Government of Canada Gouvernement du Canada

Microbial risk assessment framework (MRAF) under the *New Substances Notification Regulations (Organisms)* of the *Canadian Environmental Protection Act, 1999*

Canada

Executive summary

The *Canadian Environmental Protection Act, 1999* (CEPA), Part 6, and the *New Substances Notification Regulations (Organisms)* (NSNR (Organisms)), provide the authority to request information from manufacturers and importers of new living organisms. This requirement allows for the pre-market assessment and, any risk management required to protect the environment and human health from the manufacture, import and use in Canada of animate products of biotechnology (living organisms). The NSNR (Organisms) is administered jointly by Health Canada (HC) and Environment and Climate Change Canada (ECCC) through the New Substances (NS) program.

CEPA defines biotechnology as "the application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms."

Living organisms encompass both micro-organisms (for example, bacteria, fungi, viruses, algae, etc.) that are modified or unmodified, as well as organisms other than micro-organisms (in other words, higher organisms such as genetically modified livestock animals, fish and insects).

This framework supports a science-based approach to risk assessments and applies only to micro-organisms subject to notification under CEPA.

Section 0 introduces the context, purpose, and scope of this framework. Section 2 provides an overview of the risk assessment approach used by the NS program and provides context on practices and processes that are appropriate for the assessment of micro-organisms. Section 3 illustrates how the framework applies to new and existing micro-organisms. Section 4 elaborates on the general practices and processes for microbial risk assessment which include hazard identification, exposure assessment, hazard characterization and risk characterization.

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List of acronyms

CEPA: *Canadian Environmental Protection Act, 1999*

DSL: Domestic Substances List

MIFRA: Microbial Identification Framework for Risk Assessment

NSNR (Organisms): *New Substances Notification Regulations (Organisms)*

NS program: New Substances program

SNAc: Significant New Activity

UA: Uncertainty Analysis

WoE: Weight of Evidence

Glossary of terms

The terms included in this glossary are defined in CEPA, the NSNR (Organisms) or used by Canada's NS program.

Biotechnology: Defined in CEPA as the application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms.

Consortium: A culture other than a pure culture that is a complex unformulated natural combination of micro-organisms.

Contained facility: Defined in the NSNR (Organisms) as an enclosed building with walls, floor and ceiling, or an area within such a building, where the containment is in accordance with the physical and operational requirements of a level set out in either the Canadian Biosafety Standards and Guidelines or Appendix K of the NIH Guidelines.

Environment: Defined in CEPA as the components of the Earth and includes:

a. air, land and water;
b. all layers of the atmosphere;
c. all organic and inorganic matter and living organisms; and
d. the interacting natural systems that include components referred to in paragraphs (a) to (c).

Environmental species (in other words. "non-human species"): Terrestrial or aquatic vertebrate, invertebrate, plant or microbial species occurring within the Canadian environment.

Existing micro-organism: A micro-organism that was deemed to have been in Canadian commerce or manufactured or imported into Canada between 1984 and 1986 and is included on the Domestic Substances List (DSL). Micro-organisms assessed under a full NSNR(Organisms) Schedule 1 may also be added to the DSL.

Exposure assessment: The qualitative and/or quantitative estimate of the magnitude, frequency, duration, route and extent of environmental or human exposure to a micro-organism.

Hazard assessment: The qualitative and /or quantitative determination of the inherent capacity of a micro-organism to cause an adverse effect on the environment or human health based on its unique biological and ecological characteristics.

Higher organism: An organism other than micro-organism. Includes but is not limited to genetically modified livestock animals, insects and fish.

Infectivity: The capacity of a micro-organism to become established within a host species.

Living organism: Defined in CEPA as an "animate product of biotechnology". May be either a micro-organism or any organism other than a micro-organism.

Micro-organism: Defined in the NSNR(Organisms) as a microscopic organism that is:

a. classified in the Bacteria, the Archaea, the Protista, which includes protozoa and algae, or the Fungi, which includes yeasts;
b. a virus, virus-like particle, or sub-viral particle;
c. a cultured cell of an organism not referred to in paragraphs (a) and (b), other than a cell used to propagate the organism; or
d. any culture other than a pure culture .

New micro-organism: A micro-organism that is not already on the DSL and must be notified and assessed prior to import or manufacture in Canada under the NSNR (Organisms).

Notifier: A person or company who provides information and/or data on a micro-organism under the NSNR (Organisms) prior to manufacture in or import into Canada.

Pathogenicity: The capacity of a micro-organism to infect a host and cause disease.

Receptor species: Any species (including humans) which is susceptible to the hazardous properties of a particular micro-organism.

Risk assessment : The process to determine the likelihood that a specific adverse effect will occur following exposure to a hazardous agent.

Stakeholder(s): Any interested person who may or may not be regulated by the NSNR (Organisms) and may include other governmental departments, agencies or jurisdictions, non-governmental organizations, academics, researchers or industry or Indigenous peoples.

Strain history: Information on the historical record of the notified micro-organism from its original isolation until its final development.

Surrogate organism(s): A suitable alternative organism that may be used to satisfy information requirements and data gaps.

Toxicity: The capacity of any micro-organism to cause harm to humans, animals, plants or to other micro-organisms.

Toxigenicity: The ability of a micro-organism to produce a toxin.

