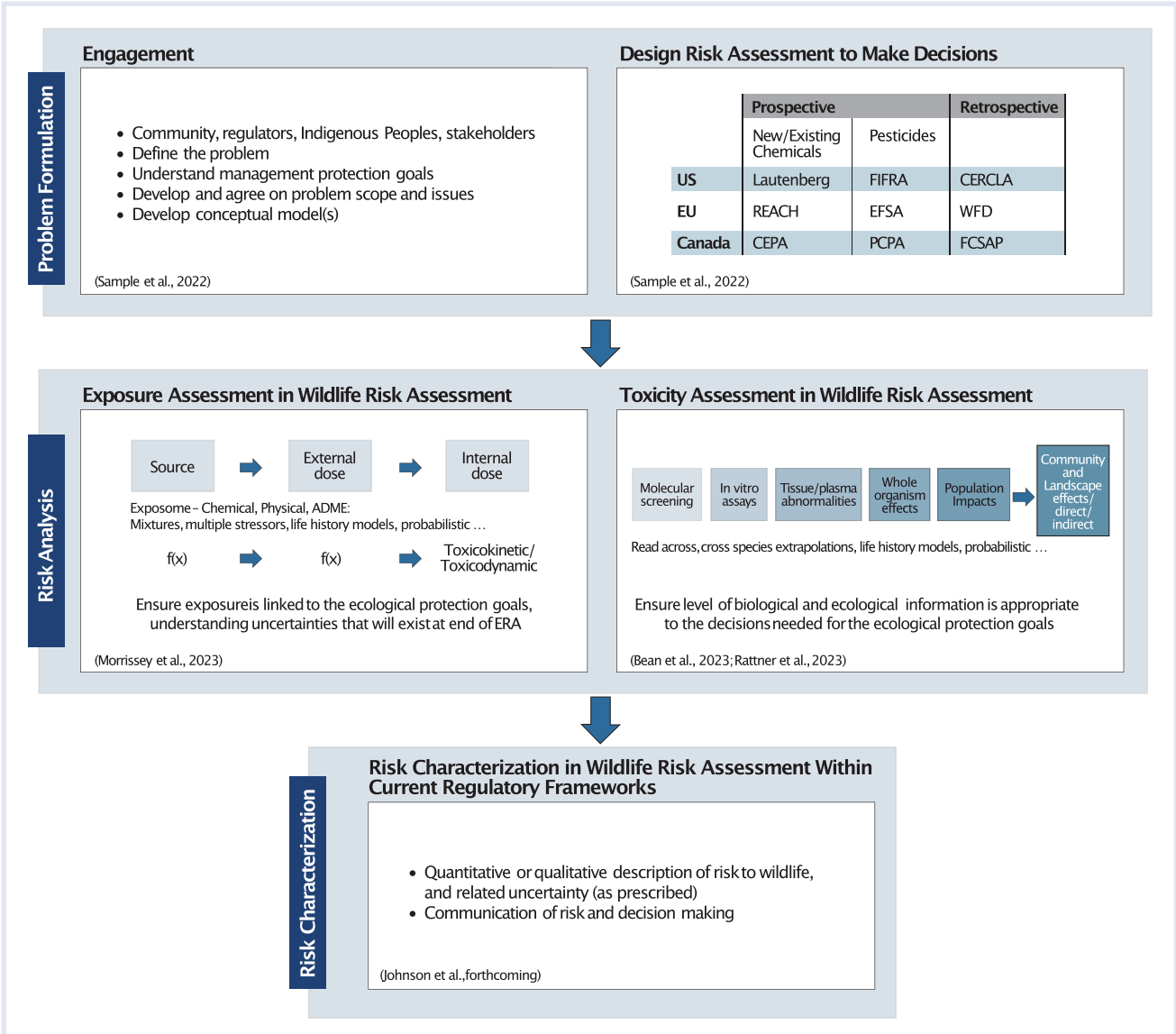

FIGURE 1 Generic approach to ecological risk assessment. The different components formed the basis for the Wildlife Toxicology Interest Group's four work groups: (i) problem formulation, (ii) exposure assessment, (iii) effects assessment, and (iv) risk characterization

more generic than retrospective assessments, which are often site-specific.

In the context of WERA, prospective and retrospective environmental risk assessments develop from similar basic concepts. The terms used vary from jurisdiction to jurisdiction, but they are fundamentally the same. For the purposes of this article, we use these terms: problem formulation, exposure assessment, effects assessment, and risk characterization (Figure 1). Issues related to problem formulation include: (1) definition of protection goals (e.g., individual organisms versus populations, focal species, surrogate protection goals); (2) inclusion of both direct and indirect effects; (3) application of so-called tiered approaches, going from simple conservative approaches to more complex ones; (4) completion of environmentally realistic assessments; (5) application of empirical versus modeling approaches; and (6) promotion of in vitro and/or in silico methods.

Wildlife environmental risk assessment is applied in various regulatory environments so the workshop, and therefore this article, required jurisdictional focus. We decided to focus on Canada, the EU, and the US, including both prospective and retrospective approaches, developed to support management decision-making. Because most of such regulations and guidance are often applied more broadly, that is, to other organisms such as plants, invertebrates, and fish, pulling out wildlife-specific requirements proved challenging. Table 1 summarizes the jurisdictions and regulatory programs where WERA is most commonly used and provides examples of applicable guidance.

