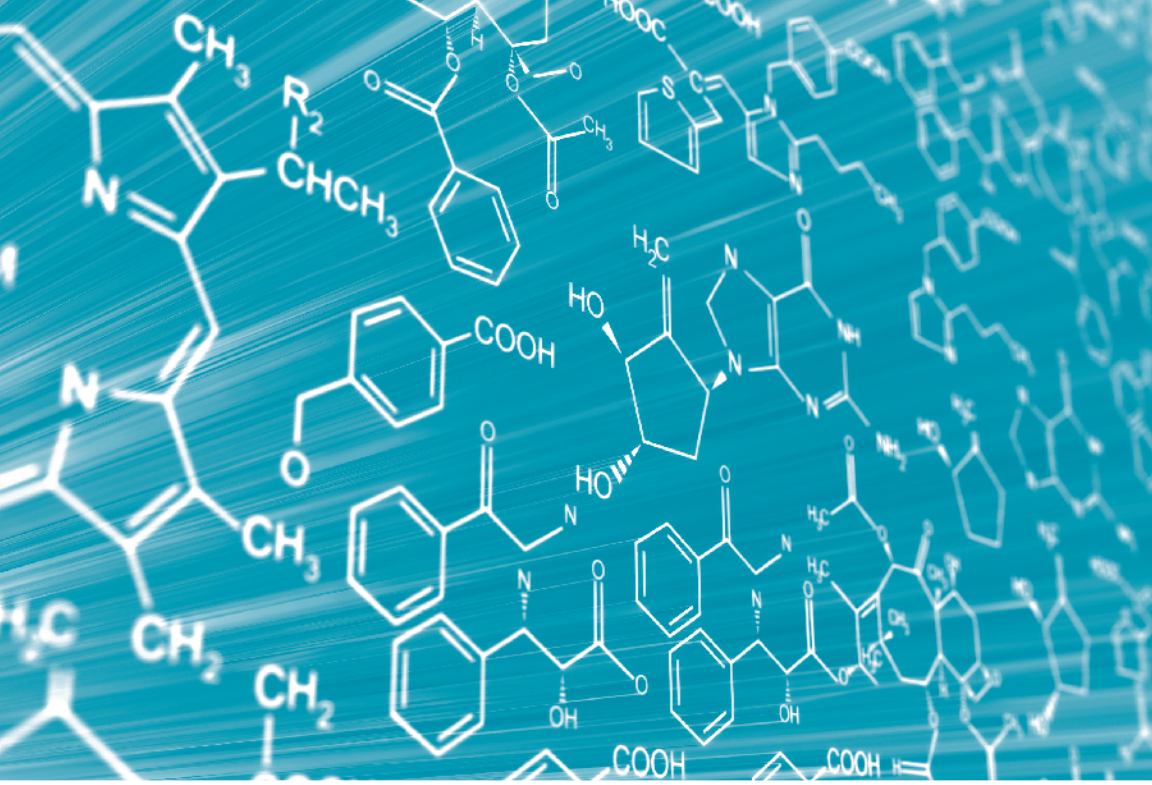

Integrating Emerging Technologies into Chemical Safety Assessment

Executive Summary

Council of Canadian Academies
Conseil des académies canadiennes

Science Advice in the Public Interest

INTEGRATING EMERGING TECHNOLOGIES INTO CHEMICAL SAFETY ASSESSMENT

The Expert Panel on the Integrated Testing of Pesticides

THE COUNCIL OF CANADIAN ACADEMIES
180 Elgin Street, Ottawa, ON Canada K2P 2K3

Notice: The project that is the subject of this report was undertaken with the approval of the Board of Governors of the Council of Canadian Academies. Board members are drawn from the Royal Society of Canada (RSC), the Canadian Academy of Engineering (CAE) and the Canadian Academy of Health Sciences (CAHS), as well as from the general public. The members of the expert panel responsible for the report were selected by the Council for their special competences and with regard for appropriate balance.

This report was prepared for the Government of Canada in response to a request from the Minister of Health on behalf of the Pest Management Regulatory Agency via the Minister of Industry. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the authors, the Expert Panel on the Integrated Testing of Pesticides, and do not necessarily represent the views of their organizations of affiliation or employment.