1 Introduction

1.1 Background information

Under CEPA, biotechnology is defined as: "the application of science and engineering in the direct or indirect use of living organisms or parts or products of living organisms in their natural or modified forms". Part 6 of CEPA provides the Minister of Environment and Climate Change and the Minister of Health (the Ministers) with the authority to assess and manage risks to the environment, its biodiversity and human health posed by living organisms prior to their import into or manufacture in Canada. A living organism may be a **micro-organism** as defined in subsection 1(1) of the *New Substances Notification Regulations (Organisms)* [NSNR (Organisms)] or a higher organism (in other words, organism other than a micro-organism).

The Domestic Substances List (DSL), as specified in Part 5 of CEPA, is an inventory of substances (chemicals, polymers and living organisms) manufactured in, or imported into Canada on a commercial scale. The original publication included substances deemed to have been in Canadian commerce or manufactured or imported into Canada between 1984 and 1986, including 68 micro-organisms. The DSL is regularly amended to add substances meeting statutory criteria for eligibility. A micro-organism may be added to DSL after notification and assessment of the information outlined in Schedule 1 of the NSNR (Organisms).

A new substance is any substance that is not included in the CEPA Domestic Substances List (DSL). The DSL is a searchable database available online as part of the CEPA registry.

Substances not appearing on the DSL are considered new to Canada and are subject to notification prior to their manufacture or importation. According to subsection 106(1) of CEPA, no person shall manufacture or import a living organism that is not specified on DSL, before the prescribed information (as set out in the NSNR (Organisms)) has been provided to the Minister of Environment and the prescribed assessment period has expired. The New Substances (NS) program assesses information provided under the NSNR (Organisms) on behalf of the Ministers.

Under Part 6 of CEPA, the risk assessment of a substance that is a living organism (including a micro-organism) pertains to whether it meets the criteria under section 64 of CEPA; notably, a micro-organism is entering, or may enter, the environment in a quantity or concentration or under conditions that:

a. have, or may have, immediate or long-term harmful effects on the environment or its biological diversity.
b. constitute, or may constitute, a danger to the environment on which life depends; or
c. constitute, or may constitute, a danger in Canada to human life or health.

1.2 Purpose

The purpose of this framework is to provide an overview of how micro-organisms are assessed for their risk to the environment and human health under CEPA. Additionally, the publication of this document serves to inform stakeholders about the approaches and considerations the Government of Canada uses for assessing micro-organisms under CEPA.

1.3 Scope

This microbial risk assessment framework outlines approaches and considerations for informing the risk assessment of micro-organisms under CEPA, including both existing micro-organisms (in other words, micro-organisms on the DSL), and new micro-organisms (in other words, micro-organisms not on the DSL) when notified under the NSNR (Organisms). This framework includes considerations for both modified (for example, genetic modifications made for a specific function) and naturally occurring (in other words, unmodified) micro-organisms as both could be developed and used in biotechnological applications. The scope of this assessment excludes products regulated under other Acts and Regulations listed in Schedule 4 of CEPA, in other words, Acts and regulations that meet CEPA requirements for notification and assessment of new living organisms for toxicity. For example, the *Food and Drugs Act* (*FDA*) and its associated Regulations are not listed in Schedule 4; therefore, substances intended for use in products regulated under the FDA (for example, drugs) are subject to the NSNR (Organisms).

Micro-organisms have been used as a green technology for use in applications, such as cleaning products and biofuel production. The use of micro-organisms in personalized medicine, oncolytics (in other words, therapies that destroy tumour cells), novel vaccines, as well as cell and gene therapies (CGT) also represent a growing class of innovative medicines. New uses of micro-organisms in all of these applications are subject to the NSNR (Organisms) and are in scope for this framework.

Though higher organisms (in other words, organisms other than micro-organisms) are also captured in the definition of living organism under CEPA, they are outside the scope of this framework.

2 Overview of risk assessment framework for micro-organisms

2.1 Risk assessment process

The risks posed by a substance are determined both by its hazardous properties and by the nature of the exposure that takes place. Scientific risk assessments are conducted under CEPA to determine whether there are risks resulting from exposure of Canadians to a substance or from releases of a substance into the environment, and the specific ways Canadians or the environment can be affected.

For the purposes of this framework, a risk assessment is a scientific process used to determine the likelihood that a specific adverse effect will occur following exposure to a micro-organism based on intended, known or potential uses. The risk assessment brings together the estimated level of exposure, the likelihood that exposure will result in an adverse outcome based on identified hazards, and the severity of those outcomes to develop an overall description and assessment of the risk associated with the notified micro-organism. The hazard associated with a micro-organism is its inherent ability to cause adverse effects to the environment**,** its biodiversity and to humans. Exposure considers the concentration or amount of the micro-organism that reaches the environment and its components, including humans, and its intensity, frequency, and duration.

The risk assessment of micro-organisms follows well-known and established principles including an analysis of uncertainty and the application of weight of evidence (see section 2.3). These principles can also be used to identify scenarios where the conclusion of the assessment would be fundamentally

changed if an underlying assumption were not valid and thus possibly warrant the consideration of risk management measures.

2.2 Problem formulation

The key to developing a robust and science-based risk assessment is a clear understanding of the specific risk(s) to be addressed. This involves:

- Describing clearly the problem being explored;
- Defining a specific risk question(s) to be answered by the risk assessment;
- Specifying the scope of the assessment; and
- Clearly understanding the constraints (for example, regulatory timelines, resources, limited data, etc.). This is an overarching principle that can affect other parts of the problem formulation.

A conceptual model for problem formulation and scoping is presented in Figure **1** below to establish and organize the conduct of the process of a risk assessment of the micro-organism.

