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New Substances Notification Regulations (Organisms) (NSNR(O)): Microbial Characterization and Key Elements for Importation to Canada

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Abstract

Any new substance imported into or manufactured in Canada is subject to New Substances Notification (NSN) under the Canadian Environmental Protection Act (CEPA) of 1999. The manufacturer or importer needs to comply with the New Substances Notification Regulations (NSNR) before the substance can be sold in the Canadian marketplace. While the section of the NSNR for biotechnology products has been in place since September 1, 1997, few microorganisms have been reviewed. The regulations also apply to various "higher" organisms such as fish, livestock, and insects (depending on the type of use). Applicants are required to provide a variety of technical information about their products in their NSN submissions to Environment Canada, the regulatory agency responsible for approving new substances in Canada. However, improper interpretation of the regulations leads to challenges for manufacturers/importers in the application process. There are ways to reduce an application's major deficiencies and/or potential for rejection. This paper aims to emphasize best practice tips for bringing new microorganisms to the Canadian marketplace that can benefit biotechnology product manufacturers at the forefront.

Keywords: genetically engineered (GE) microorganisms, importation, Canada, new substance notifications (NSN), Environment Canada, domestic substance list (DSL), environmental fate, ecological impact

1. Introduction

Importation and production of microorganisms in Canada are regulated by Environment and Climate Change Canada (ECCC) under the Canadian Environmental Protection Act (CEPA) (S.C. 1999, c.33) and the New Substances Notification Regulations (Organisms) (NSNR (O)). The CEPA 1999 controls new substances through a pre-import or pre-manufacture notification and assessment process. "Animate products of biotechnology" under CEPA s. 3(1) includes genetically modified cells and cells manufactured and processed by genetic manipulation. Under the NSNR (O), no new microorganism can be introduced into Canada before it is evaluated for risks to the environment and human health.

Importers or manufacturers of any new substance must submit a New Substance Notification (NSN) application to ECCC. The Canadian regulatory landscape for approving new substances is complex, and navigating it can be a challenge. The majority of NSN submissions have major deficiencies or are rejected the first time. Manufacturers and importers who intend to introduce new microorganisms into Canada can reduce their chances of rejection by obtaining expert advice.

Submitting incomplete or inappropriate test reports will result in rejection or a notice of deficiencies.This can be frustrating to industry professionals, who may give up hope of selling their product in Canada. To help applicants avoid rejection, ECCC has provided a guidance document that clarifies the contents and format required for the NSN [7]. However, industry professionals may benefit from consulting experts in this process for further guidance. This paper aims to provide best practice tips on tackling the key challenges and documentation required to bring a new microorganism to the Canadian market.

2. New Substance Notification Regulations (NSNR)

By definition, "a substance is any matter, whether organic or inorganic, animate (live) or inanimate (lifeless)" [9]. In Canada, the Domestic Substance Lists (DSLs) include known substances (chemicals, organisms, etc.) that were in Canadian commerce between 1984 and 1986 or have been added to the DSLs after undergoing CEPA 1999 toxicity risk assessments, referred to as "New Substances Notifications". Substances listed in the DSLs may or may not have usage conditions or

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restrictions assigned. Further, DSL substances associated with Significant New Activities (SNAcs) are identified with an "S" flag indicating that they require additional notifications and assessments beyond approved intended use. Any substance not listed in the DSL is considered a "New Substance". New substances may be used in a wide variety of products such as cosmetics, natural health products, food additives, novel foods, and personal care products, as well as in many industrial processes.

The Non-Domestic Substance List (NDSL) includes substances that are listed on the Toxic Substances Control Act (TSCA) Chemical Substance Inventory in the United States, but are new to Canada. These substances require a NSN with different restrictions. Any new substance being imported or manufactured needs to go through the approval process prescribed by Environment Canada, and the manufacturer or importer needs to comply with the NSNR [10] before the substance can be sold in the Canadian marketplace. Since new substances may have adverse effects on human health and the environment, the notification requirements may include upfront base-set testing. Government evaluators from Health Canada and Environment Canada review the notification and determine whether the substance poses a risk to the environment and human health.