Challenges in wildlife risk assessment identified by the work groups

Problem formulation in wildlife risk assessment

The first and most important step in the risk-assessment process is to define the scope of the problem correctly. That includes accurate characterization of exposure scenarios (beyond expected exposure pathways inclusive of food web interactions), species-specific toxicity, and how ecological interactions could affect them, directly or indirectly. Specific statements are required to document the issues, questions (hypotheses), and levels of protection. Those statements must inform decision-making, while being considered relative to the data and collection methods (Sample et al., 2022). As the science has advanced in a variety of areas (Bean et al., 2023; Morrissey et al., 2023; Rattner et al., 2023), there are many emerging technologies available to risk assessors to understand and quantify the extent and magnitude of risks to wildlife. The advancements identified included improved quantification of the bioaccessibility of substances in various media, development of species-specific toxicokinetic modeling to extrapolate toxicity data between species, the use of spatially explicit models to better capture movements based on behavior (improving) exposure assessments, and application of wildlife-specific cell lines. Moreover, our understanding of factors such as metapopulation dynamics is expanding for some taxa, as are factors influencing relative abundance. However, those tools must be identified and formally accepted for use in guidance and related policy. Without both changes in guidance, and regulations in some cases, increasing awareness by practitioners alone will not be enough to result in the use of new tools to improve wildlife risk assessments. Some of the specific challenges to their use were identified (Sample et al., 2022) and are summarized as follows.

Challenge: The need to ensure that risk-management goals are protective, reliable, and reflective of ecological and social values. During problem formulation, risk-management goals must be developed that inform the scope, focus, and conduct of the risk assessment. In concert with the risk conclusions produced through the risk assessment, these management goals should directly inform subsequent management actions. The challenge herein lies in defining risk-management goals that reflect the ecological and social characteristics of the problem related to wildlife, and then tying those goals to ecological measures. Additionally, those goals and their associated measures must be selected to limit uncertainty, while remaining logistically feasible. An important issue in this respect is, for example, the need to focus on individual organisms or their populations.

Challenge: Accounting for improving methods in effects and exposure assessments during problem formulation. In recent years, improved methods have helped make effects and exposure assessments more realistic, less invasive, and less uncertain. For example, current effect-assessment methods rely largely on data from individual health parameters (clinical chemistries, histopathology, behavior, etc.), whereas risk-management goals are typically established at the population level. To bridge the gap between those two levels of organization, it is commonly assumed that effects can be extrapolated from individual to population (Bean et al., 2023; Rohr et al., 2016). During exposure assessments, the level of complexity at which the receptor's life history is represented influences the accuracy of risk conclusions. Integrating increasingly sophisticated, and therefore realistic, life-history knowledge at this step could greatly improve risk estimates. New and developing tools such as spatially explicit and life-history models help to simplify such integration of complex data for estimates of both effect and exposure. The challenge is accounting for the application of the data generated from these new tools during the problem formulation, to ensure that the appropriate data are collected, and that decisions can be made from them to provide the range of possible outcomes.

Challenge: Incomplete use of toxicity information to ascertain the threshold for adverse effects for different wildlife species. Defining the level of protection and predicting exposures and effects are both useful in assisting decision-making, given inherent variability and uncertainty, especially

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TABLE 1 Summary of regulations and guidance documents related to risk assessment, with a focus on wildlife, for the US, Canada, and the European Union

	Retrospective	Prospective	
Jurisdiction	Contaminated sites	Pesticides	New substances and chemicals
United States of America	Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA; US House of Representatives, 1986)	Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA; US House of Representatives, 1947)	Toxic Substances Control Act/ Lautenberg Chemical Safety for the 21st Century Act (TSCA; US House of Representatives, 1976)
	Resource Conservation and Recovery Act (RCRA; US House of Representatives, 1976)		
	Hazardous and Solid Waste Amendments (HSWA; US House of Representatives, 1984)		
	Federal Facility Compliance Act (FFCA; US House of Representatives, 1991)		
Canada	Ecological Risk Assessment Guidance document (Canadian Council of Ministers of the Environment, 2020)	Pest Control Products Act (PCPA; Government of Canada, 2002)	Canadian Environmental Protection Act (CEPA; Government of Canada, 1999)
	Federal Contaminated Sites Action Plan—Ecological Risk Assessment Guidance (Environment and Climate Change Canada, 2012)	PMRA Guidance Document, a framework for risk assessment and risk management of pest control products (Pest Management Regulatory Agency, 2021)	New substances notification regulations (chemicals and polymers; Environment and Climate Change Canada, 2022)
	Federal Contaminated Sites Action Plan—Ecological Risk Assessment Guidance—Module 3: Standardization of wildlife receptor characteristics (Environment and Climate Change Canada, 2012)	Pest control products regulations (Government of Canada, 2021)	Guidance document for the new substances notification regulations (chemicals and polymers; Environment and Climate Change Canada, 2022)
	Federal Contaminated Sites Action Plan (FCSAP) Ecological Risk Assessment Guidance. Module 7: Default wildlife toxicity reference values recommended for federal contaminated sites (Environment and Climate Change Canada, 2021)		Overview of ecological assessment of substances (Government of Canada, 2012)
European Union	Water Framework Directive (European Commission, 2000)	Risk assessment for birds and mammals (European Food Safety Authority, 2023)	Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH; European Commission, 2006)
	Technical guidance for implementing Environmental Quality Standards (EQS) for metals: Consideration of metal bioavailability and natural background concentrations in assessing compliance (European Commission, 2019)	Focal species candidates for pesticide risk assessment in European rice fields: a review (Vallon et al., 2018)	Scientific statement on the coverage of bats by the current pesticide risk assessment for birds and mammals (Hernández-Jerez et al., 2019)
	Technical Proposal for Effect-Based Monitoring and Assessment under the Water Framework Directive (Carere et al., 2021)	Focal species of birds in European crops for higher tier pesticide risk assessment (Dietzen et al., 2014)	

