2010

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Journal of Toxicology and Environmental Health, Part B: Critical Reviews
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uteb20

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Published online: 21 Jun 2010.

To cite this article: Vicki Dellarco, Tala Henry, Phil Sayre, Jennifer Seed & Steven Bradbury (2010) Meeting The Common Needs of a More Effective and Efficient Testing and Assessment Paradigm for Chemical Risk Management, Journal of Toxicology and Environmental Health, Part B: Critical Reviews, 13:2-4, 347-360, DOI: 10.1080/10937404.2010.483950

To link to this article: http://dx.doi.org/10.1080/10937404.2010.483950

Journal of Toxicology and Environmental Health, Part B, 13:347–360, 2010

ISSN: 1093-7404 print / 1521-6950 online
DOI: 10.1080/10937404.2010.483950

Taylor & Francis
Taylor & Francis Group

MEETING THE COMMON NEEDS OF A MORE EFFECTIVE AND EFFICIENT TESTING AND ASSESSMENT PARADIGM FOR CHEMICAL RISK MANAGEMENT

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Significant advances have been made in human health and ecological risk assessment over the last decade. Substantial challenges, however, remain in providing credible scientific information in a timely and efficient manner to support chemical risk assessment and management decisions. A major challenge confronting risk managers is the need for critical information to address risk uncertainties in large chemical inventories such as high- and medium-production-volume industrial chemicals or pesticide inert ingredients. From a strategic and tactical viewpoint, an integrated approach that relies on all existing knowledge and uses a range of methods, including those from emerging and novel technologies, is needed to advance progressive and focused testing strategies, as well as to advance the utility and predictability of the risk assessment by providing more relevant information. A hypothesis-based approach that draws on all relevant information is consistent with the vision articulated in the 2007 report by the National Research Council, *Toxicity Testing in the 21st Century: A Vision and a Strategy*. This article describes the current practices in evaluating chemical risks and ongoing efforts to enhance the quality and efficiency of risk assessment and risk management decisions within the Office of Prevention, Pesticides, and Toxic Substances at the U.S. Environmental Protection Agency.

CHEMICAL RISK ASSESSMENT AND MANAGEMENT CHALLENGES

The Office of Pesticides, Prevention, and Toxic Substances (OPPTS) is responsible for managing chemical risks from pesticides in agricultural, urban, and residential settings, and industrial chemicals during production including import, distribution, and use in industrial, commercial, and consumer applications. The legal authority to ensure that chemicals produced, sold, and used in the United States do not pose an unreasonable risk to health and the environment is provided by several federal statutes such as the Toxic Substances Control Act; Federal Food, Drug, and Cosmetic Act; Federal Insecticide, Fungicide, and Rodenticide Act; Food Quality Protection Act of 1996; and Endangered Species Act. Under these laws, the U.S. Environmental Protection Agency (EPA) must evaluate new and existing chemicals for their potential risks to human and ecological health risks, and find ways to prevent or reduce those risks before the chemical is put into use or released into the environment. In doing so, the U.S. EPA must maintain reliable schedules and meet statutory deadlines.

In managing chemical risks, new scientific challenges always arise that need to be addressed. Some contemporary examples include the need to consider risks to children and other susceptible populations, potential health impacts from new technologies (e.g., nanomaterials), emerging knowledge about

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modes or mechanisms of chemical toxicity (e.g., endocrine disruption), and the risks posed by multiple chemical exposures and non-chemical multiple stressors. The amount and quality of data available vary extensively among different chemicals, ranging from data-rich situations such as for the food use conventional pesticide active ingredients to data-limited situations such as for many of industrial chemicals and pesticide inert ingredients.