Library and Archives Canada Cataloguing in Publication

Council of Canadian Academies. Expert Panel on the Integrated Testing of Pesticides Integrating emerging technologies into chemical safety assessment [electronic resource]/The Expert Panel on the Integrated Testing of Pesticides.

Issued also in French under title: Nouvelles technologies et évaluation de la sécurité chimique.

Includes bibliographical references and index.
Electronic monograph in PDF format.
Issued also in print format.

ISBN 978-1-926558-38-7

1. Pesticides – Toxicity testing. 2. Pesticides – Government policy – Canada. I. Title.

SB959.6.C68 2012 632'.95 C2011-907899-6

Disclaimer: The internet data and information referenced in this report were correct, to the best of the Council's knowledge, at the time of publication. Due to the dynamic nature of the internet, resources that are free and publicly available may subsequently require a fee or restrict access, and the location of items may change as menus and web pages are reorganized.

Council of Canadian Academies
Conseil des académies canadiennes

Canada This assessment was made possible with the support of the Government of Canada.

The Council of Canadian Academies

Science Advice in the Public Interest

The Council of Canadian Academies is an independent, not-for-profit corporation that supports independent, science-based, expert assessments to inform public policy development in Canada. Led by a 12-member Board of Governors and advised by a 15-member Scientific Advisory Committee, the Council's work encompasses a broad definition of "science," incorporating the natural, social and health sciences as well as engineering and the humanities.

Council assessments are conducted by independent, multidisciplinary panels of experts from across Canada and abroad. Assessments strive to identify emerging issues; gaps in knowledge; Canadian strengths; and international trends and practices. Upon completion, assessments provide government decision-makers, academia, and stakeholders with high-quality information required to develop informed and innovative public policy.

All Council assessments undergo a formal report review and are published and made available to the public free of charge in English and French. Assessments can be referred to the Council by foundations, non-governmental organizations, the private sector, or any level of government.

The Council is also supported by its three founding Member Academies:

The Royal Society of Canada (RSC) is the senior national body of distinguished Canadian scholars, artists, and scientists. The primary objective of the RSC is to promote learning and research in the arts and sciences. The RSC consists of nearly 2,000 Fellows — men and women who are selected by their peers for outstanding contributions to the natural and social sciences, the arts, and the humanities. The RSC exists to recognize academic excellence, to advise governments and organizations, and to promote Canadian culture.

The Canadian Academy of Engineering (CAE) is the national institution through which Canada's most distinguished and experienced engineers provide strategic advice on matters of critical importance to Canada. The Academy is an independent, self-governing, and non-profit organization established in 1987. Members of the Academy are nominated and elected by their peers to honorary Fellowships in recognition of their distinguished achievements and career-long service to the engineering profession. Fellows of the Academy are committed to ensuring that Canada's engineering expertise is applied to the benefit of all Canadians.

The Canadian Academy of Health Sciences (CAHS) recognizes individuals of great accomplishment and achievement in the academic health sciences in Canada. The Academy provides timely, informed, and unbiased assessments of urgent issues affecting the health of Canadians. CAHS also represents Canada on the InterAcademy Medical Panel (IAMP), a global consortium of national health science academies whose aim is to alleviate the health burdens of the world's poorest people; build scientific capacity for health; and provide independent scientific advice on promoting health science and health care policy to national governments and global organizations.

The Expert Panel on the Integrated Testing of Pesticides

Leonard Ritter (Chair) Executive Director, Canadian Network of Toxicology Centres; and Professor of Toxicology, University of Guelph (Guelph, ON)

Christopher P. Austin Director, Chemical Genomics Center, National Institutes of Health (Bethesda, MD)

John R. (Jack) Bend Distinguished University Professor, Departments of Pathology; Physiology and Pharmacology; and Paediatrics in the Schulich School of Medicine and Dentistry, University of Western Ontario (London, ON)

Conrad G. Brunk Professor of Philosophy, University of Victoria (Victoria, BC)

