Use of new approach methods (NAMs) in risk assessment

Fact sheet series: Topics in risk assessment of substances under the *Canadian Environmental Protection Act*, 1999 (CEPA 1999)

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New approach methods (NAMs)

The traditional approach to chemical risk assessment relies on toxicity testing in animals to evaluate a range of possible adverse health effects. However, studies in experimental animals are expensive, time consuming, and may be of limited biological relevance, in addition to presenting animal ethical concerns. New approach methods (NAMs) present a desired alternative to traditional animal-based methods for chemical toxicity testing.

NAMs are broadly defined as any technology, methodology, approach or combination thereof that can be used to replace, reduce or refine animal toxicity testing and allow for more rapid or effective prioritization and/or assessment of chemicals. These methods may include the use of computer-based (computational) models, modernized whole-organism assays or assays with biological molecules, cells, tissues or organs, as well as exposure prediction approaches. Examples of modernized whole-organism NAMs include zebrafish embryonic tests as models for mammalian and ecotoxicity endpoints. Assays with biological molecules can include “omics” studies that determine the chemical dose at which molecular changes begin to occur (for example, an in vitro or 5-day rodent transcriptomics study). While some NAMs may still make use of animals, the methods are refined to provide new mechanistic knowledge and associated dose-response data. This is an important step towards reducing the total number of animals used in research, product development and chemical risk assessment until the necessary NAMs become available to replace animal toxicity testing.

NAMs can be used to improve understanding of the mechanisms underpinning adverse effects and to identify doses below which effects are not expected to occur from a human or ecological toxicity perspective. Data generated by NAMs are increasingly being used to provide hazard, exposure, and risk information for prioritizing chemicals for further action and can contribute to the weight-of-evidence in chemical risk

assessments. Additionally, NAM data can highlight where further testing may be needed in an integrated or tiered testing strategy.

Importance of NAMs

There is an ongoing international effort to replace, reduce or refine the use of traditional whole animal-based toxicity tests. NAM data can be used to augment the datasets considered in both ecological and human health risk assessments. The mechanistic nature of NAM data can improve our understanding of how a chemical or mixture causes toxicity. Additionally, NAMs can provide data with greater human or ecological relevance compared to standard toxicity tests conducted using animals. For example, in contrast with animal studies, cell- and organ-based approaches allow for the use of human tissues, and therefore toxicity data obtained from these NAMs may be more relevant to inform human health risk assessments.

NAMs are especially useful in data-poor situations, as the generation of data may be done using computational models, with cell-based tests or using alternative approaches that are often less resource intensive and higher-throughput (meaning more data can be generated in the same amount of time) than traditional animal toxicity methods. The NAM-based approaches used in chemical risk assessment under CEPA have been demonstrated to be as protective of human health and the environment as traditional animal methods. The incorporation of NAMs into the risk assessment framework is important to reduce reliance on the use of traditional animal tests while maintaining scientific rigor to ensure that regulatory decisions will continue to keep Canadians and the environment safe from harmful substances.

How Canada is using NAMs under CEPA 1999

A major goal of the continued development, validation and use of NAMs in Canada is to reduce reliance on animals for toxicity testing while addressing data needs for risk assessment in the transition toward replacement of animal test methods. For many years, the Government of Canada has been actively identifying areas where NAMs can support risk assessment. This has included consulting with an external advisory body, the Chemicals Management Plan (CMP) Science Committee, to seek advice on considerations for integrating NAMs under the CMP. As part of the ongoing process to incorporate NAMs into regulatory programs, Government of Canada scientists continue to work towards the development, standardization and validation of NAMs, identifying areas of uncertainty, as well as establishing frameworks to guide continued incorporation of NAMs data. This work helps to ensure confidence in the application of NAMs to chemical risk assessment in order to continue to protect human health and the environment. NAMs are used in various decision-making contexts (for example, screening, prioritization, and informing risk assessment decisions) in both the Canadian Existing Substances and New Substances programs under CEPA 1999.

