January 2012

Report in Focus

INTEGRATING EMERGING TECHNOLOGIES INTO CHEMICAL SAFETY ASSESSMENT

Protecting human health and the environment is of paramount importance to Canadians. As such, there has been an increasing demand for improved regulation of chemicals in Canada. Nevertheless, recent estimates suggest that toxicity data are lacking for over three quarters of the chemicals on the market. In fact, this paucity of data can extend to the other components within a chemical product. For example, the active ingredients in pesticides are among the most stringently regulated compounds on the market; however, the final pesticide product may also contain data-poor formulants. Added to enhance the use or increase the stability of the pesticide product, formulants are not typically subjected to the full battery of toxicity tests that the active ingredients must undergo.

The data-rich and data-poor nature of pesticide formulation is a metaphor for the dichotomy that exists for most industrial chemicals. While there are some substances for which we have an enormous amount of data, such as pesticide active ingredients, the vast majority of industrial chemicals are extremely data-poor.

KEY DEFINITIONS:

Pesticide: The end-use pest control product. A pesticide typically contains both an active ingredient and formulants.

Pesticide active ingredient: The ingredient that controls the pest. It must be clearly identified on the product label.

Pesticide formulants: The non-active ingredients added to a pest control product, typically to improve or enhance its properties (e.g., stability).

***In vivo*:** Within a living organism. For example, toxicity tests conducted in animal models (a laboratory animal used as a human surrogate in order to identify potential adverse health outcomes due to exposure to toxicants).

***In vitro*:** In an artificial biological environment outside of a living organism.

***In silico*:** Using a computer or by computer simulation.

With the increasing global interest for improved regulation of chemicals, regulatory agencies around the world are addressing the issue of data-poor chemicals. While the current testing scheme for certain chemicals, such as pesticide active ingredients and pharmaceutical drugs, is extensive and has contributed significantly to our understanding of the toxicity of these products, on a practical level it cannot be applied to the thousands of chemicals that governments worldwide have not yet categorized. Consequently, there is a significant gap between need and capacity in toxicity testing.

Many of the current toxicity tests, based largely on testing in laboratory animal *in vivo* studies, were developed over 30 years ago and have changed little since. Today, these tests are inadequate to address the backlog of data-poor chemicals. The task of evaluating thousands of data-poor compounds cannot be completed using the existing *in vivo* toxicity program.

Advances in information sciences, molecular, cellular and systems biology, and computational toxicology are contributing to the rapid evolution of new tools for toxicity testing. By building on these advances, toxicity testing could more effectively incorporate knowledge founded on *in vitro* and *in silico* methods that evaluate changes in biological processes in humans, rather than relying primarily on animal testing. Although there is not yet a complete set of alternative methods that can replace the current *in vivo* testing paradigm for data-rich chemicals, there are already some changes taking place globally to develop new approaches to testing. These integrated testing strategies are more predictive, more reliable, faster, less expensive, and provide mechanism-based, chemical-specific toxicity information to better inform human health risk assessment.

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.

CANADA'S ROLE IN CHEMICAL AND PESTICIDE REGULATION

Many chemical substances are subject to international regulations for research and development as well as for marketing. Differences between national requirements can create inconsistencies and barriers to international trade. Several international organizations are working to minimize such impediments; they also aim to reduce duplication of data collection while remaining vigilant about ensuring the protection of human health and the environment. Some of these organizations (for example, the North American Free Trade Agreement Technical Working Group on Pesticides) are responsible for developing regulatory policies; others (for example, the Organisation for Economic Co-operation and Development) inform policy development. The Government of Canada actively participates in these international cooperative initiatives. Individual Canadians knowledgeable in various aspects of pesticides regulation, use and safety contribute to discussions about the coordination of domestic and international policies for assessment of pesticide risk.

Canada is a world leader in the development and implementation of *in silico* screening and prioritization tools. In 1999, the Canadian Environment Protection Act required that the approximately 23,000 substances on the Domestic Substances List be categorized and prioritized for assessment by September 2006. As a result of coordination between federal agencies, Canada became the first country to systematically evaluate all chemicals currently in commercial use, with 4,300 chemicals prioritized for further testing and 500 classified as being of highest priority.