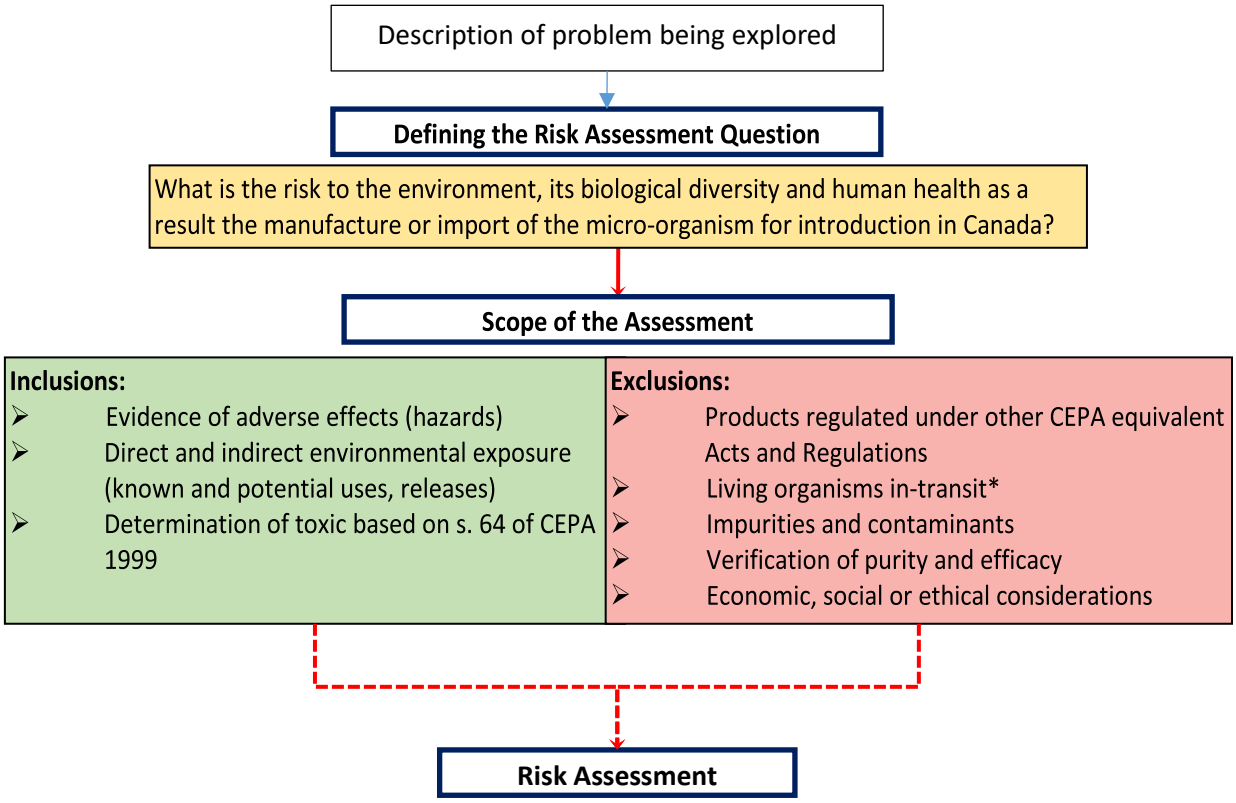

Figure 1. Problem formulation and scoping of a risk assessment question

*Section 2(2) of the NSNR(Organisms) states: "These Regulations do not apply in respect of an organism that is loaded on a carrier outside Canada and moved through Canada to a location outside Canada, whether or not there is a change of carrier during transit."

2.2.1 Describing the problem being explored

To characterize and evaluate the potential risks of a micro-organism to the **environment** and human health, the following elements must be identified and described prior to commencing the risk assessment:

- The taxonomic identification of the micro-organism;
- Information on genetic modifications (if applicable);
- Information on the potential for adverse effects to the environment, biodiversity and human health;
- The activity being notified (for example, manufacture or import);
- The potential use (for example, biofuel production, enzyme production, attenuated vaccine, etc.).
- The release type (for example, full release or use in a contained facility);
- Duration of release (short term or long term); and
- Lifecycle of the product from introduction to termination/disposal.

2.2.2 Defining the risk assessment question

Examples of risk questions for a new micro-organism are presented in Appendix 1. The problem formulation should address the risk assessment question and define the scope for risk assessment for that specific release or use scenario. In general, the risk question should specify the hazard and the endpoints of interest, spatial and time dimensions as well as the likely receptor species.

2.2.3 Specifying the scope of the risk assessment

The scope of a particular risk assessment is mainly determined by the following considerations:

- What is already known about the potential harmful effects of the micro-organism to the environment, biodiversity and human health, whether based on direct studies or from suitable surrogate organisms;
- The nature of the micro-organism being assessed (for example, vegetative cells/spores, genetic modifications, presence of toxins/metabolites, etc.);
- Specific endpoints (infectivity/virulence in humans and other environmental species, antimicrobial susceptibility, ecosystem effects, etc.);
- The type of release of the micro-organism to the environment, specific activities of use, product formulations, areas of distribution, etc.;
- The environment and/or specific locations into which releases of the micro-organism may occur and which environmental species or humans may be exposed; and
- The information provided by the notifier and other relevant information available to the NS program.

The scope of a risk assessment of a living micro-organism does not include:

- An assessment of the import or manufacture of a micro-organism for uses that are regulated under the authorities of other Acts in Canada listed under Schedule 4 of CEPA;
- An assessment of a micro-organism in-transit through Canada;
- An assessment of the efficacy of the micro-organism for its intended use;

- An assessment of impurities and contaminants found in the medium or substrate or that are the result of secondary reactions that occur during the preparation of the micro-organism; and
- An assessment of other aspects of economic, social, or ethical value.