Substances that are regulated under the Pest Control Products Regulations, Feeds Regulations, Fertilizers Regulations, Seeds Regulations, and Health of Animals Regulations do not go through the NSN process, as these products have a separate and distinct notification procedure.

3. NSNR "O" and Related Concepts

Substances regulated under NSNR are subdivided into three categories: 1) chemicals, 2) polymers, and 3) biotechnology products. The section of the NSNR for biotechnology products has been in place since September 1, 1997 [6]. Animate products of biotechnology are living organisms used in microbial products or to produce various biomolecules. The regulations also apply to various "higher" organisms such as fish, livestock, and insects (depending on the type of use). In some cases, ECCC has agreements with other federal departments to conduct assessments of certain types of living organisms.

Living organisms are categorized into generic classes: microorganisms and organisms other than microorganisms. In particular, "microorganism" means a microscopic organism such as:

- Bacteria, archaea, protists, fungi, yeasts;
- Virus, virus-like particles (VLPs), or sub-viral particles;
- Cultured cells of an organism; and
- Any culture other than a pure culture.

The last category includes consortia of microorganisms that are not pure cultures and have been deliberately formulated using more than one microorganism isolated from sludge or soil.

In addition, manufacturers and importers must select the group that applies to their product from among these notification groups:

- Introduce anywhere in Canada
- Introduce in an ecozone where not indigenous
- Introduce in accordance with confinement procedures
- Introduce in an ecozone where indigenous
- Import to a contained facility (not for outside release) or for export only
- Introduce in experimental field testing
- Introduce at the same site where isolated

The technical information required for the application varies based on the identified notification group. In the NSN package, the technical information is divided into five schedules:

Schedule 1. Information related to subject microorganism

Schedule 2. Microorganism manufactured in Canada or imported to a contained facility (not for field release or for export only)

Schedule 3. Information related to experimental field release of subject microorganism

Schedule 4. Microorganisms manufactured at the same site from which they were isolated for introduction into the same site

Schedule 5. Information required for other organisms (not microorganisms)

3.1. General microbial information and related description

Applicants are required to furnish a significant amount of technical data on the identification of their microorganism as a new substance to ensure that it is recognizable in the environment. Taxonomy is a means of organizing microorganisms into their relative relatedness. It is imperative to discuss the taxonomic features of the subject microorganism for its identification and history. Accurate identification of the microorganism with known characteristics allows identification of its taxonomic group and assists in the necessary risk assessment studies. On the other hand, inaccurate identification can lead to a misleading determination of the microbial hazard level, resulting in either potential impacts to human and environmental health or unnecessary risk management for low-hazard microorganisms.

When a microorganism is an active ingredient in the final finished product, providing the phenotypic and genotypic characteristics of the microorganism allows its placement in a specific taxonomic group. The taxonomic level may vary depending on the specificity of techniques utilized for microbial identification. Generally, the regulatory agency recommends that organisms be identified up to species level utilizing phenotypic and genotypic characteristics. If the microbial species contains several subspecies, strains, or serovars, it is appropriate to identify each species up to strain or specific serovar level so that

related ambiguities between clinical isolates and environmental isolates can be determined and the risk analysis can be performed accordingly. For example, microorganism *Escherichia coli* contains multiple serotypes in clinical and environmental isolates, and each serotype has a different degree of pathogenicity [22]. Therefore, it is important to identify the serotypes of *E. coli*, and likewise of other microorganisms such as *Bacillus spp.* to ensure that their usage in the environment is safe for human and environmental health.