The major challenge for the risk management of environmental chemicals is that the pace of conducting safety and risk assessments is typically limited by the amount, quality, and type of toxicity information for many existing chemicals. A paradigm that focuses the regulated community, government, and interested parties on chemicals and endpoints of greatest concern would significantly improve health and environmental protection and increase efficiency. Test paradigms that include batteries of standard toxicology studies, primarily *in vivo*, which generate data on a range of different endpoints and often in multiple species, are both time- and resource-intensive processes that require the use of many animals. In situations where extensive *in vivo* data are available, in practice, only a portion of that data serves as the basis for the final risk assessment and risk management decision. Even for the endpoints covered in the Screening Information Data Set (SIDS) established by the Organization of Economic Cooperation and Development (OECD; www.chem.unep.ch/irptc/sids/oecdsids/sidspub.html), there are reasons to lessen the dependence on *in vivo* testing of all chemicals for all endpoints. These concerns are "amplified" given that, when considering large chemical inventories and the breadth of potential toxicity endpoints, only a small percentage of compounds are likely to be identified to pose a significant hazard in any given test guideline. As an example, when Health Canada used exposure- and hazard-based screening tools to identify the highest priority for assessment among 23,000 existing chemicals, approximately 20% of several thousand substances were efficiently set aside as nonpriorities based on conservative criteria (Hughes et al., 2009, Meek & Armstrong, 2007). Thus, in effectively addressing information needs for large numbers of chemicals in a timely manner, an approach that integrates hazard and exposure screening tools is needed that focuses *in vivo* testing on those chemicals and endpoints/adverse outcomes most likely to present a risk of concern.

ENHANCED INTEGRATED APPROACHES TO CHEMICAL PRIORITIZATION AND TESTING

A number of recent reports reflect the growing recognition that more efficient prioritization approaches and testing strategies are needed in both ecological and human health risk assessments (Bradbury et al., 2004; NRC, 2007; OECD, 2008). Broadly, there are various hazard- and exposure-based tools that can be integrated to advance the screening of untested or data limited chemicals. One set of tools that needs to be integrated into a framework/paradigm is (quantitative) structure–activity relationships ((Q)SAR) to identify and group similar chemicals, and to estimate relevant endpoint values to form prioritization schemes. The U.S. EPA Office of Pollution Prevention and Toxics (OPPT) has long used (Q)SAR to identify and prioritize information needs and estimate hazards of industrial chemicals. The applications of (Q)SAR are being advanced in both ecological and human health risk assessments. In the area of ecological risk assessment, (Q)SAR–based expert systems such as ASTER (U.S. EPA, 2009a) and ECOSAR (U.S. EPA, 2009b) are used to estimate toxicity to fish, invertebrates, and algae. In the area of human health risk assessment, analogs and chemical categories are used to estimate hazards of new chemicals under TSCA and to target potential follow-up testing. For example, OPPT recently made publicly available the Analog Identification Methodology (AIM), a tool designed to identify chemical analogs that have existing experimental (measured) data available in a specific set of publicly available databases (U.S. EPA, 2009c). Expert systems for prediction of carcinogenicity, such as

OncoLogic (U.S. EPA, 2005a), along with toxicity data from studies of similar chemicals can help to reduce uncertainties regarding potential carcinogenicity of a chemical for which there are no actual cancer studies. These SAR-based expert systems are generally used as part of an overall weight of the evidence approach to better characterize potential risk concerns for industrial chemicals as well as pesticide metabolites and contribute to decisions regarding additional data requirements.

In collaboration with OPPT, other agency programs applied these methods in situations where there are limited data. For example, in the assessment of inert ingredients, SAR was used to identify structurally similar compounds to form categories of chemicals. SAR principles are used to identify chemical "analogs"—chemicals that are closely related to the chemical of interest, but for which data are available and can be used to predict the properties and/or hazards of a chemical of interest that is lacking data. An extension of the analog concept is chemical categories—where a group of analogs are used to provide a basis for extrapolation.

The use of faster high-throughput (HTP) *in vitro* screens that profile the biological activities is emerging. Enormous efforts are underway by the research community to develop and apply these methods (e.g., http://www.epa.gov/ncct/toxcast). The integration of exposure, (Q)SAR, and HTP methods has the potential to enhance our ability to effectively screen compounds for risk. Thus, in achieving the goal of effective and focused chemical testing and generation of more relevant information, an initial and practical focus is to apply an integrated approach to testing and assessment to better prioritize across specific chemical inventories where toxicity data are needed to inform risk assessments for chemicals that do not have extensive *in vivo* toxicity information, including high-production-volume chemicals, pesticide inert ingredients, and certain antimicrobial pesticides, metabolites, and degradates of chemicals. This approach involves maximizing the use of existing data and combining different types of information on a similar chemical or group of structurally similar compounds, including predictive computer modeling and *in vitro* HTP assays.