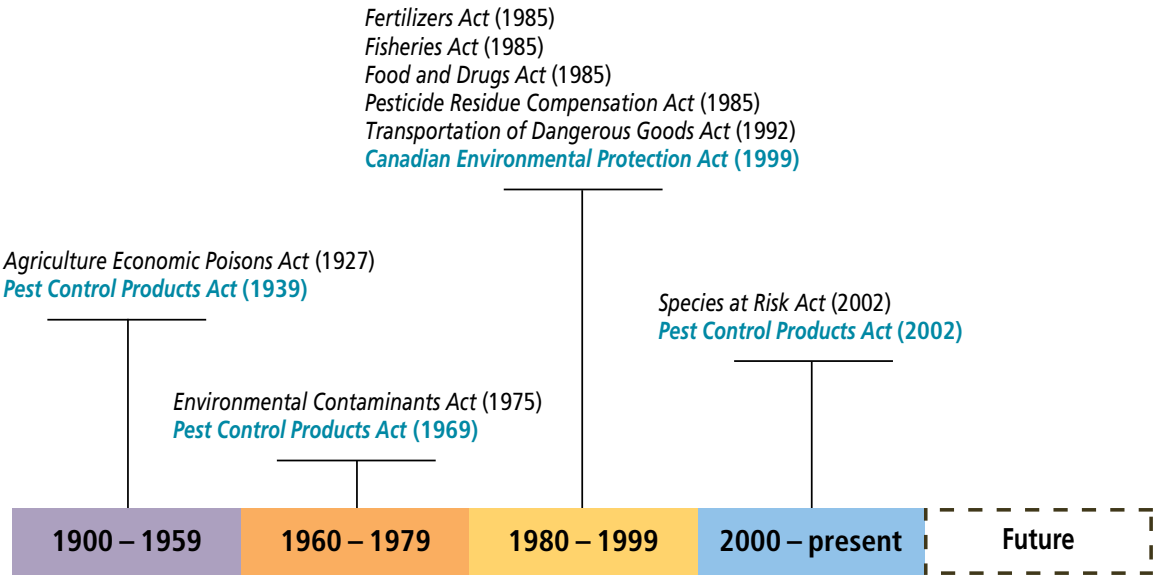


Figure 1: A history of federal pesticide regulation in Canada.

A significant change in Canadian pesticide regulation occurred in 1995, with the establishment of the PMRA within Health Canada and the transfer of the responsibility for the regulation of pest control products from Agriculture Canada.[1]

Responding to the Question

All levels of government in Canada play a role in regulating the sale and use of pesticides; however, the federal government is responsible for the registration of pest control products in Canada. In May 2009, the Minister of Health, on behalf of the Pest Management Regulatory Agency (PMRA), approached 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."

In response to this question, the Council assembled a multidisciplinary panel of 15 eminent experts from Canada and the United States. This Expert Panel was chaired by Dr. Leonard Ritter, Professor of Toxicology in the Department of Environmental Biology at the University of Guelph, and Executive Director of the Canadian Network of Toxicology Centres. The report of the Expert Panel provides an in-depth assessment of the current state of the science of integrated testing strategies by addressing the following questions:

- 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 report is based on a review of scientific literature, expert witness submissions, analysis of international developments, and the Panel's own extensive expertise.

UNDERSTANDING RISK

Risk is a function of both a chemical's inherent toxicity (i.e., its hazard) and the probability of sufficient exposure to elicit an adverse effect on the health of a susceptible individual. Toxicity testing is carried out to evaluate the hazard of a particular chemical. Hazard is an intrinsic property of the chemical of interest; susceptibility is inherent to the affected organism and exposure is a result of the environment into which the chemical is released.[2]

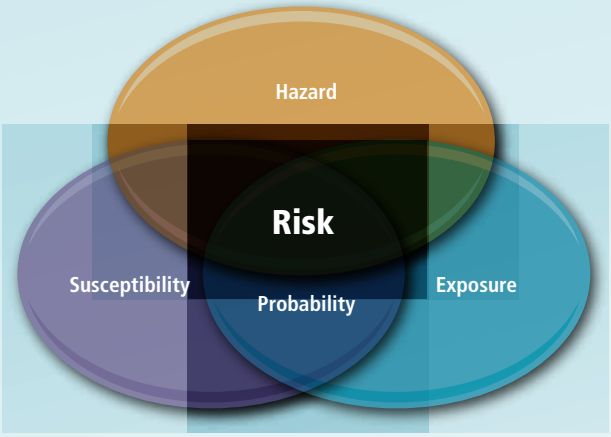


Figure 2: Risk is a function of Hazard, Exposure, and Susceptibility.