2.2.4 Exposure pathway identification

The potential exposure pathways that are considered in a risk assessment are identified once the problem formulation and the scope of the assessment is determined. This is important because the risks posed by a substance are determined both by its hazardous properties and by the nature of the exposure that takes place. Identifying the ways in which exposure to a micro-organism occurs is an essential component of any risk assessment and helps inform what data are needed to make a determination of whether there are risks resulting from exposure of Canadians to a substance or from releases of a substance into the environment. An example of an exposure pathway is provided in the yellow and green boxes on the right side in Figure 2 below.

Based upon the type of release to the environment and how the micro-organism is intended to be applied, relevant exposure routes (in other words, dermal, inhalation, or ingestion) are identified (with rationales for why they are or are not included as part of the risk assessment). This approach helps to design an exposure assessment that is clearly articulated, focused and robust for the particular use scenarios involving the organism.

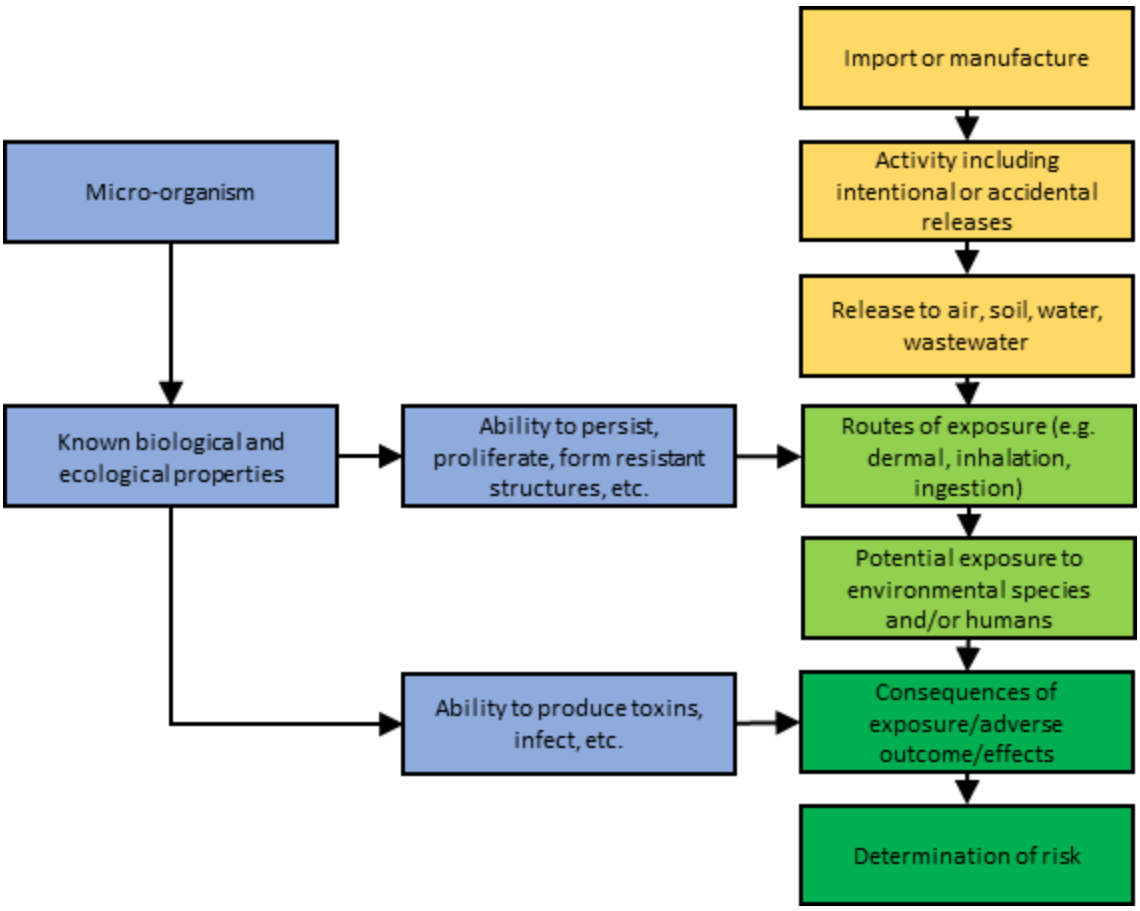

Figure 2. Considerations of the properties of the micro-organism and the exposure pathways in the determination of risk.

2.3 Application of weight of evidence, precautionary principle and scientific uncertainties to the risk assessment of micro-organisms

2.3.1 Weight of evidence

Weight of evidence considers several lines of evidence in order to reduce overall uncertainty in the assessment as much as possible. Appendix 2 outlines the influence of different levels of WoE on overall uncertainty. Lines of evidence are weighted based on many factors, including:

- The number of studies supporting a particular line of evidence;
- Study design (multivariate, randomized, statistical analysis);
- Number of tested hypotheses;
- Sample size;
- Validity and degree of extrapolation (spatiotemporal, species extrapolation);
- Data quality;
- Relevance to and alignment within the scope of the risk assessment (same or closely related strain, climate of study area, etc.); and
- Magnitude of effect

Weight of evidence allocation criteria and overall determinations are further detailed in Appendix 2.