(*Continued*)

TABLE 1 (*Continued*)

	Retrospective	Prospective	
Jurisdiction	Contaminated sites	Pesticides	New substances and chemicals
		Working document on the work-sharing of the southern zone member states under Regulation EC 1107/2009 (European Commission, 2017)	
		Guidance document on work-sharing in the northern zone in the authorization of plant products (Northern Zone, 2021)	
	Guidance on harmonized methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals (European Food Safety Authority, 2019)		

for nonstandard wildlife species. However, most wildlife risk assessments still rely on simple hazard quotient methods of reducing exposure to a single value and comparing it with a single value to represent toxicity. Often, those values are subsequently subjectively refined as needed. The use of no-observed-adverse-effect levels (NOAELs) generally ignores more advanced information such as dose–response (DR) relationships generated from toxicity studies. Differences between wildlife species are often ignored or at best treated as uncertainties, and there is little guidance on how to consider interspecific variation in response. Models and methods now exist to make more complete use of toxicity data and to better inform species differences that include evidence integration of field data with controlled laboratory in vivo studies with mode of action and/or mechanistic data (considering physiological and biological conservation of pathways) to make informed extrapolations between species.

Challenge: Working within constrained regulatory frameworks. The steps taken during problem formulation are guided by specifications set out in the relevant guidance documents for the jurisdiction, although often little focus is provided for wildlife per se (Sample et al., 2022). Some of these specifications are based on legal precedent or outdated science that no longer provide meaningful guidance on the problem formulation process. Inflexible, outdated, and highly prescriptive guidelines can inhibit the use of new tools that allow for more accurate representation of the problem, and ultimately more accurate, realistic risk assessments.

Exposure assessment in wildlife risk assessment

There is a regulatory need to refine exposure assessments so they represent more environmentally relevant scenarios. Routes of exposure may differ between species and habitats, demanding a clear selection of the addressed exposure scenarios in WERA. New approaches to the quantification of chemicals in different environmental matrices (including diet items), exposure modeling, and assessment of diet composition are available, which allow further detailing of species-specific exposure to different chemicals. Furthermore, other routes of exposure, in addition to oral ingestion, have gained increasing interest in wildlife. Inclusion of such new methods and approaches would facilitate the development of more environmentally relevant exposure assessment; however, several challenges must be addressed.

Challenge: The need to include environmental and interspecies complexity. Chemicals occur in the environment at concentrations that vary over space and time. Such complex spatiotemporal variability results in variable exposures of organisms, which may be driven by species-specific traits. When refining chemical risk assessments, such variability must be accounted for in the exposure scenarios. This may be overlain with the spatiotemporal variability in factors that drive the bioavailability of chemicals, such as soil properties, which may result in even more complex exposure conditions for organisms. Exposures of species may be influenced differently by this complexity, depending on the organism's species-specific traits with respect to, for example, spatially explicit foraging ecology, diet or prey items, and migratory behavior.

Challenge: The need to include chemical and species-specific routes of exposure and absorption, distribution, metabolism, and excretion. Routes of exposure may also be species-specific. Generally, ingestion is considered to be the main route of exposure for wildlife. However, recent studies indicate that other routes may be relevant, such as the dermal route in case of bats (Hernández-Jerez et al., 2019). Other absorption, distribution, metabolism, and excretion (ADME) processes may also be affected by chemical properties and species-specific traits related to, for instance, metabolic processes or elimination of more volatile chemicals in air-breathing organisms (Kelly et al., 2007). Assessing such species-specific ADME traits, in combination with chemical properties and user and/or release profiles, could help to understand interspecies differences in internal kinetics of chemicals and ultimate risks. The potential not only for species-specific metabolic pathways for elimination but also for potentiation (i.e., increasing toxicity) of chemicals is

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therefore deemed highly relevant to improving WERA. For this, labor-intensive physiologically based pharmacokinetic (PBK) models, as those used to extrapolate rodent data to humans, can be developed for wildlife species to improve accounting for toxicokinetic differences between species.

Challenge: The need to address uncertainty and assumptions. Currently, when defining more relevant exposure scenarios to further refine risk assessment, basic but conservative assumptions (e.g., worst-case dietary exposure) are replaced with assumptions that are thought to be more realistic. In such cases, however, the "known unknowns" may be replaced by "unknown unknowns," potentially changing the character of the uncertainty and, therefore, affecting the scientific underpinning of risk assessment, that is, conducting a standardized versus bespoke risk assessment. Furthermore, such assumptions must be verified, and their impacts on uncertainty must be identified and, where possible, quantified. Approaches such as probabilistic models and Bayesian statistical approaches may help address this.