The current regulation of pesticides is based on risk assessment and risk management. The purpose of risk assessment is to answer the question: "What is the risk that exposure to a particular hazard (e.g., a pesticide) will result in harm?" Risk management then seeks to mitigate this risk and evaluate the impacts of regulatory measures on this risk.[3]

KEY DEFINITIONS:

Assay: A form of scientific experiment; the experimental process for determining the effects of a test substance on a biological system.

IATA: Integrated Approaches to Testing and Assessment. IATA permits the adoption and integration of tools and techniques from a wide variety of disciplines in a transparent and scientifically sound manner. These approaches could shift regulatory testing away from the current one-size-fits-all prescribed battery of toxicity tests and exposure studies and towards a refined and focused testing strategy that could be tailored to the toxicity profile and intended use of the chemical.

Mechanistic Endpoints: are those that can be measured in assays that are designed to evaluate a specific cellular or physiological response.

"The issues inherent in the current approach to chemical testing are 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. The Panel believes that these challenges can be best met by adopting an Integrated Approach to Testing and Assessment (IATA)."

– Leonard Ritter, Chair of the Expert Panel

INTEGRATED APPROACHES TO TESTING AND ASSESSMENT (IATA)

Integrated Approaches to Testing and Assessment (IATA) represent a pragmatic approach that will move toxicology away from describing *what* happens towards an explanation of *how* it happens. Toxicity testing will no longer depend on the one-size-fits-all hazard-based checklist of tests currently used but rather be based on a refined and focused testing strategy tailored to the toxicity profile and intended use of the chemical in question. An IATA strategy uses a tiered approach to help categorize and prioritize higher risk chemicals; all of the existing data on a substance are compiled at the start of the testing process in order to evaluate what data gaps exist and what testing approaches would be most appropriate to understand the precise toxicological profile of that substance.

IATA adopts and integrates tools and techniques (*in vitro*, *in vivo*, and *in silico*) from a wide variety of disciplines in a transparent and scientifically defensible manner in order to focus testing resources on potential toxicity endpoints more quickly (see Figure 3). Its strength lies in the breadth of information used to develop an understanding of the toxicological profile of a chemical; ultimately, the collective information is used to more reliably inform a regulatory decision.

The Panel anticipates that 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.