2.3.2 The precautionary principle

The precautionary principle is one of the guiding principles set out in the preamble of the CEPA, and states that " in a manner that protects the environment and human health, applies the precautionary principle that, where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." Sound scientific information remains the cornerstone of all assessments. The application of the precautionary principle in risk assessment means using conservative but realistic assumptions to account for uncertainties, while the degree of precaution applied is in proportion with the degree of uncertainty. In situations where sound scientific information is limited but where the impacts could potentially be significant, the approach to risk management measures is prudent, to protect the environment and human health.

2.3.3 Scientific uncertainties

Risk estimates always contain some level of uncertainty resulting from the limited availability of scientific data, and the challenge of extrapolating available data to real situations. The effect of these uncertainties on risk estimates must be thoroughly considered and documented, including:

- Identification of major data gaps and, where appropriate, indication of whether more data would enhance the overall confidence in the assessment conclusion;
- Assumptions used to bridge data gaps, and the basis for those assumptions; and
- Identification of any 'unacceptable' uncertainties requiring application of the precautionary principle until new data become available to mitigate the uncertainty.

Uncertainty exists at each step of the risk assessment and influences the risk conclusion. An important step during a risk assessment is the evaluation of the lines of evidence, their associated uncertainties, and their strengths, to support a conclusion[1].

Key components of the risk assessment with high uncertainty should be explored further to determine the possible impact on risk assessment conclusions. In addition, scenarios should be identified where the conclusion of the assessment would be fundamentally changed if an underlying assumption was not valid.

3 Risk assessment of micro-organisms under CEPA

Risk assessments conducted under CEPA are performed using a "lifecycle" approach, in other words, from manufacture/import to final disposal.

3.1 New versus existing micro-organisms

3.1.1 New micro-organisms

A new micro-organism that is not listed on the DSL, requires notification prior to manufacture or import into Canada. The NS program evaluates the risk of a new micro-organism to the **environment**, its biodiversity and human health. For these micro-organisms, the environmental and human health risk assessments are conducted using information submitted to the NS program as per the regulatory requirements that are prescribed in the NSNR (Organisms) Schedules (Table 1), as well as any additional relevant information found in the wider scientific literature. The CEPA requirements apply to all new

living organisms, including micro-organisms, unless they are imported or manufactured for a use regulated under one of the federal Acts listed in Schedule 4 of CEPA (currently, the Feeds Act, the Fertilizers Act, the Seeds Act, the Health of Animals Act and the Pest Control Products Act).

NSNR (Organisms) Schedules for new micro-organisms[2]

Notification schedule 1

- **Release type:** Manufactured or imported for release anywhere in Canada.
- **Assessment period (calendar days):** 120

Notification schedule 2

- **Release type:** Manufactured in or imported to a contained facility that are not for introduction outside the contained facility or that are for export only.
- **Assessment period (calendar days):** 30

Notification schedule 3

- **Release type:** For introduction in an experimental field study.
- **Assessment period (calendar days):** 90

Notification schedule 4

- **Release type:** Manufacture at the site from which there were isolated for introduction into the same site.
- **Assessment period (calendar days):** 30

3.1.2 Existing micro-organisms

An existing micro-organism (in other words, those on the DSL) is a micro-organism that was either (i) in Canadian commerce between January 1, 1984, and December 31, 1986, or (ii) that were added to the DSL in accordance with CEPA 1999 after assessment of the information outlined in Schedule 1 of the NSNR (Organisms). A micro-organism on the DSL does not require notification prior to manufacture or import. However, notification requirements may apply when the Significant New Activity (SNAc) provisions of CEPA 1999 are applied. The SNAc provisions of CEPA 1999 establish an obligation for any person considering undertaking a significant new activity in relation to a micro-organism to provide specific information about that micro-organism to the Minister of Environment and Climate Change Canada. A significant new activity (or activities) is specific to each substance and is found in the relevant SNAc publication in the *Canada Gazette.*[3] Upon receipt of the complete information, the NS program would conduct further assessment of the micro-organism for potential risks to the environment and human health, and, if necessary, propose risk management measures before the activity is undertaken.

Micro-organisms that were nominated to the DSL upon its inception have been assessed and the screening assessment reports are available online. Though the assessments have been completed, as

[2] The Schedules are outlined in the regulations here
Guidance on how to fulfill the requirements in the regulations is found here. [2] How weight of evidence, precaution and uncertainty influence each other is further detailed here.
[3] All SNAc orders/notices under CEPA are listed here

new information and/or tools supporting microbial risk assessment become available, the Government of Canada could choose to revisit the assessments to ensure that the conclusions are still valid.

4 Risk assessment of new micro-organisms under the NSNR (Organisms)

A risk assessment of a new micro-organism considers information about both exposure and hazard provided by the notifier as well as found in the available scientific literature, to determine whether there is a suspicion of toxicity (Figure 3).