Timothy Caulfield, FRSC, FCAHS Professor, Faculty of Law and School of Public Health; Research Director, Health Law Institute; and Canada Research Chair in Health Law and Policy, University of Alberta (Edmonton, AB)

Vicki L. Dellarco Science Advisor, Office of Pesticide Programs, United States Environmental Protection Agency (Washington, DC)

Paul A. Demers Director, School of Environmental Health, College for Interdisciplinary Studies; and Professor, School of Population & Public Health, Faculty of Medicine, University of British Columbia (Vancouver, BC)

Warren Foster Professor, Department of Obstetrics and Gynaecology; and Director, Centre for Reproductive Care, McMaster University Health Sciences Centre (Hamilton, ON)

Claire Infante-Rivard Professor, Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University (Montréal, QC)

Catherine Jumarie Professor, Department of Biological Sciences, Université du Québec à Montréal (Montréal, QC)

Sam Kacew Associate Director of Toxicology, R. Samuel McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa (Ottawa, ON)

Robert J. Kavlock Director, National Center for Computational Toxicology, United States Environmental Protection Agency (Durham, NC)

Daniel Krewski Director, R. Samuel McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa (Ottawa, ON)

Paul G. Mezey Canada Research Chair in Scientific Modelling and Simulation, Memorial University of Newfoundland (St. John's, NL)

Terry W. Schultz Emeritus Professor, Department of Comparative Medicine, College of Veterinary Medicine, University of Tennessee (Knoxville, TN)

Letter from the Chair

This report on the integrated testing of pesticides reflects the efforts and contributions of 15 panellists who brought a wealth of experience, knowledge, and perspective to this assignment. First and foremost, I am sincerely and deeply grateful to my colleagues on the Panel who contributed countless hours, days, and weeks so that our findings would be relevant, timely, and well-informed. Please know that your dedication to the task at hand did not go unnoticed. It was very much a pleasure and privilege to have had the opportunity to lead such a distinguished international group through many lively discussions and report drafts; and, to all of you, for having accorded me this opportunity, I am grateful. I am also indebted and grateful to Council staff for their support and assistance, and in particular for ensuring that we were in the right place at the right time and that we respected Council practices and policies. I want to specifically acknowledge and thank Renata Osika, Christina McMahon, and Michael Tyshenko.

I have reserved a very special thank you for Maria Trainer, Program Director at the Council with primary responsibility for this particular Panel. From the moment I first met Maria to respond to the invitation to serve as Chair of the Panel, her enthusiasm and spirit were infectious. In the year and a half that ensued to complete the work of the Panel, Maria brought rare talent, focus, discipline and, simply, boundless energy to complete a daunting task. I know my fellow Panellists join me in extending a heartfelt thank you to this outstanding young scientist.

Finally, my personal thank you to Elizabeth Dowdeswell, President of the Council, for your trust and confidence, both of which are very much appreciated.

Leonard Ritter
Chair, Expert Panel on the Integrated Testing of Pesticides

Project Staff of the Council of Canadian Academies

Assessment Team:	Maria A. Trainer, Program Director Christina McMahon, Program Coordinator
With Assistance from:	Renata Osika, Program Director Michael G. Tyshenko, Substantive Editor Joanna Ordowaz, Stylistic Editor Accurate Communications, Report Design Benoît Thouin, Translator, En-Fr (Canada), TETRACOMM inc. Mary-Christine Thouin, Editor, French, TETRACOMM inc.

Report Review

This report was reviewed in draft form by the individuals listed below — a group of reviewers selected by the Council of Canadian Academies for their diverse perspectives, areas of expertise, and broad representation of academic, industrial, policy, and non-governmental organizations.

The reviewers assessed the objectivity and quality of the report. Their submissions — which will remain confidential — were considered in full by the panel, and most of their suggestions were incorporated into the report. They were not asked to endorse the conclusions nor did they see the final draft of the report before its release.

Responsibility for the final content of this report rests entirely with the Expert Panel on the Integrated Testing of Pesticides and the Council of Canadian Academies.