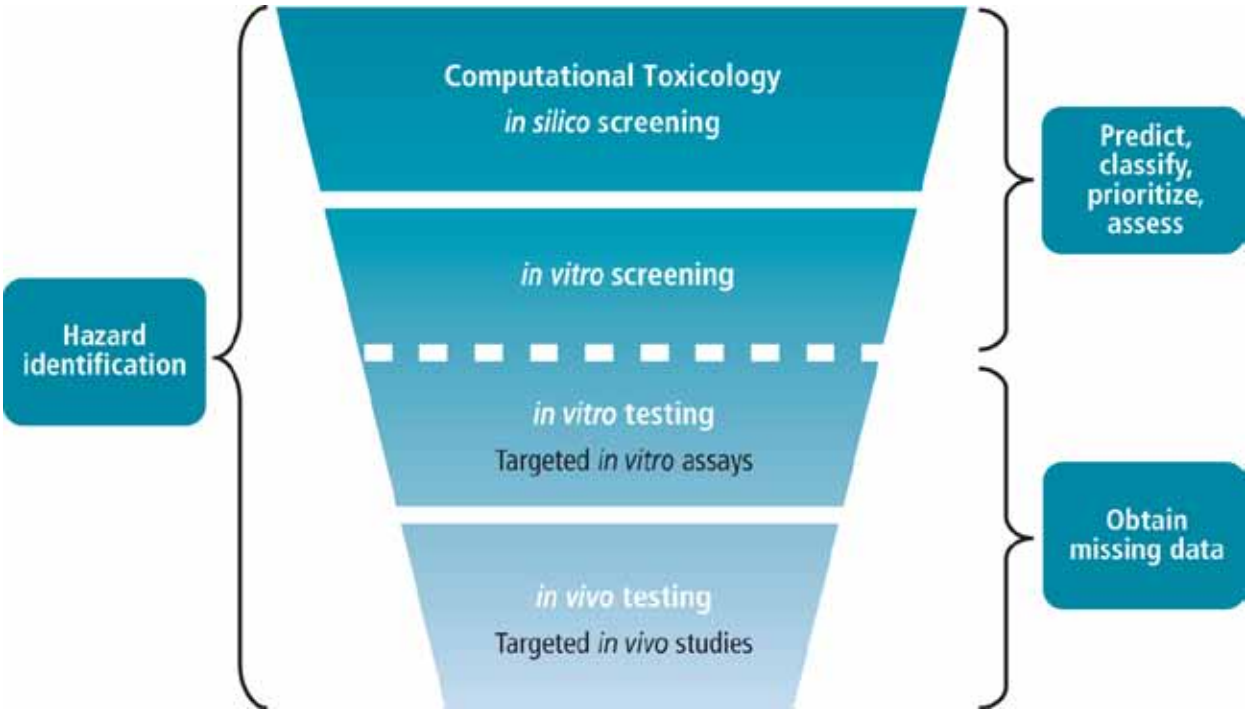


Figure 3: The purpose of an IATA approach is to focus testing on the endpoints of concern.

It is time to move away from thinking about alternative toxicity assessment approaches and their validation in terms of a one-for-one replacement of an existing animal study and towards a new approach that is anchored in an understanding of the underlying biology.

Assessing the Evidence

Although the existing approach to toxicity testing for data-rich chemicals is well-established, this approach also has some limitations. There are, for instance, inherent challenges in attempting to extrapolate high-dose responses in laboratory species and apply those to human populations outside of the lab, which are typically exposed to much lower levels of chemicals. High doses of a chemical may trigger responses in metabolic pathways that would not be affected at lower levels of exposure. Conversely, effects that might manifest at low dose levels would be missed because subtle interactions would remain undetected.[4] These outcomes could potentially result in false positives or false negatives. Furthermore, toxic responses may differ depending on the route of exposure and path of entry of the toxicant into the body. Although some dermal (skin) or inhalation data may be available, the standardized suite of animal-based toxicity tests almost exclusively considers exposure via the oral route. Other limitations include the inability to evaluate the effects of interactions with a combination of chemicals; and the fact that the physiological responses of lab species may differ from those of humans. The Panel determined, based on the existing evidence, that the transition to an integrated approach to toxicity testing could significantly enhance the existing regulatory framework for both data-poor and data-rich chemicals. This in turn would help to improve protection of human health and the environment.

This paradigm shift will necessitate a new and transparent approach to test development, validation, and regulatory acceptance on a national and international scale. It will also require active participation and meaningful engagement on the part of regulatory authorities, the regulated community, and other stakeholders in order to shape and adopt new approaches.

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

To date, the use of alternative approaches to existing toxicology testing have primarily been used to support regulatory decision-making for data-poor chemicals. There are also a number of examples of the use of components of IATA in a regulatory context for industrial chemicals and personal care products. Although the Panel is not aware of a complete set of alternative methods that could replace the entire testing paradigm for data-rich chemicals, the state of the science is evolving rapidly. As alternative tools and approaches continue to be developed, they will likely be increasingly integrated in the decision-making process for both data-rich and data-poor chemicals.

Although not yet used in a regulatory setting, emerging technologies and scientific methods provide a practical bridge between the traditional *in vivo* paradigm and the new hypothesis driven IATA toxicity testing for regulatory use.

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

The past five years have seen significant research and development of new approaches and models for predictive toxicology. Opportunities now exist to address some of the previous limitations. Further advances will likely uncover previously unidentified limitations. These 21st century problems need 21st century solutions. Although IATA may not be able to address all of these issues, it represents a transparent and pragmatic blueprint for change. IATA tools offer great promise in the regulatory context for data-poor chemicals, for which regulatory decisions are currently based on little (or no) primary data.

There is no one single IATA; rather there are numerous approaches at various stages of readiness. Their applicability to regulatory use can be achieved via engagement with the international regulatory community and through proof-of-concept studies that build confidence and familiarity in new approaches.

IATA would enhance the reliability of the existing approach by integrating new science into the current regulatory framework while also making it possible to assess the safety of the data-poor chemicals that have not yet received extensive analysis.

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?

As mentioned earlier, while components of IATA are used in regulatory contexts for industrial chemicals and personal care products, there is no single example of a comprehensive deployment of IATA in a regulatory context.

The Panel anticipates that the regulatory adoption of IATA strategies will vary depending on the type of chemicals in question and the nature of the decision-making process:

- The new approaches offer promise for data-poor chemicals, for which regulatory decisions are currently made with little (or no) primary data.
- Data-rich chemicals undergo an extensive battery of toxicity tests. For these chemicals, replacing the existing toxicological testing paradigm and establishing the relevance of IATA may take longer and will require building and establishing trust in new and novel methods.