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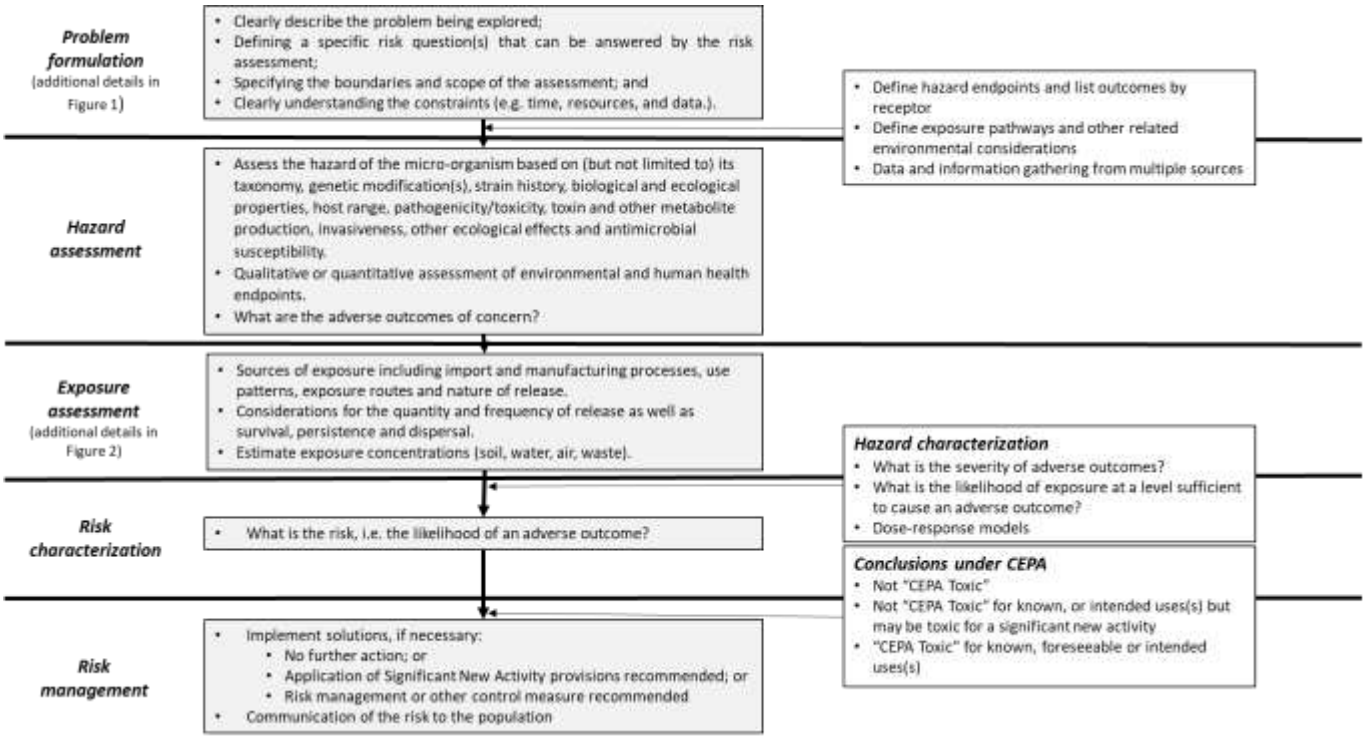

Figure 3. Risk assessment approach for micro-organisms under the New Substance Notification Regulation (Organisms)

4.1 Hazard assessment

The hazard assessment of a micro-organism is the determination of its inherent capacity to cause an adverse effect on the environment or human health based on its unique biological and ecological characteristics. Information about the micro-organism including, but not limited to, taxonomic identification, strain history, genetic modifications and data from pathogenicity and toxicity studies is used when assessing its potential hazard.

A valid and well-supported taxonomic identification is used to determine the hazard of a notified micro-organism and to distinguish it from potential pathogens of clinical or environmental significance. Inaccurate identification can lead to an imprecise determination of the hazard of a micro-organism. This inaccuracy may potentially lead to a risk assessment conclusion that will not be applicable to the actual micro-organism being notified. The Microbial Identification Framework for Risk Assessment (MIFRA) provides guidance on the required information for identifying micro-organisms.

In the case of a genetically modified micro-organism, information on all modifications is considered in the risk assessment. This includes the methods used to modify the organism (for example, recombinant DNA, gene editing); source, nature, and function of any inserted genetic material; as well as the stability of the modifications. This information helps to determine whether the modifications confer any potentially hazardous traits to the micro-organism.

This part of the risk assessment also considers the biological and ecological properties of the micro-organism to determine its potential for adverse effects to the environment and humans, as well as the influence its environmental fate may have in producing these effects. The following is not an exclusive list but are examples of the types of information that are considered for the hazard assessment component:

- life cycle;
- **infectivity**, **pathogenicity**, **toxicity** and **toxigenicity**;
    - severity and reversibility of adverse effects;
    - susceptibility and resistance to antimicrobial agents, controls or treatments;
    - ability to induce allergenicity or other immunological effects;
    - ability to transfer genetic material leading to the transfer and spread of characteristics such as antibiotic resistance and virulence factors;
- involvement in biogeochemical cycling;
- the conditions required for, and conditions that limit, its survival, growth and replication;
    - conditions that may select for dispersal of traits of pathogenicity, toxicity, and invasiveness,
    - geographical distribution, habitats and host range;
- the mechanisms of its dispersal and the modes of interaction with any dispersal agents; and
    - ability to be shed, to disperse, survive, reproduce, or replicate in a given environment.

The ability of a micro-organism to proliferate under favourable conditions or form resistant structures under unfavourable conditions may alter its environmental fate as well as its hazard and exposure profiles, and therefore change its potential for harm to the environment and human health.

4.2 Data considerations for a risk assessment of micro-organisms

Data and information are gathered by evaluators from multiple sources (for example, notification submission[4], scientific literature, risk assessments from like-minded regulatory authorities). Data collection and information gathering occur throughout the risk assessment process. Data relevant for the Canadian context (for example, products used in Canada, Canadian species, or environmental conditions representative of the Canadian environment) are preferable when selecting and using data sources for the purposes of a risk assessment. Risk assessments also rely on multiple lines of scientific evidence including test data or results from studies specific to the micro-organism under assessment, or a closely related surrogate micro-organism. The selection of data also relies on the exposure pathways that have been identified (section 2.2.4).