The Council wishes to thank the following individuals for their review of this report:

Pierre Ayotte Associate Professor, Department of Social and Preventive Medicine; Member of the Public Health Research Unit, CHUQ-Laval University Medical Research Centre, Laval University (Ste-Foy, QC)

Alan R. Boobis Professor, Department of Medicine, Imperial College London (London, United Kingdom)

Gail Charnley Principal, HealthRisk Strategies (Washington, DC)

Mark Cronin Professor, School of Pharmacy and Chemistry, Liverpool John Moores University (Liverpool, United Kingdom)

Julia Fentem Senior Manager, Safety & Environment Assurance Centre (SEAC), Unilever (Bedfordshire, United Kingdom)

Claire A. Franklin Director, The LifeLine Group (Annandale, VA)

Thomas Hartung Director, Center for Alternatives to Animal Testing (CAAT), Johns Hopkins Bloomberg School of Public Health (Baltimore, MD)

Michael P. Holsapple Executive Director, International Life Sciences Institute's Health and Environmental Science Institute (ILSI-HESI) (Washington, DC)

Kannan Krishnan Professor, Occupational and Environmental Health, Faculty of Medicine, Université de Montréal (Montréal, QC)

Martin Stephens Senior Research Associate at the Johns Hopkins University Center for Alternatives to Animal Testing (Baltimore, MD)

Andrew Worth Leader, Computational Toxicology Project, Institute for Health & Consumer Protection, European Commission (Ispra, Italy)

The report review procedure was monitored on behalf of the Council's Board and Scientific Advisory Committee (SAC) by **Dr. Judith Hall**, Professor of Pediatrics and Medical Genetics, University of British Columbia. The role of the report review monitor is to ensure that the panel gives full and fair consideration to the submissions of the report reviewers. The Board of the Council authorizes public release of an expert panel report only after the report review monitor confirms that the Council's report review requirements have been satisfied. The Council thanks Dr. Hall for her diligent contribution as review monitor.

Elizabeth Dowdeswell, President and CEO
Council of Canadian Academies

Executive Summary

INTRODUCTION

Pesticides are widely used in agriculture, industrial applications such as those to maintain hydro rights-of-way and, until recently, urban landscapes. The safety of pesticides has attracted enormous attention, particularly uses in urban and residential landscapes, and many provinces have already implemented, or are considering restrictions of these uses. The issue of pesticide safety, in general, and the assessment of pesticide safety by government authorities, such as Canada's Pest Management Regulatory Agency (PMRA) is a matter of health and environmental concern for many Canadians. Pesticide products typically comprise two components: an active ingredient that works against the target pest, and secondly a mixture of solvents and adjuvants in which the active ingredient is dissolved and which often aids in the intended action of the active ingredient.

In vivo:
Within a living organism. For example, toxicity tests conducted using animal models.
In silico:
Performed on a computer or by computer simulation.
In vitro:
In an artificial biological environment outside of a living organism.
Mechanistic endpoints:
Mechanistic endpoints are those that can be measured in assays that are designed to evaluate a specific cellular or physiological response. The precise mechanism in question depends on the level of biological organization at which the phenomenon is observed.

The active ingredients of pesticides are among the most stringently regulated compounds in commerce; the toxicological assessment (laboratory studies) of the active ingredient follows a regimen similar to the preclinical safety assessment of a prescription drug. Risk assessors use the toxicological data on pesticides to evaluate the ecological risks, the human health risks (including those from residues in foods), and risks arising from occupational and bystander exposures. This extensive evaluation of the active ingredients, however, contrasts with the data requirements for the other components of the final pesticide product. These formulants, which are added to pesticide products to improve their physicochemical properties, enhance their use, or increase their stability, are not typically subject

to a full battery of toxicity tests, and are often data-limited. As a result, the final pesticide product contains a combination of data-rich and data-poor chemicals.

The data-rich and data-poor nature of a pesticide formulation is a metaphor for the dichotomy that exists for most industrial chemicals. While there are some substances that have an enormous amount of data (e.g., pesticide active ingredients and pharmaceutical drugs), the vast majority of industrial chemicals are extremely data-poor. Indeed, recent estimates suggest that toxicity data are lacking for 87 per cent of chemicals on the market (reviewed in Hartung, 2009). Although regulatory agencies around the world are addressing these issues, the task of evaluating the safety of thousands of compounds cannot be fulfilled using the existing *in vivo* toxicity paradigm.