RISK ASSESSMENT PARADIGM

Regardless of the technology being used, problem formulation is the first step in risk assessment, where risk management goals, scope, relevant exposure scenarios, assessment endpoints, and methodology are explicitly stated and an analysis plan is developed to evaluate the potential consequences of these scenarios. The importance of problem formulation has long been recognized in the U.S. EPA (U.S. EPA, 1997, 1998a, 2003). As emphasized by the recent National Academy of Sciences (NAS) report *Science and Decisions* (NRC, 2009), a properly executed approach assures the relevance of the risk assessment outputs for decision making. Often, a tiered approach may be used that begins with qualitative approaches and progresses to more sophisticated such as probabilistic methods approaches. A worst-case screening-level analysis may indicate a low level of potential concern with appropriate conservative assumptions or default safety factors. In some situations, a higher tier and more accurate analysis may be performed in response to regulatory compliance needs, setting regulatory standards, or for informing risk management decisions on suitable alternatives or trade-offs.

The current risk assessment paradigm of problem formulation, hazard, dose response, exposure, and risk assessment/characterization (U.S. EPA, 1997, 1998a, 2003; NRC 1983,1993, 2007) along with the source-to-adverse outcome pathway (Figure 1) is a good foundation for integrating existing and information from new technologies into a more efficient, hypothesis-driven approach. In particular, the source-to-adverse outcome pathway is a means by which data from different sources can be organized, integrated and linked at different levels of biological organization. As shown in Figure 1, this pathway begins with the presence of the chemical in the environment, the uptake and distribution of the chemical in the organism,

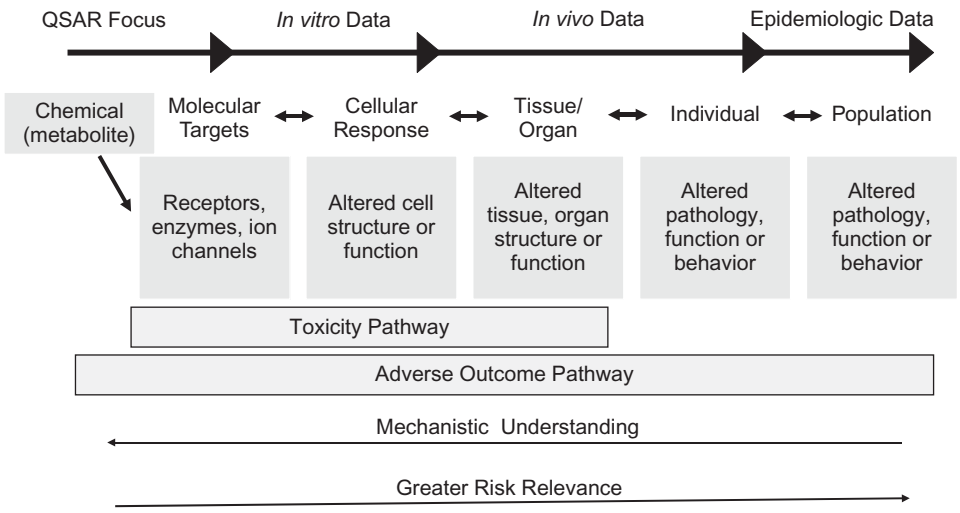

FIGURE 1. Source-to-Adverse Outcome Pathway: Understanding the linkage of key events across a continuum of biological organization for an adverse outcome will focus information needs and support mechanism-based screening and risk assessment (modified from Bradbury *et al.,* 2004).

the presence of the active chemical at a target site, and the series of biological or key events [mode of action (MOA)] that lead to an adverse outcome. There are a number of uncertainties that lie along this continuum; the type and magnitude of the uncertainties are dependent, in part, on the available chemical information.

More recently, the NRC (2007) updated the risk assessment testing and assessment paradigm by emphasizing the concept of toxicity pathways to help advance context and focus for MOA information that evolved over the last decade. In its 2007 report, NRC promotes a transformative paradigm shift in testing and assessment with the expectation that data acquired using *in vitro* models such as HTP systems, genomics, and computational methodologies will make it possible to predict pathways of toxicity that reflect mechanisms or modes of toxicity that could occur in humans. The increased use of *in vitro* systems and predictive modeling would provide a broader characterization of chemicals, chemical mixtures, and toxicity endpoints in a more time- and cost-effective manner, as well as resulting in reduce animal testing. This paradigm will not only address the need to efficiently evaluate the thousands of chemicals that lack toxicity data, but provide information that is more relevant to assessing risk, thus improving the basis of risk assessment by reducing uncertainties in the source to adverse outcome continuum.