The dynamic nature of IATA requires that test development and regulatory acceptance reflect the needs of the new paradigm. The challenges to overcome stem from more traditional approaches and thinking:

- Alternative methods typically target specific cellular or physiological responses, precluding a one-for-one approach to validation (i.e., it may not be reasonable to expect a one-for-one *in vivo* tests and data with *in vitro* or *in silico* tests and data).
- Test development will require 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. Moreover, stakeholder engagement (including industry and advocacy groups) must be engaged throughout the development process.
- Capacity-building initiatives are needed 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.

Although components of IATA have been used in a regulatory context and the adoption of IATA strategies might refine and streamline testing of chemicals as well as enhance the reliability of the outcome, there are no known applications that can completely replace the current test requirements. As a result, widespread adoption of IATA is not expected in the short term. Implementation of IATA will require a paradigm shift in thinking as well as capacity-building to develop proficiency, trust, and familiarity with the new methods and data.

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 risks associated with chemical pesticides often give rise to particularly passionate concerns among the public. Changes in the way these risks are assessed and managed will undoubtedly attract attention. One question that may arise is whether these changes enhance public safety by providing a more reliable assessment of health and environmental risks, or whether they are a means of streamlining the regulatory process in ways that sacrifice safety for other social or economic benefits.

Transparency is critical. The public will need to be reassured that the new methods are at least as precautionary as those in the current system. In order to build public confidence, it is important that IATA be introduced incrementally and the new tools explained as clearly and accurately as possible.