Challenge: The need to apply animal-friendly techniques (3R-approaches). Currently, most wildlife-toxicology-related risk assessments rely on animal use. Not only does this raise ethical considerations, but animal testing is often resource-intensive and difficult to perform under field conditions. Regulatory bodies have developed policies to limit the use of test animals in risk assessments, including with respect to wildlife. New approaches are being considered based on in vitro–in vivo extrapolation of uptake and ADME processes, potentially coupled with in silico PBK modeling of exposure under explicit spatiotemporal scenarios. Alternatives, such as using noninvasive or nonlethal samples, have also been proposed (Espín et al., 2020).

Toxicity assessment in wildlife risk assessment

There remains a need for animal-friendly techniques that focus on nonstandard effect endpoints at the individual level (e.g., behavior) and at other levels of biological organization (e.g., molecular, cellular, population, ecosystem) to provide evidence of potential interrelationships among these organizational levels. New approach methods (NAMs) for wildlife are under development to include vertebrate-specific cell lines (Bean et al., 2023; Rattner et al., 2023). Furthermore, approaches applying inferential methods including statistical, modeling, and read-across to better predict hazards and improve the ecological relevance of outcomes are needed. During application of these methods, it is essential to emphasize their limitations and to recognize and attempt to define sources of uncertainty and challenges.

Challenge: The need to employ alternative methods to live animal experimentation while recognizing that much valuable information may be lost. Studies employing methods other than live animals, for example, to predict or reveal cytotoxicity, mutagenicity, or other markers of wildlife toxicity, can provide valuable data when the ultimate objective is, for example, to survey for alternative products, end development of a new product, or reject manufacturing, marketing, or use of a compound or chemical class (Khalil et al., 2020). Such decisions increase efficiency by redirecting funds to more promising active ingredients or products. Although these methods are both more economical and more humane, relying solely on predictive models and in vitro test systems may fail to detect possible sublethal effects, such as behavior and disorientation, organ dysfunction, pain, and suffering in exposed wildlife. Consequently, overreliance on alternative methods such as these could reduce the generation of valuable toxicokinetic, toxicodynamic, pathologic, and higher order effects data, which may be very useful as inputs for predictive models. Such a reduction in available information could result in the outcome that the only source of data related to wildlife toxicology is from postrelease incident case reports. In such a case, WERA would rely largely on conjecture until enough poisoning events in nontarget wildlife species are documented. Failure to adequately anticipate and predict hazards and risks could also have economic and reputational consequences for both regulators and product registrants. Optimally, all of this information could be used in an integrated approach to derive more precise toxicity values that would be protective.

Challenge: Increase the use of omics and other technologies while recognizing there will be a continuing need for in vivo studies. Including omics and other technologies to predict or document adverse effects of chemicals on wildlife is ongoing, and it is already playing a role in the discovery and development of new chemicals. However, we expect that studies of intact animals will continue to be fundamental to chemical risk assessment for some time, both for registrants seeking approval to market a new commercial chemical and for risk managers making decisions on damages and setting remediation goals for a polluted site. In vivo validations will be needed to support integration of NAMs in hazard evaluation and, potentially, in risk assessment. Similarly, for ecological in silico models (which connect effects at lower levels of biological organization to effects on individuals and at the population level) to play a larger role in WERA, in vivo data will likely be needed as model inputs for some time to come.

Challenge: The need for guidance from regulators on acceptable protocols and designs for field studies. Field studies of the effects of contaminants on wildlife offer environmental realism that cannot be gained from a 96-well plate in the laboratory. Both a challenge and strength of in situ studies is the integration of a plethora of variables that are uncontrollable and may not even be recognized at the time. Guideline protocols for controlled laboratory studies are well defined and engrained in the risk assessment framework; see for instance the revised guidance on risk assessment for birds and mammals of the European Food Safety Authority (EFSA) et al. (2023). However, what is lacking is guidance from regulators as to what constitutes

acceptable designs for *field* studies. Such guidance is urgently needed so that high-quality data for free-ranging animals can be used to better address unanswered questions that may remain after the lower tier risk assessment. Thus, integrating NAMs and controlled in vivo testing, coupled with our expanding knowledge of population ecology, could produce an integrated approach to greatly improve our understanding of the influence of chemical exposure on wildlife species.

Challenge: Increase the use of NAMs in laboratory and field studies while reducing the numbers of test animals. To build confidence in the incorporation of NAMs, such as in chemico, in vitro, and in silico methods, there is a need for validation processes that use data from in vivo animal models or field studies. The work group concluded that, for end users to accept assessments of pesticides, industrial chemicals, metals, and pharmaceuticals, in vivo protocols will remain essential for many more years. Therefore, the immediate challenge is to improve on the current methods employed in laboratory animal and field-effect assessments, while working simultaneously to judiciously reduce the number of test subjects. The approach judged as most likely to improve the quality of WERA is to apply existing and emerging alternative methods combined with animal-based research and testing within an evidence-integration framework.

Challenge: Reducing the use of animals in toxicity testing while maintaining relevance of the WERA. There is an important opportunity to reduce the use of animals in toxicity tests and improve predictive capability, relevance, and reliability of WERA through the incorporation of endpoints other than survival, growth, and reproduction. However, insufficient data and technical and regulatory challenges limit the extent to which risk assessors and regulators have embraced nonstandard endpoints in WERA. This is especially important for wildlife species of high conservation concern, for which protection of individuals may be needed, which is not standard in the current ERA paradigms.