The 2007 NRC charge and report centered on advancing toxicity testing for assessing the potential human health effects associated with exposure to environmental agents. However, under environmental legislative mandates including the Toxic Substances Control Act, the Federal Insecticide, Fungicide, and Rodenticide Act, and the Clean Water Act, most U.S. EPA programs must regulate chemicals to ensure that both environmental and human health risks are properly managed. As in the human health arena, development and application of computational and molecular approaches and identification of toxicity pathways apply to ecotoxicology and risk assessment as well (U.S. EPA, 2005b). Notable progress is being made on the development and use of toxicity pathway models and the creation of prioritization schemes, toxicology knowledgebases, and systems biology models in the field of environmental science (Schmieder et al., 2004; Degitz et al., 2005; Ankley et al., 2009). The bringing together of relevant disciplines to share data and integrate

models is critical to fully achieve increased efficiency in toxicity testing and a reduction in animal usage for both human health and environmental risk assessment.

REGULATORY APPLICATIONS OF COMPUTATIONAL TOXICOLOGY

To advance more predictive screening and risk assessment, a strategic hypothesis-based and progressive testing paradigm is needed, consistent with the recommendations of the NRC (2007). Such a paradigm should integrate, in a tiered fashion, existing knowledge of exposure and hazard combined with predictive information from newer in silico and *in vitro* technologies to target *in vivo* testing on the most likely risks of concern, and generate specific data needed for human health and ecological risk assessments. Described next are examples of how information from new technologies can be integrated into regulatory assessment scenarios.

Chemical Prioritization

To efficiently focus on those chemicals that are likely to pose a risk, existing data, in silico models such as SAR and *in vitro* data such as HTP assays combined with estimates of exposure, can be used to determine which chemicals and specific endpoints need to be focused on in *in vivo* testing. As shown in Figure 2, an entire chemical inventory that has limited or no toxicity data may be screened using a battery of predictive models and *in vitro* assays, applied in a tiered fashion, to determine the potential of chemicals to initiate molecular interactions that are the basis for producing adverse effects. At each level of biological organization (starting with molecular and cellular interactions) the potential for a chemical (or a group of chemicals) to exert particular toxicological effects is refined, such that there is a reduction in the amount of testing needed at each higher level of biological organization. Thus, instead of every chemical being tested for every possible endpoint in an *in vivo* test battery, only those tests that are

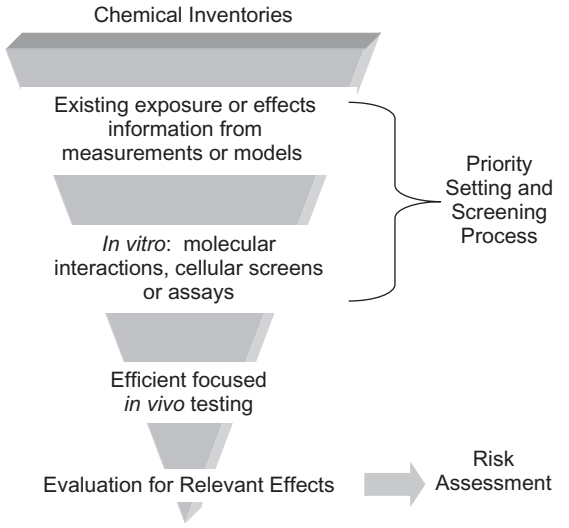

FIGURE 2. Integrated Testing & Assessment: Combine exposure and effects information from measures or models, such as (Q)SAR, thresholds of toxicological concern, read-across methods integrated with newer HTP *in vitro* data to prioritize and focus *in vivo* testing for efficient and effective chemical risk assessment and risk management.

rational for the chemical's toxicological potential are required. Such a screening process would efficiently filter through a large chemical inventory, assigning higher priority for *in vivo* testing to those chemicals with a greater potential for risk.