[4] For the risk assessment of a new micro-organism, prescribed information required under NSNR (Organisms) and submitted by notifiers serve as a primary data resource.

Default values or professional judgment may be used to generate assumptions and select values that are protective of the environment or human health. Default values for environmental conditions (for example, temperature) and environmental releases (for example, in effluents or in air emissions) will be derived from what is known about intended and potential notified uses to formulate relevant exposure scenarios for the assessment of the micro-organism. Uncertainty in the data (for example, due to data gaps, reliance on surrogate information), relevance of available data to the assessment, and the level of confidence in the relevant or available data are considered when determining the most appropriate values or inputs for use in the risk assessment. Assumptions and uncertainties should be fully documented including the specific data points used in the data available, and the limitations of that data within the context of the assessment.

Information on a micro-organism can be collected from publicly available databases (for example, virulence, antibiotic susceptibility, antibiotic resistance, secondary metabolites, toxins, risk group designations, allergenicity, etc.). Some of these publicly available databases serve as additional sources of data to inform the risk assessment. Various biological and ecological characteristics of a micro-organism (for example, ability to form spores, nutrient availability) can also be used to predict its persistence in the environment.

4.3 Exposure assessment

Information on how a micro-organism is to be manufactured, imported and used in Canada is critical for characterizing environmental and human exposures. This part of the risk assessment also looks at exposure to a micro-organism because of intentional release (in other words, as part of its intended or possible use) and potential accidental releases (for example, from facilities, during transport).

Environmental species and humans may be exposed as a result of the release of the micro-organism to the air, water, soil or wastewater streams. Various exposure routes (for example, dermal, inhalation, ingestion) are considered depending on the types of release being assessed, what is known about the micro-organism (for example, ability to sporulate or survive under certain conditions) and the various application parameters (frequency, quantity, method (for example, spray or injection) etc.).

The exposure assessment of a micro-organism aims to estimate the level of exposure to a hazard for all receptor species that result from each of the routes specified in the exposure pathway (section 2.2.4). The concentration of the micro-organism released to the environment may be estimated using the information/data collected during the assessment. The concentration or amount of the micro-organism released into the environment is relevant to determine exposure to the environmental species and humans.

The exposure assessment also considers the environmental fate of the micro-organism once it is released into the environment. It is a determination of the behaviour of the micro-organism in the air, water, or soil compartments (in other words, to what extent it survives, replicates, disperses in the environment, etc.) and the potential impacts on environmental species and humans. Variability in environmental conditions (for example, pH, nutrient content, moisture, etc.) are also an important consideration as these factors can modulate the fate of a micro-organism (for example, these factors may result in vegetative cells or resistant forms, such as spores.

The assessment of the environmental fate of a micro-organism also considers the biology and life cycle of that micro-organism which can be used to further inform:

- the ability of the micro-organism to survive, persist, disperse, proliferate and become established in the environment to which it is released;
- the potential for dispersal or transport to other environmental sites or compartments;
- the potential for dispersal of traits conferred by transferred genetic material (in the case of genetically modified micro-organisms); and
- the potential for persistence and bio-accumulation of toxins, metabolites and structural components of the micro-organism.

Information on the micro-organism source (release type and levels) and environmental fate, as well as routes of exposure to the micro-organism, is used to conduct a fulsome exposure assessment. In this way, the exposure assessment reflects the estimated exposure to the micro-organism from each relevant pathway, for the Canadian population and environmental receptor species.

4.4 Hazard characterization

For environmental endpoints, different approaches can be used to determine the severity of harm to environmental species following exposure to a micro-organism. This is determined by the data or information provided by the notifier as well as that available from the literature regarding the pathogenicity/toxicity of a micro-organism on representative terrestrial and aquatic plants, invertebrates and vertebrates. In the absence of quantitative or empirical data or , a qualitative analysis of the available literature can be based on key considerations that include the following: data from taxonomic identification; the nature and stability of any genetic modifications; biological and ecological properties; and adverse effects.

For human health endpoints, the dose-response model describes the relationship between the exposure, or dose, and the probability of the occurrence of a specific outcome (for example, infection, illness, death, or other specific health conditions).

Additional factors that are used in the hazard characterization of a micro-organism include a determination of:

- whether it is a known pathogen or is closely related to another human or animal pathogen;
- the reversibility of adverse effects;
- information on infectivity, duration of infection, severity of adverse effect, etc.;
- uncertainty related to its taxonomic identification or biological and ecological properties;
- history of safe use;
- potential for horizontal gene transfer.

4.5 Risk characterization of the micro-organism

Risk characterization is the final step in a risk assessment and is an integrated decision supported by information from both the hazard and exposure components of the assessment, which can include both qualitative and quantitative approaches. To develop an overall description and assessment of the risk associated with the micro-organism, risk characterization brings together the estimated level of

exposure, the likelihood that the exposure will result in an adverse outcome and the severity of those outcomes. Risks are separately characterized for the environment and for human health. It is important to ensure that the various components outlined in the initial problem formulation are addressed by the risk assessment conclusion.

As mentioned in section 2.3, risk characterizations apply precaution and a WoE approach. Additionally, uncertainty associated with each step of the risk assessment will be recognized and integrated into the assessment and the conclusion of the risk characterization to maintain transparency through the assessment process.