The international harmonization efforts among Organisation for Economic Co-operation and Development (OECD) member countries have led to the definition of standard data sets that must be submitted with all pesticide approval applications. As a result of these observations, the Panel concluded that pesticides make an excellent model group for developing a blueprint or framework for integrating new testing techniques into the existing approach.

"Today, we are neither effectively translating scientific discoveries into therapies nor fully applying knowledge to ensure the safety of food and medical products. We must bring 21st century approaches to 21st century products and problems…"

"Most of the toxicology tools used for regulatory assessment rely on high-dose animal studies and default extrapolation procedures and have remained relatively unchanged for decades, despite the scientific revolutions of the past half-century. We need better predictive models to identify concerns earlier in the product development process to reduce time and costs. We also need to modernize the tools used to assess emerging concerns about potential risks from food and other product exposures…"

Margaret A. Hamburg (Commissioner of the U.S. Food and Drug Administration) (2010), Advancing Regulatory Science. Science, 331 (6020), 987.

THE CONTEXT

Regulatory toxicology has traditionally relied on studies in laboratory animals coupled with estimates of human exposure to define the hazards and risks of chemicals. The current testing requirements for pesticide active ingredients prescribe an

extensive battery of tests that generate data on potential adverse effects for a wide range of endpoints, in different species, for different exposures, and over critical life stages and processes. Data from animal tests are used to identify potential adverse effects and develop dose-response relationships that are integrated with modelled (or measured) estimates of human exposure to serve as the basis for risk assessment for various pesticide use scenarios.

Over the last several decades, the testing of pesticide active ingredients has been extensive. As a result, these chemicals are among the most data-rich in commerce. Nonetheless, the current testing scheme for pesticides is expensive and time-consuming and, as such, cannot, on a practical level, be applied to the thousands of chemical entities which governments worldwide must now categorize. Consequently, there is a significant gap between need and capacity in toxicity testing.

Many of the current toxicology tests were developed over 30 years ago. As science has evolved in recent decades, so has our understanding of physiology; however, these advances have not been reflected in changes to the battery of toxicity tests that are required for regulatory decision-making (reviewed in Seidle & Stephens, 2009). Many of the standardized tests that are used in the existing toxicity testing battery, although state of the art at the time of their inception, "… have remained relatively unchanged for decades, despite the scientific revolutions of the past half-century. We need better predictive models to identify concerns earlier in the product development process to reduce time and costs. We also need to modernize the tools used to assess emerging concerns about potential risks from food and other product exposures" (Hamburg, 2010). Moreover, traditional toxicology protocols were not designed to generate (or incorporate) data pertaining to molecular mechanisms and signalling pathways.

The issues inherent in the current approach are therefore two-fold: to address the lack of toxicity data for the vast majority of industrial chemicals and to recognize that regulatory decisions must be based on the best available science. As a result, there is a need for new approaches that are more predictive, more reliable, faster, less expensive, and that provide mechanism-based, chemical-specific toxicity information in order to better inform human health risk assessment.

Building on advances in information sciences, biology (molecular, cellular, and systems), and reliable high-throughput screening assays pioneered in the drug discovery field, toxicology is about to transform into a science that incorporates knowledge of the biological pathways by which chemicals exert adverse health

effects. This will permit the evaluation of more substances and provide a better understanding of the intrinsic toxicological properties of different chemicals. Besides application to individual chemicals, these new approaches will also enable new methods for assessing the effects of combinations of chemicals and new ways of characterizing exposures.

IATA

Integrated Approaches to Testing and Assessment (IATA) describes a fundamental paradigm shift in the field of regulatory toxicity testing. This shift could move regulatory testing away from the one-size-fits-all prescribed battery of toxicity tests currently used to evaluate data-rich chemicals and towards a refined and focused testing strategy. This testing strategy could be tailored to the toxicity profile and intended use of the chemical in question and would be flexible enough to address the large number of chemicals with little (or no) toxicity data.