One example of a potential use of in silico and *in vitro* technologies is ranking the chemicals that should have the highest priority for endocrine screening. In the United States, the Food Quality Protection Act (FQPA) mandates the U.S. EPA to determine whether pesticide chemicals (active and inert ingredients) may exert an effect similar to an effect produced by naturally occurring estrogen or other endocrine effects. The U.S. EPA has developed an Endocrine Disruptor Screening Program (EDSP) that initially includes estrogen, androgen, and thyroid hormone systems and includes an evaluation of potential effects in both humans and wildlife as in fish, birds, amphibians and aquatic invertebrates (http://www.epa.gov/scipoly/oscpendo/index.htm). Given the large number of compounds that need to be screened, an effective method is needed that combines exposure and effects information to sort and prioritize large chemical inventories

for evaluation in the Tier 1 assays. With regard to effects information, the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) encouraged the U.S. EPA to evaluate the use of HTP assays for receptor binding and transcriptional activation and (Q)SAR for these endpoints to obtain empirical or predicted information on chemicals for which no data were available to support prioritization (U.S. EPA, 1998b). The U.S. EPA has ongoing efforts to develop medium- and high-throughput assay methods including biochemical assays of protein function, cell-based transcriptional reporter assays, multicell interaction assays, transcriptomics on primary cell cultures, and developmental assays in zebrafish embryos—for examples, see http://www.epa.gov/ ncct/toxcast—and (Q)SAR methods (for example, see http://www.epa.gov/scipoly/sap/meetings/2009/082509 meeting.html) to support future prioritization efforts for chemicals that contain little or no *in vitro* or *in vivo* endocrine effects data. An effective chemical prioritization approach would enable the U.S. EPA to initially focus EDSP screening on the chemicals most likely to pose a risk. Although the use of HTP systems and (Q)SAR is initially envisioned for chemical priority setting, as these approaches evolve and are used over time, they could be used as the Tier 1 screen to focus the need for the *in vivo* Tier 2 testing.

MECHANISM-BASED RISK ASSESSMENT

For years, there has been an interest in incorporating mode of action information into risk assessment so as to more accurately characterize what effects may be biologically plausible in humans and what susceptible populations may be more impacted by chemical exposure. To bring structure, rigor, and transparency to the evaluation of MOA data, a framework was put forth in conjunction with work by the International Programme for Chemical Safety (IPCS) (Sonich-Mullin et al., 2001) and by the U.S. EPA (2005c). This MOA framework provides a weight-of-evidence approach that is based on considerations for causality as originally articulated by Bradford Hill in epidemiologic studies, and includes considerations of dose response and temporal concordance, consistency, specificity, biological plausibility and coherence. Later, the International Life Sciences Institute (ILSI) further developed this MOA framework by incorporating a human relevance component (Meek et al., 2003; Seed et al., 2005). Once an animal MOA is established, qualitative and quantitative comparisons of each key event between the experimental animal and humans are conducted, including consideration of comparative biology, kinetics/metabolism, anatomical variations, and relevant human disease states. This enables a conclusion as to likely relevance of MOA for human risk. In 2006, the IPCS updated its 2001 paper and incorporated the ILSI human relevance part of the analysis (Boobis et al., 2006, 2008).

The IPCS/ILSI Mode of Action/Human Relevance framework provides an important tool to promote and formalize the use of MOA data in risk assessment regardless of whether the information comes from traditional approaches or new technologies. This framework also provides a structured and transparent approach to transition to the recommendations by the 2007 NRC to move away from phenomenologic approaches by using molecular technologies to identify (1) the ways environmental agents are changed though metabolic processes, (2) dose at the affected organ system, and (3) how an agent perturbs normal cellular pathways to produce their adverse effects.