Challenge: How to apply nonapical endpoints without losing relevance to wildlife. The application of nonapical endpoints in WERA must be done cautiously. Outcomes measured at lower levels of biological organization do not necessarily lead to adverse effects that are relevant to wild animals. Efficiencies gained by use of systems biology-based, high-throughput NAMs can result in new technical challenges, including the need for method validations and knowledge translations (van der Zalm et al., 2022). For regulatory decisions based on NAMs to be defensible and used by practitioners, method validations are needed to ensure that apical effects predicted by the NAMs are accurate. Furthermore, the use of NAMs in WERA should have a strong link to exposure assessment to go beyond a hazard assessment.

Challenge: Time gaps between registration and evidence of ecologically relevant adverse effects. Much time may be used in accumulating clear and documented evidence of ecologically relevant adverse effects before regulatory action can be taken. Extreme delays could lead to drastic population level effects. A classic example is that of the Asian vultures and the impact of diclofenac where populations of three vulture species declined to critical levels (two declined by more than 95%) since the early 1990s, and a national ban on the nonsteroidal anti-inflammatory drug being instated by the Indian Government only in 2005 (Oaks & Watson, 2011). Therefore, the process of reevaluating registered chemicals could be improved by application of available NAMs to the postregistration assessments. One innovative approach is to use data, where available, from related compounds that share the same or similar modes of action and response metrics (Ågerstrand et al., 2017).

Challenge: The need to improve integration of population models and linkage to organism-level responses. The value of models that connect organisms to population or higher level responses is widely recognized. Their application has, however, been reduced by the limitations of current modeling approaches. A viable solution has been to create an integrated modeling framework and decision guide (Pop-GUIDE; Raimondo et al., 2018, 2021). This method facilitates the selection of appropriate model complexity that is compatible with the quality and quantity of data needed to match the risk objectives and uncertainties.

Risk characterization in wildlife risk assessment within current regulatory frameworks

Jurisdictions and legislation vary in their flexibility to incorporate data from new and emerging science in risk assessments for wildlife. Most jurisdictions allow data from new methods to be incorporated to assist decision-making for contaminated sites; however, regions, territories, and districts may vary on the acceptance of such data. People entrusted with overseeing such risk assessments may resist using these data if they are uncomfortable with the scientific foundation or demonstration of the method.

Risk assessments for wildlife species are rarely considered for new chemical production. Most often, environmental releases occur through wastewater discharges where it is assumed that aquatic invertebrates and fish are more sensitive than wildlife and have greater exposure, that is, the focus of wastewater discharge is on aquatic test species. Typically, wildlife species are considered in wastewater evaluation only when data suggest there is potential for biomagnification or significant trophic transfer.

Methods for understanding toxicity from proposed pesticides and biocides are rigid and, although harmonized (e.g., OECD methods), they do not allow for deviations from established methods or even interpretation of results. Changes will therefore be needed to allow data from new methods and approaches to be incorporated once these have been sufficiently verified and validated. Many of the currently used methods, but also NAMs, focus on direct toxicity and may not consider indirect effects from use or

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abuse. Such indirect effects must be included in WERA, which would potentially demand read-across regulatory silos (e.g., use results from risk assessments to nontarget arthropods to indicate potential effects on food availability for invertivorous wildlife species).

Many emerging scientific methods are being used in the preregulatory space in the area of green chemistry, where alternatives are evaluated and assessed in a life-cycle context as part of a phased approach (Anastas, 1999; Eck et al., 2013). Specific methods using wildlife-derived cell lines or models have not yet been demonstrated in regulatory contexts. However, it is critical that any new method or tool be used in a predetermined way to assist with making decisions. It is typically considered unacceptable to review the data after they are generated to determine if they are applicable or useful.

SUMMARY OF WORK GROUP RECOMMENDATIONS

The work groups provided recommendations to address each of the challenges associated with wildlife risk assessment. The key recommendations from the work group articles, that is, problem formulation, exposure assessment, effect assessment, and risk characterization, are summarized here.

Problem formulation in wildlife risk assessment

During problem formulation, conceptualizing the problem relative to regulatory statute and management goals remains the focus. Emerging methods and science that support these goals provide opportunities to improve accuracy and make sound environmental decisions. However, in nearly all cases, decision criteria must be explicit and outlined before data are collected. Alternative lines of evidence can be used to help reduce uncertainty associated with traditional approaches, and new methods and tools can have current, direct applicability to them. The problem formulation work group's article (Sample et al., 2022) describes these opportunities for integration of new tools and methods, and the associated challenges.

Clearly identify protection goals and define data collection procedures. If new tools are to be integrated into risk assessment practices, the resulting data must be planned for during the formulation of the problem. Clearly identifying protection goals and defining data collection procedures that are appropriate to use in decision-making will facilitate that integration. If decision-making based on risk conclusions is going to be effective and useful, both ecological effects to wildlife and ecological services should inform protection goals.

Work toward comprehensive conceptual site models. Comprehensive conceptual models describe the focal chemical exposures and receptors, but also describe other factors that may influence risks to wildlife and management decisions. The incorporation of knowledge from new tools can inform the development of ecologically relevant conceptual and computational models. Such approaches should also consider indirect effects and multiple stressors relative to actual or expected anthropogenic chemical exposure.