IATA adopts a hypothesis-driven approach that can incorporate new scientific advancements into the existing toxicity testing system in a transparent and scientifically credible manner. As such, it relies on a range of tools and techniques (*in vitro*, *in vivo*, and *in silico*) in order to focus testing resources on the toxicity endpoints of concern. Its strength lies in the breadth of information that is used to understand the toxicological profile of a chemical; ultimately, the collective information can more reliably inform a regulatory decision.

IATA: A tiered approach to data gathering, testing, and assessment that integrates different types of data (including physicochemical and other chemical properties as well as *in vitro* and *in vivo* toxicity data). When combined with estimates of exposure in an appropriate manner, the IATA provides predictions of risk. In an IATA, unsuitable substances are screened out early in the process. This reduces the number of substances that are subjected to the complete suite of regulatory tests. Plausible and testable hypotheses are formulated based on existing information and/or information derived from lower tier testing and only targeted testing is performed in the higher tiers. Failure to satisfy the toxicity requirements at a lower tier typically precludes further testing at a higher tier.

THE QUESTION

In May 2009, the Government of Canada, through the Pest Management Regulatory Agency (PMRA) of Health Canada, asked the Council of Canadian Academies to appoint an expert panel to answer the question, "What is the

scientific status of the use of integrated testing strategies in the human and environmental regulatory risk assessment of pesticides?" The charge to the Panel was further specified in a series of sub-questions:[1]

- What is the state of the science of the tools and data sources associated with integrated testing strategies?
- What is the current status of the use of integrated testing strategies for the risk assessment of pesticides, pharmaceuticals, industrial chemicals, and other chemical substances by regulatory agencies around the world?
- Could there be potential impacts on the public's perception and confidence in regulatory risk assessment and risk management decisions for pesticides if integrated testing strategies were implemented?

THE FINDINGS

What is the scientific status of the use of integrated testing strategies in the human and environmental regulatory risk assessment of pesticides?

> "We propose a shift from primarily *in vivo* animal studies to *in vitro* assays, *in vivo* assays with lower organisms, and computational modeling for toxicity assessments."
>
> Francis Collins (Director of the National Human Genome Research Institute and now Director of the US National Institutes of Health Toxicology) (2008). Transforming Environmental Health Protection. Science, 319 (5865), 906-907.

To date, aspects of computational toxicology (i.e., the use of alternative approaches to traditional animal testing) have primarily been used to support regulatory decision-making for data-poor chemicals such as pesticide formulants. Although the Panel is not aware of a complete set of alternative methods that could replace the entire testing paradigm today (even for data-poor chemicals), the state of the science is evolving rapidly. With the continued development of such tools and approaches, the Panel expects to see increased use of integrated testing strategies in decision-making, with an eventual adaptation to inform decisions involving data-rich chemicals. As such, these emerging technologies, integrated with existing data, are a pragmatic means by which new testing methods could be used to augment the regulatory paradigm and help bridge the transition to a hypothesis-driven approach to testing and assessment.

1 Although environmental and human health risk assessments share many of the same basic properties, they differ substantially in scope and underlying philosophy. As a result, the expertise needed to address the charge from the perspective of environmental risk assessment would be quite distinct from that of human health risk assessment. For this reason, given its expertise, the Panel chose to focus its assessment primarily on test methods that form the basis of human health risk assessment. While this report does not explicitly address creating toxicity pathways based on the biology of the target species of ecotoxicity testing, there is overlap and the report tries to draw linkages where possible.

What is the state of the science of the tools and data sources associated with integrated testing strategies?

Integrated Approaches to Testing and Assessment (IATA) represent a pragmatic approach that will move toxicology away from describing *what* happens towards explaining *how* it happens. There is no single IATA however. Fundamental to the use of any IATA is the existence of an adverse outcome pathway (AOP), which causally relates key events at different levels of biological organization to the *in vivo* endpoint of regulatory interest. Advances in numerous scientific disciplines are contributing to the rapid evolution of new and relevant tools. At the heart of this evolution are the fields of systems biology and computational toxicology.