Currently, the IPCS/ILSI Mode of Action/Human Relevance Framework has been used primarily in a top-down fashion. Thus, an *in vivo* toxicology study shows a toxicological response, and further studies are conducted to determine the key events in the MOA for that particular endpoint. There are numerous examples of this Mode of Action/Human Relevance Framework as applied to different environmental and pharmaceutical chemicals, endpoints, life stages, and MOA that can be found in Meek et al. (2003), Klaunig et al. (2003), Seed et al. (2005), Pastoor et al (2005), Boobis et al. (2006), and Holsapple et al. (2006). As illustrated by these examples, this

type of analysis has employed a variety of short-term *in vivo* assays, and more recently the use of more sophisticated technologies such as knock-out rodent models. An example using conazoles illustrates how new methods such as microarray analyses have informed MOA. Using an integrated approach involving histopathological and clinical chemistry results with gene expression profiles, a nongenotoxic mechanism of rodent hepatocarcinogenesis involving activation of the constitutive androstane receptor (CAR), hepatocyte hypertrophy, induction of CYP2B, induction of cell proliferation, and inhibition of apoptosis was found for specific conazoles (Chen et al., 2009; Peffer et al., 2007). Such MOA analyses will be valuable in revealing early biomarkers of disease using HTP methods. These HTP data can be obtained with fewer resources and less time, and provide valuable information regarding MOA. As an example, gene expression profiles from livers of rats treated up to 14 d have been successfully used to extract biomarkers discriminating groups of nongenotoxic and genotoxic hepatocarcinogens to calculate classifier profiles with up to 88% accuracy (Ellinger-Ziegelbauer et al., 2005, 2008).

The challenge for the future will be to use the Mode of Action/Human Relevance Framework in the opposite direction—that is, as a predictive tool for assessing specific toxicological responses. This will require an increased understanding of specific MOA and toxicity pathways, and most importantly of the quantitative relationships among the key events. It is then envisioned that diagnostic *in vitro* assays for early key events will be sufficient to predict toxicological outcomes, or enable limited *in vivo* studies.

MOVING TOWARD HYPOTHESIS, MECHANISM-BASED TIERED/ INTELLIGENT TESTING

One of the principle challenges of risk assessors is to provide risk managers with sufficient toxicological and exposure information to manage risks. It is important to note that the specific risk management needs may in fact differ depending on the nature of the risk management decision that is being made. Thus, greater uncertainty on potential toxicological hazards may be acceptable under conditions of defined and limited exposure, whereas more information may be necessary for chemicals with widespread exposure. Examples of the use of different data sets for context-based decision making are discussed by Doull et al. (2007). Components of an intelligent testing strategy include the use of exposure information (Christensen, 2003), thresholds of toxicological concern (TTC) (Kroes et al., 2005; Munro et al., 2008; Dekant et al., 2009), QSAR, categories and read-across methods, and diagnostic *in vitro* biochemical and cellular testing (HTP) methodologies.

Various approaches have been utilized by OPPTS to evaluate data limited chemicals. For example, OPPT's New Chemical Program has long used chemical categories to identify potential hazards and make decisions regarding testing requirements for new chemicals, for which few test data are typically available. In the category approach, closely related chemicals are considered as a group, or category, rather than as individual chemicals, and not every chemical needs to be tested for every endpoint. Rather, the physical–chemical properties and hazards of untested chemicals are inferred by comparison to a similar chemical or chemicals for which the properties of interest are known (U.S. EPA, 2002a; OECD, 2007a). This inference, variously called "read-across" and "bridging" in various programs within U.S. EPA, is based largely on structural similarity. The basic assumption is that similarity in structure implies similarity in activities or properties. The New Chemicals categories consist of a category statement that is typically defined by a simple molecular structure (structural alert), a description of the physical–chemical and fate properties and hazards expected for chemicals that fit the definition, and a tiered testing scheme that U.S. EPA may require for further evaluation of chemicals that fit within the category (http://www.epa.gov/ oppt/newchems/ pubs/chemcat.htm). The development and use of the New Chemicals Categories was originally

necessitated by constraints on availability of data and short review timelines required under TSCA, but the concept has also been applied widely in the U.S. High Production Volume Challenge Program and the OECD High Production Volume Chemicals Programme as well. Although the New Chemicals Categories do include knowledge of hazards associated with tested chemicals within chemical classes accrued from experience reviewing new chemical submission notices (i.e., premanufacture notices, PMN) and the formulation of HPV chemical categories strives to provide a mechanistic justification for the chemical grouping, the fundamental basis for forming categories is currently structural similarity. Systematic generation of new types of data (e.g., genomics, metabonomics, bioprofiling), using the chemical category concept as the basis for testing the similarity hypothesis, has the potential to greatly enhance the biological/mechanistic underpinnings of chemical categories and expand the use of this approach to characterizing chemicals.