Improve uncertainty estimates and our understanding of the relative influence of uncertainty. Consideration of uncertainties should begin during problem formulation, informing the selection of data collection procedures. Nearly all data collection methods rely on the use of assumptions, resulting in inherent uncertainty. These method-specific uncertainties and their relative influence on risk estimates can be characterized and used to inform the problem formulation. Use of new models that integrate more of the DR relationships (e.g., benchmark dose) along with in vitro assays can reduce uncertainty and improve accuracy. Use of adverse outcome pathways can inform uncertainty by allowing more accurate extrapolation of toxicity information between wildlife species where there are biologically conserved pathways. Use of Bayesian networks can also be linked within exposure and effects networks to better inform risk prediction.

Exposure assessment in wildlife risk assessment

To address the challenges identified by the work group, some conceptual recommendations were developed. It is clear that exposure assessment will never be able to envelop all potential cases under field conditions, potentially resulting in increased uncertainty and even blind spots in WERA. Acknowledging these challenges is of great importance, and adopting recommended approaches to exposure assessment will improve WERA outcomes.

Development and use of a priori, scenario-based approaches. Exposure assessments in WERA could be improved by developing and applying standardized, scenario-based assessments instead of the current tiered approaches. This will enable assessors to better capture potentially relevant environmental variation in exposures. An a priori definition of a suite of environmentally relevant scenarios, focusing specific (focal) species and habitats, which must be accepted in a regulatory context, may provide a better balance between realism and uncertainty in exposure assessments. It is essential to communicate uncertainty transparently, including all the assumptions underlying the different scenarios and approaches. This may allow risk assessment to move away from worst-case scenarios, which are generally overly conservative. Applying probability approaches may help to illustrate the effects of specific assumptions and related uncertainty on the outcomes of a risk assessment.

Establish and implement postregistration, remediation, and/or restoration monitoring guidance. Wildlife ERA will not prevent all potentially adverse outcomes, so it is recommended that postregistration, remediation, and/or restoration monitoring be performed to account for unexpected

exposure events. These may be related to unexpected environmental conditions or sources that may have been missed. An established process for such monitoring programs will also illustrate the effectiveness and accuracy of the overall risk assessment, risk-management practices, and mitigation and/or restoration strategies. It is essential that data and results of such monitoring are timely and transparent, for example, according to the FAIR (findability, accessibility, interoperability, and reusability) principles. Similarly, field-collected data, including raw data and species-specific information data, should be accessible to risk assessors and/or managers through open-source data repositories and public databases.

Operationalization of animal-friendly techniques for exposure assessment. Several animal-friendly techniques have been developed that may be helpful to screen potential exposure scenarios, for instance in vitro assays assessing potential for crossing gut-epithelium (e.g., Caco2 cell-line; Peters et al., 2020) or quantifying metabolic pathways using microsomal incubations (which can be performed wildlife species-specific using primary microsomes, see Boon et al., 1998, for an example). Furthermore, passive sampling techniques may be applied, whereas nondestructively collected samples such as blood, preen oil, and biopsies become more useful related to improved analytical methods with lower detection limits (Espín et al., 2020). Together with development of species-specific, physiologically based models, the above-mentioned in vitro approaches can inform wildlife-specific exposure assessments without, or with limited, use of animals.

Effect assessment in wildlife risk assessment

Ecological risk assessments for wildlife would benefit greatly from including new approaches and methods for measuring the effects of chemicals. To that end, the effects work group organized their efforts around two themes and prepared separate articles (Bean et al., 2023; Rattner et al., 2023). First, a review was provided about improving standard in vivo test methods and how to advance the use of field studies in WERAs, based on the assumption that such tools will be needed in the foreseeable future (Bean et al., 2023). The key recommendations of this article are listed below.

Revisit the option of updating standard test protocols. Reconsider updating or refining the existing in vivo protocols, which could be done through a workshop organized by SETAC/OECD/HESI. Methods must focus on optimizing data quality and ensuring the biological relevance of test results. They must be geared toward improving the capacity to derive more useful effects concentrations (e.g., Benchmark Dose [BMD] methods) without increasing animal use and, ideally, by using fewer vertebrates to generate effects data for risk assessments.

Fill critical knowledge gaps on the sensitivity of amphibians, reptiles, and bats compared with current animal models. For reptiles, amphibians, and bats, a key knowledge gap is whether existing effects data and risk assessments are protective. To address this question rigorously, critical knowledge gaps must be addressed around sensitivity and, although beyond the scope of this article, extent of exposure. This should be done before resources are invested to develop new risk assessment frameworks for these taxa. If results demonstrate that existing animal models and risk assessments are not protective, then investigations that use traditional test methods coincident with promising new methods (e.g., in vivo omics and other NAMs) should be accelerated.

Reduce uncertainty in extrapolations. To extrapolate data more accurately from model species experiments to wildlife, generate and analyze data by making broad use of wildlife-specific, physiologically based toxicokinetic models, toxicokinetic and/or toxicodynamic models, and quantitative structure activity relationships. All of this should be done initially in a hazard assessment framework where each toxic endpoint is judged whether sufficient evidence exists considering each data stream. Then, DR information can be used to develop points of departure for extrapolation considering mode of action and physiological differences.

Develop and validate modeling approaches to individual and population level effects. To develop and validate modeling approaches to wildlife risk assessments that regulators will accept (e.g., as higher tier refinements), collaboration across sectors should be strongly encouraged and facilitated so that researchers pool their knowledge and contribute the required data.