The New Substances program accommodates the use of NAMs to meet technical information requirements prescribed by the *New Substances Notification Regulations (Chemicals and Polymers)* (see section 8.4 of the Guidance Document for the Notification and Testing of New Substances: Chemicals and Polymers). In a chemical risk assessment, NAM data may be substituted in place of traditional data when the NAM is determined to provide a scientifically valid measure of the endpoint under investigation that is deemed sufficient for the purposes of the risk assessment. NAMs at earlier stages of standardization and validation can be used to identify data gaps and provide mechanistic information as part of a weight-of-evidence-approach.

For the Existing Substances Program, data generated from NAM-based approaches were increasingly used to support grouping and read-across, prioritization, and assessment of the potential for risk from data-poor substances under the CMP. NAMs that are starting to be used for prioritization and assessment of existing substances under CEPA 1999 are described in science approach documents (SciADs). For example, a human health SciAD describes an approach to convert a concentration that causes an effect in exposed cells (bioactivity) to a dose expected to cause an effect in humans using non-animal and high-throughput computational methods. The resulting human equivalent dose (or point-of-departure) is then compared with the human exposure estimate for that chemical, and the ratio between these numbers (that is, the bioactivity-exposure ratio) presents a quantitative risk-based approach that can serve as a protective surrogate in the absence of traditional hazard data. This provides a promising approach for chemical prioritization and screening level assessment that does not require the use of animals. On the environmental side, a SciAD describes the Ecological Risk Classification (ERC) approach for prioritizing organic substances (version 2.0, also called ERC2). The ERC2 approach is a high-throughput approach that integrates data across various NAMs with traditional animal data in order to prioritize substances and classify potential ecological risk (additional information is available on the ERC Approach fact sheet).

Despite significant advancements in their development, NAMs are still at an early stage on the trajectory to completely replace animal testing. While cell and tissue-based tests can be excellent for assessing local toxicity (for example, skin), more complicated endpoints, such as developmental or reproductive toxicity or carcinogenicity, can be more difficult to fully assess using NAMs. For example, an important factor for assessing any type of systemic toxicity includes an evaluation of the process by which compounds are absorbed and distributed throughout the body, and these processes can be difficult to capture with cell-based NAMs. Moreover, currently available cell-based NAMs, may lack complete biological coverage (that is, to be representative of all tissues) within the human body. Improved computational models and more complex tissue-based NAMs (for example, microphysiological systems), among other strategies, are currently being developed to improve these areas of uncertainty.

International activities to advance NAMs

The Government of Canada supports research, international collaborations, and work with the Organisation for Economic Co-operation and Development (OECD) and international regulatory partners to develop, validate and use alternatives to traditional animal toxicity testing. For example, Health Canada (HC) and Environment and Climate Change Canada (ECCC) are participating in the development and validation of NAM-based toxicity test guidelines through the OECD Test Guidelines Program. These test guidelines become standards by which chemical hazards are identified. In addition, HC and ECCC lead and participate in the development and harmonization of chemical assessment methods using the most current science through the OECD Working Party on Hazard Assessment. This includes the OECD case studies project to develop integrated approaches to testing and assessment (IATA), which aims to combine various sources of information, such as data from NAMs and traditional testing methods, in order to characterize chemical hazard. Canada also co-leads Accelerating the Pace of Chemical Risk Assessment (APCRA), an international governmental collaboration developed to facilitate the translation of research into applications by strategically addressing barriers and identifying opportunities to advance the use of NAMs in chemical risk assessment. Additionally, both HC and ECCC participate in various working groups focused on the development of specific NAMs [for example, the OECD Advisory Group on Endocrine Disrupters Testing and Assessment, the OECD Developmental Neurotoxicity Zebrafish working group, and the OECD Advisory Group on Emerging Science in Chemicals Assessment (ESCA AG) (formerly the Extended Advisory Group on Molecular Screening and Toxicogenomics)].