QSAR and structural category approaches have also been used in the U.S. EPA Drinking Water Program to identify and prioritize testing and monitoring for disinfection by-products in drinking water (Woo et al., 2002). The process involved identification and structural classification of disinfection by-products (DBP) of potential concern, review of physical–chemical property and toxicity information for each structural class, development of a SAR knowledge base of each structural class, and generation of relative concern for each compound, in the context of exposure via water. The outcome of this application of SAR and chemical category approaches was a list of DBP, prioritized based on toxicological concern level. This list was subsequently adopted for U.S. EPA National Monitoring Study (U.S. EPA, 2002b) and prompted initiation of new research on the chemicals.

Tiered testing approaches have also been utilized in a variety of programs. In some cases, the tiered testing has been largely hazard-based. For example, the results of short-term *in vivo* studies are frequently used as a decision tool for the need for longer term *in vivo* studies in OPPT's New Chemical Program. In other programs, tiered testing has been based on both hazard and exposure information such as in the Voluntary Children's Chemical Evaluation Program (http://www.epa.gov/oppt/vccep/pubs/basic.html#tiers). Other programs have utilized a defined standard battery of tests such as in the assessment of food-use pesticides. However, regardless of the specific testing approach, all these programs are based on standard *in vivo* toxicology studies. In practice only a subset of the *in vivo* data forms the basis for the final risk assessment and risk management decision. 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.

A more mechanistic, hypothesis-driven approach would be more effective for chemical prioritization and tiered testing. As knowledge of MOA and critical toxicity pathways increases, in silico and *in vitro* technologies could be more widely used to create ways to efficiently and credibly predict toxicity potential and potency. Predictive tools for estimating exposure parameters also need to be further developed and implemented in order to achieve a more hypothesis-driven testing paradigm. These predictions would help assessors make reasonable decisions regarding whether additional *in vivo* studies are required to further refine a risk assessment. Combes et al. (2003) 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." This perspective also addresses responsible use of animals in *in vivo* testing (Combes et al., 2003; ECETOC, 2004).

PARTNERSHIPS

Partnering between the research community and regulatory agencies is critical to ensuring

coordination and alignment of goals, resources, plans, and to achieving the full scope of an efficient testing and assessment paradigm that improves our capacity to make credible risk assessments and risk management decisions. This requires the early involvement of regulatory programs in the planning of research to ensure the end results are relevant to regulatory decision making. In other words, new technologies need to be designed for a purpose (problem solving). Collaboration between the ultimate users of the technology and the developers will help clarify regulatory expectations and facilitate timely application of the new techniques.

Partnering among federal agencies and international organizations/agencies is also essential to improve the existing testing and assessment paradigms in a manner that is internationally harmonized. For example, in 2007 the OECD started the Molecular Screening Project, which evaluates a number of selected chemicals in a series of molecular screening *in vitro* HTP assays, with the aim of establishing a strategy for rationally and economically prioritizing chemicals for further evaluation based on molecular properties and categories linked to potential toxicity (see (http://www.oecd.org/document/29/0,3343,en_2649_34377_34704669_1_1_1_1,00.html). OECD member countries have long recognized the potential of (Q)SAR approaches for conducting initial hazard assessments for thousands of untested chemicals. The OECD countries developed a substantial body of information and guidance on using (Q)SAR approaches, including analogs and categories, in assessing chemicals (OECD, 1994, 2004a, 2004b, 2006, 2007a, 2007b). These efforts culminated in the development of the OECD (Q)SAR Application Toolbox, which aims to make (Q)SAR technology readily accessible, transparent, and less demanding in terms of infrastructure costs (http://www.oecd.org/document/23/0,3343,en_2649_34379_33957015_1_1_1_1,00.html).

The OECD also recently held a workshop on Integrated Approaches to Testing and Assessment (IATA)—*in vivo* and *in vitro* testing, (Q)SAR models, toxicogenomics, category and read-across assessment methodologies, weight-of-evidence and exposure considerations to facilitate information exchange and discussion aimed at increasing the understanding and application of (Q)SAR approaches and data generated by emerging technologies in chemical assessment (OECD, 2008). The workshop consisted of sharing national experiences in the use of such approaches to fulfill regulatory information requirements such as prioritization, classification and labeling, and risk assessment. Workshop conclusions included a range of strengths and current limitations for the use of various types of data, and recommendations were made to address these limitations so that a broader range of approaches to testing and assessment can be integrated into chemical assessments in the future.