Obtain clear regulatory guidance on field study design. For field studies, clear guidance from regulators must be solicited about what constitutes acceptable and robust design, both for exposure and effect assessments. That would help ensure that data quality and analysis are acceptable for use in risk assessments. Such guidance, together with adherence to the study designs, could increase the inclusion of field studies and monitoring in wildlife risk assessments for prospective and retrospective risk assessment.

Validate in vitro omics and other NAMs. Methods for in vitro omics and other NAMs need further development and must be validated against data from in vivo omics, tissue, organismal, and population studies for both legacy contaminants and newer chemistries. That would allow pathways from NAMs data to be linked to information from animal-based research, thereby improving the predictive ability and quality of ERAs for wildlife and supporting the transition from animal testing to NAMs.

Employ a holistic approach. With the goal of producing reliable and robust toxicity reference values, develop a framework that does not abandon methods with intact animals, which have taken decades to produce. Rather, develop a framework that builds on existing knowledge and integrates all lines of evidence from validated and soon-to-be validated techniques.

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In addition to the advancement of in vivo and/or field approaches, the effects work group focused on new and promising technologies to improve WERA (Rattner et al., 2023). For a long time, characterization of adverse effects in WERA has relied principally on data for survival, growth, and reproduction. Although these higher level endpoints will continue to be used in wildlife risk assessment, endpoints at many levels of biological organization could improve efficiency, reliability, and realism in estimating exposure–response relationships, including their ecological significance. These endpoints would therefore be a valuable addition to WERA through a weight of evidence approach. Further, the group concluded that, although the value of NAMs to ecotoxicological hazard assessments has been long acknowledged, their application has been mainly on aquatic species and phylogenetically lower forms, whereas their use in work with terrestrial wildlife, that is, amphibians, reptiles, birds, and mammals, is much less common. To address the identified challenges, the group explored a range of possible solutions, summarized here as recommendations.

Systematic reviews and improved evidence-integration techniques. The thorough collection, evaluation, and documentation of available evidence used to assess risks for human health should be more widely applied to wildlife, when possible. For wildlife, data should be collected from all levels of biological organization where there is biological relevance. Data from new tools such as NAMs, in silico predictions, and models can augment data collected from traditional toxicology studies (e.g., controlled laboratory animal studies).

Adverse outcome pathways. More focused research is needed to quantitatively link data on molecular mechanisms of toxicants to population outcomes. Specifically, more research at higher levels of organization is needed, particularly populations, to link to the extensive molecular data, for example, further exploration of methods in bioenergetics, such application of dynamic energy budget theory as a tool for quantitative linking across levels of biological organization.

Dose–response curves and meta-analyses. The use of DR relationships for wildlife ERA is recommended over the NOAEL and the lowest-observed-adverse-effect level (LOAEL) values when available; among other benefits, DRs can afford quantitative insights into the degree of the responses if an effect threshold is exceeded (Allard et al., 2010; Mayfield et al., 2014). Other useful tools include BMD models developed for human health risk assessment, which are now being applied to wildlife (Mayfield & Skall, 2018). More recently BMD models have also begun to incorporate Bayesian methods (Jensen et al., 2019).

Probabilistic approaches. Probabilistic risk assessment avoids compounded overestimation of risk, often a problem with deterministic RAs and the use of very conservative parameter estimates for models. Deterministic WERAs remain useful in screening approaches and may still be warranted; however, continual refinement of deterministic models can be problematic and may not achieve useful predictions. Issues with probabilistic methods include time and efforts needed to estimate variable distributions responsible for risk and ensuring that assumptions based on limited data are defensible. Methods commonly used in probabilistic approaches include Monte Carlo and Bayesian simulations, but these methods are more likely to be used to assess risk from complex and diverse stress factors. Currently, probabilistic methods may be feasible only for exposure estimation.

Population modeling. Protection goals, often an attempt to consider effects at the population or community level, and population models can be useful tools in WERA; however, work group participants recognized that few models consider the local species-specific factors most responsible for metapopulation regulation. However, population models can produce more holistic conceptualization of risk when these factors are considered. Probabilistic models can also provide population risk rates that incorporate uncertainty, which is useful in decision-making.

Ecosystem service models. The concept of ecosystem services has been employed to identify, describe, and value assignment of assessment endpoints and/or protection goals in wildlife risk assessment. The application of ecosystem models can have the added benefit of placing impacts in wider ecological and societal contexts. Valid applications of ecosystem functions within an ecosystem services framework include decomposition and microbial function. However, at this stage, there has been limited acceptance of ecosystem service frameworks as acceptable decision drivers for risk management at, for example, contaminated sites.

Risk characterization in wildlife risk assessment

As reflected in summaries of the various regulatory regimes for wildlife risk assessment (Johnson et al., forthcoming), decision-makers (typically regulatory entities) require that risk assessments address clear hypotheses from which to make decisions. Guidance and methods specific to wildlife are needed to identify the discrete information that is expected and to describe how it will be evaluated. From a policy perspective, the decision criteria must be objective and developed a priori. As a result, guidance on ecological risk assessment, including for wildlife, is relatively standardized and has not been explicitly revised to reflect new approaches. However, the review of regulatory guidance on wildlife found that many jurisdictions have flexibility to include NAMs and other emerging science if it can apply in a weight of evidence approach to enhance and augment the characterization of risk (Johnson et al., forthcoming).