IATA adopts and integrates tools from a wide variety of disciplines; these tools are all at different stages of readiness and are constantly evolving. Some of these tools use computational approaches to leverage existing toxicity data; others focus on generating new data using a variety of alternative approaches that harness rapid advances in systems biology. The acceptability and applicability of these tools for use in a regulatory context will be enhanced by the functional engagement of the international regulatory community and the execution of proof-of-concept studies that build confidence and familiarity in new approaches.

Over the past five years, significant research efforts have focused on developing new approaches and models for predictive toxicology and executing robust, proof-of-concept studies. These proof-of-concept studies have highlighted the importance of comprehensive and computable data and have shown the value of legacy data in the evolution of predictive toxicology.

As a result of these studies, IATA tools can now be used to make predictions about acute toxic endpoints. In the short term (one to two years) additional IATA approaches to evaluate critical local effects will likely be available. Non-animal replacement approaches to long-term endpoints (carcinogenicity, reproductive toxicity) are more challenging, and it is likely that it will be at least a decade before they are ready to be used in a regulatory context. IATA tools can also be used in a regulatory context to address the information gap for data-poor chemicals. Currently, regulatory decisions for data-poor chemicals are made based on little (or no) primary data.

What is the current status of the use of integrated testing strategies for the risk assessment of pesticides, pharmaceuticals, industrial chemicals, and other chemical substances by regulatory agencies around the world?

There are a number of examples of the use of components of IATA in a regulatory context for industrial chemicals and personal care products; however, there is no single example of a comprehensive hierarchical deployment of IATA in a regulatory context.

The Panel anticipates that the regulatory deployment of IATA strategies will vary depending on the type of chemicals in question and the nature of the decision-making process that the data are intended to inform. For data-poor chemicals, the lack of data supporting rational hypotheses for a plausible toxicological potential may be the impetus for a new approach. Data-rich chemicals are already subject to an extensive battery of toxicity tests; therefore establishing relevance may take longer and will be predicated on building and establishing trust in the new and novel methods. Although the adoption of IATA strategies might refine and streamline the testing of these chemicals as well as enhance the reliability of the outcome, the Panel does not anticipate a widespread deployment of IATA in the short term.

IATA is predicated on the use of all existing data in order to identify data gaps and ultimately to inform decision-making. As a result, the concept of an IATA that is grounded in an understanding of the biological mechanisms that explain toxicological effects could lead to a more efficient testing strategy so that not every endpoint for every chemical needs to be evaluated in an *in vivo* test.

The dynamic nature of IATA necessitates a new approach to test development and regulatory acceptance. Alternative methods (either testing or non-testing) typically target specific cellular or physiological responses and, as such, preclude validation with *in vivo* data by a one-for-one approach. The adverse outcome pathway (AOP) allows for the use of a suite of models or assays (and subsequent databases) that are designed to target particular steps along a specific pathway. Each assay/data set in an array of information would inform the next tier of the IATA or be used as part of an overall integrated testing strategy. The scientific justification of an alternative method should therefore focus on comparing the test outcome to what is known about the underlying biology as described in the AOP. As a result, the Panel believes that the scientific validation of an alternative

test method should be based on understanding the biological AOP or mode of action (MoA). Alternative tests would therefore be validated against mechanistic endpoints and not against a current *in vivo* protocol that may not be valid for predicting adverse outcomes in human populations.

Test development should be predicated on a functional collaboration between regulators and scientists to ensure that tests evolve to fit the needs of the testing paradigm. An evaluation and peer review of the assumptions, relevance, reliability, sensitivity, and specificity of alternative methods must occur prior to regulatory acceptance. This should be coupled with capacity-building initiatives within the regulatory community to develop comfort with the science underpinning the alternative tests and to build familiarity with the data that these tests produce.

> "The reason why new concepts in any branch of science are hard to grasp is always the same; contemporary scientists try to picture the new concept in terms of ideas which existed before."
>
> Freeman Dyson, 1958.

Could there be potential impacts on the public's perception and confidence in regulatory risk assessment and risk management decisions for pesticides if integrated testing strategies were implemented?