Environmental risks are characterized based on, but not limited to, the reversibility of effects (in other words, self-limiting or requiring treatment), the potential community/ecosystem burden of disease (for example, size of the population exposed), and the potential for horizontal transmission through the population. Consideration is also given to interactions of the micro-organism with abiotic components of the environment (for example, temperature, soil nutrient/moisture levels, etc.) that can subsequently have negative impacts on environmental species. Human health risks to Canadians are characterized based on, but not limited to, use of products available to consumers, exposure via food, drinking water and environmental media, air, and with special consideration given to the potential risks to populations who may be disproportionately impacted (for example, children, pregnant women, elderly).

If, on the basis of the risk assessment, a micro-organism is determined to meet the criteria under section 64 (s. 64) of CEPA, then risk management measures are considered to mitigate the risks identified.

5 Conclusions

This framework describes the key considerations for risk assessment of existing and new micro-organisms in Canada. The risk assessment process is a science-based evaluation that determines the risk posed by a given micro-organism based on its hazardous properties, as well as the nature and extent to which Canadians and the environment are exposed. This process applies a WoE approach, precaution, as well as identifying and addressing any uncertainties. Based on this risk assessment, a determination of whether or not the micro-organism meets any of the criteria as set out under paragraphs 64(a), (b), or (c) of CEPA is made. If a micro-organism is determined to be toxic or capable of becoming toxic as defined in section 64 of CEPA, then risk management measures to prevent or control risks are identified.
Appendices

Appendix 1: Risk assessment questions for Notification Schedules and assessment timelines under the NSNR(Organisms)

General considerations

- **Scope of the assessment:** Life cycle of the micro-organism, from its introduction (import or manufacture) to termination of its use and disposal.
- **Time:** Both short- and long-term effects are considered.
- **Risk assessment question(s):** What is the risk of harm to the environment, human health or biological diversity from the manufacture or import of the micro-organism for introduction anywhere in Canada for the intended use(s) and all potential uses?
- **Note:** uses of the micro-organism that are subject to Acts and Regulations listed in Schedule 4 of CEPA 1999 are excluded from risk assessment under CEPA 1999.

Notification Schedule 1

- **Spatial considerations (introduction/release):** Anywhere in Canada
    - **Specific considerations:** None
- **Spatial considerations (introduction/release):** Ecozone where not indigenous – localized
    - **Specific considerations**: What is the potential for the micro-organism to disperse beyond the ecozone of introduction?
- **Spatial considerations (introduction/release):** In accordance with confinement procedures – localized
    - **Specific considerations**: How effective are proposed confinement procedures for limiting dispersal of the microorganism to the site(s) of introduction?
- **Spatial considerations (introduction/release):** Ecozone where indigenous – localized
    - **Specific considerations**: What is the potential for the microorganism to disperse beyond the ecozone of introduction?

Notification Schedule 2

- **Spatial considerations (introduction/release):** Into a contained facility or for export only – localized
    - **Specific considerations:** How effective are proposed containment procedures for preventing releases of the microorganism?

Notification Schedule 3

- **Spatial considerations (introduction/release):** In an experimental field study – localized
    - **Specific considerations:**

- How effective are proposed procedures for limiting dispersal of the microorganism from the site(s) of an experimental field study?
- For short-term effects, consideration is given to start and end dates (with a possibility for repetition of the field trial over time).

Notification Schedule 4

- **Spatial considerations (introduction/release):** Same site from where isolated – localized
  - **Specific considerations:** What is the potential for the microorganism to disperse beyond the site from where it was isolated?

Appendix 2: Weight of evidence allocation criteria and overall determination

Weight of evidence allocation criteria: Poor

- Evidence allocation criteria
    - **Criteria:** Data not considered reliable and there is no alternative;
        - There are inconsistencies that cannot be avoided
        - There is low relevance (for example, use of a surrogate organism which is not closely related or shares only a few characteristics with target organisms)
    - **Interpretation criteria:** Source would be a target for future data collection.
- Overall weight of evidence determination
    - **Description:** Further research very likely to have an impact on the confidence of the information and likely to change the assessment conclusions.
    - **Relationship with Uncertainty Analysis:** Uncertainty Analysis targets the lowest weight of evidence data areas and demonstrates conclusions will change in multiple instances of reasonable adjustment of information.

Weight of evidence allocation criteria: Satisfactory

- Evidence allocation criteria
    - **Criteria:** Data not considered reliable and there is no alternative; Data is considered non-ideal but can be acceptable with disclosure of uncertainties
        - Surrogate data has been used to fill information or data gaps
    - **Interpretation criteria:** Additional data collection would be beneficial if sources categorized with “poor” have been addressed.
- Overall weight of evidence determination
    - **Description:** Further research likely to have an impact on the confidence of information and may change the assessment conclusions.
    - **Relationship with Uncertainty Analysis:** Uncertainty Analysis targets the lowest weight of evidence data areas and demonstrates conclusions may change in some instances of reasonable adjustment of information.

Weight of evidence allocation criteria: Good

- Evidence allocation criteria
    - **Criteria:** Data are considered reliable

        - There is no need for a surrogate organism
        - Gaps in the data are few to none
        - Relevant
        - Consistent across lines of evidence (if applicable)
    - **Interpretation criteria:** Not a priority for future consideration as additional data would not improve the parameter estimate
- Overall weight of evidence determination
    - **Description:** Further research unlikely to change confidence in the conclusions of the assessment.
    - **Relationship with Uncertainty Analysis:** Uncertainty Analysis targets the lowest weight of evidence data areas and demonstrates conclusions are robust to reasonable adjustment of information.