Develop and implement weight of evidence approaches. Even when using conventional direct toxicity approaches to wildlife, assessors use assumptions to help extrapolate data

to address management goals. Emerging methods and tools, such as NAMs, wildlife-specific cell lines and physiologically based pharmacokinetic models, and alternative effect endpoints information (other than mortality, growth, and reproduction), can assist in weight of evidence approaches to address the influence of those assumptions and provide greater confidence in risk and/or hazard estimates. Extrapolating beyond direct toxicity to indirect effects requires greater understanding of metapopulations in multistressor environments that likely vary relative to the specific community. In many cases, ecological information that describes precise community-level regulating mechanisms for populations are absent. However, professional judgment approaches founded from recent ecological networks and science can inform improvements regarding multistressor effects (Toll, 1999; Toll & Pavlou, 1998). Models must incorporate these influences (e.g., how toxicity may affect predator vigilance, nest defense, mate selection, habitat choices, etc.). The relative influence of toxicity combined with an understanding of population (metapopulation) regulating mechanisms can be integrated in Bayesian approaches where ranges of effects can be estimated (Johnson et al., forthcoming).

OVERARCHING CONCLUSIONS AND HIGH-LEVEL RECOMMENDATIONS

After preparing the work group articles, WTIG hosted a session at the 2022 SETAC North America meeting after which various work group members continued discussions to build out overarching conclusions and high-level recommendations. The outcomes of those discussions are summarized below. We then conclude with ideas about how to achieve necessary change in the practice of wildlife risk assessment, going forward.

Integrating emerging science into WERA requires a thorough understanding of the problem and level of protection. Therefore, the measures and means to collect data must be considered relative to the problem formulation plan. Sample et al. (2022) provide recommendations for including novel methods in WERA and also document developments that consider resource use, ecosystem services, and population level effects. Clear understanding of the hypotheses and the tools suggested to help address these questions must be demonstrated, including the advantages and disadvantages of each tool's output. Ranges of potential data outcomes should be considered along with the ranges of decisions that could be made based on those outcomes. It is expected that this process will be refined as the field of wildlife risk assessment progresses and new data are collected. Use of screening approaches (such as conservative assumptions and hazard quotients) is appropriate in early stages of wildlife risk assessment; however, it is strongly recommended that screening methods not be further refined.

With respect to assessing exposure, it is essential that scientists and risk assessors cooperate to optimize acquiring data and curating wildlife studies so that risk assessment and decision-making can be improved. When engaging in this process, we recommend moving from tier-based approaches to an assessment framework based on standardized exposure scenarios that better address environmental relevance and uncertainty in a structured way. For this, a matrix checklist has been proposed (Morrissey et al., 2023). In this process, it is extremely important to characterize and quantify variation and uncertainty and to communicate the assumptions transparently. Because not all uncertainty can be addressed in prospective risk assessments, monitoring should be required for potential postregulatory exposures that may result from situations not addressed in the scenarios applied.

It is also essential to address changes in the societal contexts of chemical use. One example is the effects of environmental releases of specific antidepressant pharmaceuticals, which may, for example, affect the behavior of organisms in the environment. These releases are often unintentional and occur in the waste stream from disposal or metabolic excretion. Currently, no regulations exist to consider these pathways. Furthermore, in recent years societal impacts of zoonotic diseases have been immense, even beyond COVID-19. Exposure to immunomodulatory chemicals may affect the role that wildlife play in the dynamics of the pathogens causing these zoonotic diseases. Such risks are currently not addressed in WERA, which may be an issue, considering the potential for large-scale societal impacts. Future studies should consider influences of zoonoses relative to substance exposure. Linking influences of multiple stressors and their potential interactions to include those tied to human health (One-Health approach) may be required for informed decision-making. However, it is also recommended that risk assessors move forward proactively to facilitate such new societal developments to be included in WERA when deemed necessary.

HOW TO FACILITATE CHANGE IN WILDLIFE RISK ASSESSMENT

What will it take to advance the practice of wildlife risk assessment and its application in decision-making under the various regimes reviewed in this series of articles? Over the years, there have been education and communication about the gaps and challenges. New approaches to wildlife risk assessment have been developed through research (as reviewed in Bean et al., 2023; Morrissey et al., 2023; Rattner et al., 2023). There have been several calls to action and many presentations and discussions, which have resulted in only incremental change. Our intent in the WTIG leading this initiative was to trigger changes in practice, guidance, policy, and regulation. We encourage risk assessors and regulatory agencies to consider contributions that emerging science in ecology, toxicology, and exposure can make to increase the reliability of risk estimates and, ultimately, to improve evidence-based decision-making. We also recognize that more focus is needed to refine the steps to improve risk estimation for wildlife—this goes beyond incorporating newly available science. We look forward to continuing this dialogue among wildlife risk assessment

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professionals, ecologists, and toxicologists to refine research needs and fill remaining gaps.

AUTHOR CONTRIBUTIONS

Nico W. van den Brink: Conceptualization; data curation; formal analysis; investigation; methodology; project administration. **John E. Elliott**: Conceptualization; formal analysis; funding acquisition; investigation; methodology. **Beth Power**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration. **Clare Kilgour**: Data curation; investigation; methodology. **Mark S. Johnson**: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

This is a review solely based on literature information and discussions in the four different working groups and the authors. Therefore, no new data are provided.

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