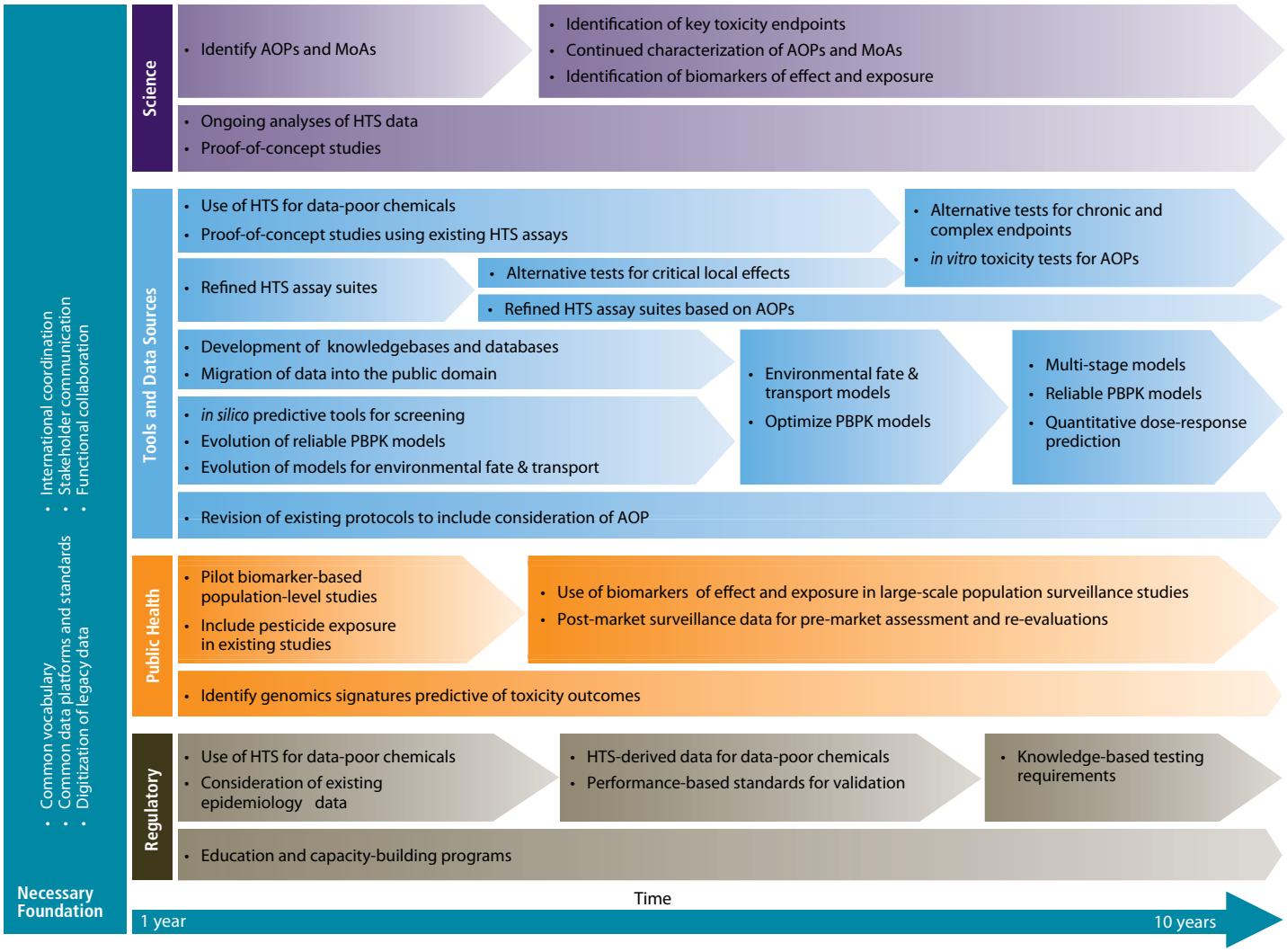


Figure 4: The Panel's vision for the evolution of IATA in the regulatory context

DEFINITIONS FOR FIGURE 4

Adverse Outcome Pathway (AOP): The sequence of events from chemical structure through the molecular initiating event to the *in vivo* outcome of interest.

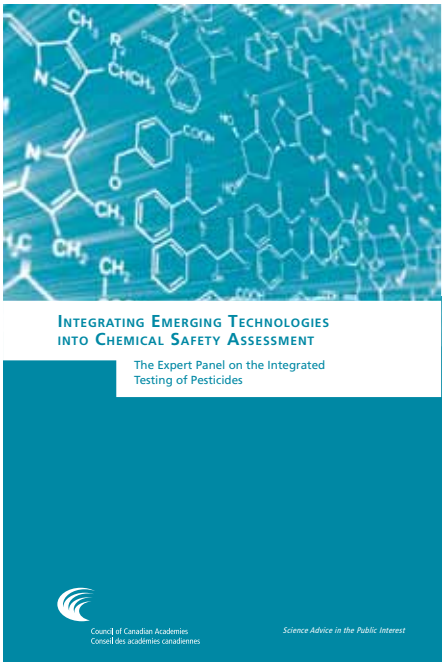
High-Throughput Screening (HTS): An approach that uses automated tools to facilitate the rapid execution of hundreds of thousands of assays per day in order to identify chemicals of concern for subsequent testing.

Mode of Action (MoA): The sequence of key cellular and biochemical events (measurable parameters), starting with the interaction of an agent with the target cell, through functional and anatomical changes, resulting in cancer or other adverse health effects. Mode of action differs from mechanism of action in that the latter describes the complete molecular sequence of events from exposure to manifestation of the toxicological outcome and implies a more detailed understanding of causality leading to an adverse outcome.

Physiologically Based Pharmacokinetic Modelling (PBPK): PBPK models are generally multi-compartment mathematical designed to predict the absorption, distribution, metabolism, and excretion (ADME) of substances by an organism. In a typical PBPK model, individual compartments correspond to different organ systems. PBPK models are often used to conduct interspecies extrapolations and to generate simulations of pharmacokinetic profiles under different physiological conditions.

Inside the Full Report

- Insights on the current toxicity testing practices in Canada.
- Examples of how the integration of different disciplines can contribute to the evolution of regulatory toxicity testing.
- A practical roadmap for IATA implementation over one-, five- and 10-year periods.
- Insights on public perception and risk.
- A review of current applications of IATA in Canada, the United States, and Europe.



Endnotes

[1] PMRA:http://www.hc-sc.gc.ca/cps-spc/pest/index-eng.php

[2] Health Canada (2002). Health Policy Research Bulletin http://www.hc-sc.gc.ca/sr-sr/pubs/hpr-rpms/bull/2002-4-environ/index-eng.php

[3] NRC (National Research Council) (1983). *Risk Assessment in the Federal Government: Managing the Process*. Washington (DC): NRC.

[4] NRC (National Research Council) (2007). Toxicity Testing in the 21st Century. A Vision and a Strategy. Washington (DC): NRC.

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This Report in Focus was prepared by the Council based on the Report of the Expert Panel on the Integrated Testing of Pesticides.

Canada
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