STAKEHOLDER INVOLVEMENT

To achieve the goals just outlined, scientific tools and knowledge must be advanced with public participation to ensure broadly based confidence. Thus, an understanding of the perspectives of all stakeholders is critical for the successful transition toward the use of greater use of molecular and computational technologies for testing and assessment. Stakeholders need to be given an opportunity for early input on key science and regulatory developments. Information needs to be clearly and transparently communicated to allow the public to "feel more comfortable" with the shift from traditional animal testing to greater reliance on in silico and *in vitro* models. There needs to be a clear understanding among all affected parties of why changes in the current paradigm are needed, and how the use of new tools can be incorporated in risk assessments or risk-based decisions. Development of the science and tools will occur faster in some areas than others and therefore, will be incorporated into regulatory programs progressively over time. Hence, it will be important to communicate regularly with stakeholders about where a regulatory program is along this transition continuum.

As an example of early stakeholder engagement, in 2008 the U.S. EPA Office of

Pesticide Programs established a workgroup to advise the regulatory program on communication and transition issues associated with the use of 21st-century toxicology/new integrated testing strategies. This stakeholder workgroup was established under the Pesticide Program Dialogue Committee, which is a federal advisory committee. Organizations including environmental, worker protection, health advocacy, industry, and animal welfare groups, as well as other federal and international government partners, participate in this process. This work group has discussed a number of key issues, including identifying a list of typical questions and concerns regarding integrative testing and assessment from the stakeholder community. This list will provide advice on issues to emphasize to improve understanding of new emerging methods and their potential applications. Another key issue considered by this workgroup includes recommending specific metrics for the U.S. EPA to consider for communicating progress toward incorporating newer computer and molecular-based technologies in advancing testing and assessment. Metrics were also considered important to evaluate the success of the new paradigm in achieving more effective and efficient protection of human health and the environment. In addition, to discussing improved approaches to predict effects, the group also considered it important to explore opportunities for improved diagnostic biomonitoring and surveillance methods to detect chemical exposures and identify causes of adverse effects. More about this stakeholder group can be found at http://epa.gov/pesticides/ppdc/testing/index.html.

There are also a number of other efforts to engage the larger scientific and stakeholder community and to allow for the exchange of different perspective on the use on new computational and molecular sciences. For example, the U.S. EPA National Center for Computational Toxicology's Chemical Prioritization Community of Practice (CPCP) was formed in December 2005 to provide a forum for promoting dialogue with U.S. EPA staff, academic scientists, the international scientific community, and other stakeholders to help advance the utilization of computational chemistry, HTP screening, and various toxicogenomic technologies to address U.S. EPA needs for chemical screening and prioritization (http://www.epa.govNCCTpractice_communitycategory_priority.html). Additionally, the Johns Hopkins Bloomberg School of Public Health, Center for Alternatives to Animal Testing (Baltimore, MD) in conjunction with other organizations (e.g., McLaughlin Centre, Environmental Law Institute [Washington, DC], Center for Animal Law Studies at Lewis & Clark Law School [Portland, OR], the Animal Legal Defense Fund [CA]) is sponsoring a series of workshops to provide an opportunity of open dialogue among various stakeholder groups on the implementation challenges and opportunities generated by the vision contained in the NRC report on toxicity testing in the 21st century(http://www.mclaughlincentre.ca/events/toxicity/index.shtml,http://aldf.org/article.php?id=1078&preview= 1&cache=0).

CONCLUSIONS

There is a critical need to generate relevant and credible data for sound risk assessment and risk management that will lead to more efficient chemical testing and assessment. The current risk assessment/management paradigm is a reliable foundation for integrating existing and new knowledge and technologies into a more efficient, hypothesis-driven approach. A realistic near-term goal is to advance technologies for prioritizing chemicals for more focus *in vivo* testing. In the longer term, the goal is to increase the relevance and utility of risk assessment by understanding modes of action or toxicity pathways. Identification of early biomarkers or key events of disease using HTP methods is highly desirable because these data can be obtained with fewer resources and less time and can provide valuable information about MOA.

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