Yes. A major question that will be raised by implementing the new IATA tools in the regulatory system will be whether these changes enhance the ability to identify the most important risks to human health and environment or whether they compromise this ability in the interest of other social and economic values. The public will likely demand assurances that the new methods reduce overall uncertainties in the assessment of chemical risk and, where new uncertainties are introduced, that these will be handled in ways at least as precautionary as in the current system (see Chapter 5).

The risks associated with chemical pesticides are a particular worry to the general public, and changes in regulatory processes are sure to trigger concerns. Regulators will need to reassure the public that these changes are being made to provide more reliable assessments of health and environmental risks rather than to streamline processes and sacrifice safety for social or economic benefits.

While the strengths and weaknesses of the current system of chemical risk assessment are not widely understood by the general public, concerned stakeholders

are likely to evaluate any changes against this historical benchmark, regardless of its inherent limitations. The questions that regulators would need to address would likely include the following:

- Will the new IATA tools be used to supplement (and thus strengthen) the current system or to replace it?
- What scientific uncertainties in the current system of chemicals management are reduced by the implementation of new IATA tools? What new uncertainties are introduced by the use of these tools?
- How will the changes in the scientific uncertainties be handled in the regulatory process?
- Will the current "margins of safety" used in the *in vivo* toxicity testing regime be reduced?
- Will this lower safety standards with respect to certain kinds of chemicals?

The Panel believes that the new IATA tools can, and should only, be introduced into the regulatory system in a supplementary manner, and this can be done in such a way as to increase the ability of the system to identify more reliably the most significant risks, especially with respect to data-poor chemicals. If done in this way, the issues of public concern summarized above can be addressed in a way that maintains, and even strengthens, public confidence in the regulation of chemical pesticides.

Transparency is a critical component in the building of public confidence in the regulatory system as IATA tools are implemented. It is important that the use of new tools is explained as clearly and accurately as possible, and that the approaches for the handling of the changes in scientific certainty and uncertainty are made clear.

SUMMARY

> "All models are wrong, but some are useful."
>
> George Box, 1987.

Recent estimates suggest that toxicity data are lacking for 87 per cent of chemicals on the market (reviewed in Hartung, 2009). While the toxicological base supporting the safety of some chemicals, such as pesticide active ingredients, is extensive and has contributed significantly to our understanding of the toxicology of these products, on a practical level it cannot be applied to the tens of thousands of chemicals that regulatory agencies worldwide must now categorize. Consequently, there is a significant gap between expectation and capacity in toxicity testing, and an urgent need for new approaches that are more predictive, more reliable, faster, less expensive, and that provide mechanism-based, chemical-specific toxicity information in order to better inform human health risk assessment.

In May 2009, the Pest Management Regulatory Agency (PMRA) of Health Canada asked the Council of Canadian Academies to appoint an expert panel to answer the following question: "What is the scientific status of the use of integrated testing strategies in the human and environmental regulatory risk assessment of pesticides?" Although a complete set of alternative methods that could replace the entire current testing paradigm does not yet exist, the state of the science is evolving rapidly, and the Panel expects to see a global evolution toward the use of integrated testing strategies in decision-making, with the anticipation that this will better inform decisions for both data-rich chemicals and data-poor chemicals, over the next two to 10 years. The Panel expects that the regulatory deployment of Integrated Approaches to Testing and Assessment (IATA) will vary depending on the types of chemicals and the nature of the decision-making process that the data are intended to inform.

The potential risks associated with exposure to pesticides are already a particular worry for many people, and adoption of new IATA strategies in regulatory processes are almost certain to further underscore and exacerbate these concerns. Regulators must recognize the need to engage the public in meaningful dialogue in order to provide assurance that the new IATA approaches seek to reduce overall uncertainties in the assessment of chemical risk. Moreover, that these changes will provide more reliable assessments of potential risks to human health and the environment, rather than to simply streamline processes and sacrifice safety for social or economic benefits.

Council of Canadian Academies
Conseil des académies canadiennes

Council of Canadian Academies
180 Elgin Street, Suite 1401
Ottawa, ON K2P 2K3
Tel: 613-567-5000
www.scienceadvice.ca