The microbial taxonomic designation provided in the application must follow the most current international code of nomenclature and standard taxonomic sources recognized by international committees [12, 13, 14]. Two such sources are *Bergey's Manual of Systematics of Archaea and Bacteria* and *The Yeasts: A Taxonomic Study*. On many occasions, identification based on peer-reviewed articles in research journals and online resources [26, 4, 15, 21] may also be acceptable.

There is no universal identification method for the entire microbial world. However, importers/manufacturers must use a reliable and scientifically advanced method to designate the phylogenetic and taxonomic relationships within genera/clade/species to conduct a robust risk assessment per regulations. The agency recommends "a polyphasic tiered approach" for accurate identification of microorganisms [8]. This approach uses data collected using different methodologies (genotypic, chemotaxonomic, and phenotypic), in tiers allowing for sequential selection of parameters in the identification of a microorganism. Tables 1 and 2 show recommended methodologies to determine phenotypic and genotypic characteristics.

The method chosen for microbial identification must be consistent with the methods used in microbial taxonomy. Figure 1 shows the relative taxonomic resolution of various techniques to identify microorganisms up to the strain level. In the case of a combination of microorganisms, or consortium, the final finished product must be screened for species pathogenic to humans such as *Salmonella* sp., *Listeria monocytogenes*, *Vibrio* sp., *Campylobacter spp.*, *Clostridium spp.*, *Bacillus anthracis*, *Pseudomonas aeruginosa*, *Yersinia spp.*, *Candida albicans*, *Aspergillus fumigatus*, fecal coliforms, and Enterococci.

The identified organisms are required to be represented by all known synonyms and common or superseded names. A historical record of the organism from its original sources of isolation to the final finished product must also be provided. The agency recommends depositing the microorganism in a permanently established and recognized culture collection facility and obtaining the accession number.

3.1.1. Genetically engineered (GE) microorganisms

ECCC requires to provide all the genetically engineered (GE) creation activities and related gene behavior in the environment. For GE microorganisms, the genetic information of the recipient and donor microorganisms is required to determine the characteristics of the final construct. For the final construct (subject microorganism), information should be included on sequences for structural genes (usually genes which encode the commercial importance), vector DNA (vehicle used to transfer the gene), and marker genes (such as antibiotic resistance), as well as any directed or intentional modifications made to the microorganism. The key points listed below should also be covered in comprehensive documentation for GE microorganisms as part of the NSN package. For inserted genes, relative data of safety and relatedness is required with its naturally occurring microbial community.

(A) Key points to provide for GE organisms

- Name of the modification and its purpose
- Description of methodology used to make the modifications
- Specify the phenotypic and genotypic changes due to GE
- Fate/stability of modifications
- Characteristics (i.e., nature, sources, function, etc.) of inserted genetic element

(B) Selection and detection of GE microorganism from environment

Selectable and non-selectable marker gene(s) in gene systems or reporter genes are used to select transformed microorganisms for potential usage. The marker genes/proteins facilitate the identification of cells expressing the cloned DNA and assist in monitoring the transformed progeny. These genes are usually co-transformed with the gene of interest into the cell. The markers can be divided into several categories, depending on whether they confer positive or negative selection and whether detection of the microorganism is conditional or non-conditional in the presence of external substrates. Positive selective markers promote cellular growth on the site, whereas negative markers result in the death of transformed cells.

Reporter gene technology is also widely used to monitor cellular events with signal transduction and gene expression. This technology has been employed to "report" the effects of a cascade of gene-signaling events due to gene expression inside the cells. The principal advantages of this technology are high sensitivity, reliability, convenience, and adaptability to large-scale measurements. Technically, reporter genes most often include light-signaling elements such as the bioluminescent bacterial (*lux*) and firefly (*luc*) luciferases, green fluorescent protein (*gfp* as well as its palette of multicolored fluorescent derivatives), and colorimetric indicators like β-galactosidase (*lacZ*) [18].

In addition to selection of GE microorganisms, microbial detection in the field is equally important. There are several commonly used GMO testing protocols, including nucleic-acid-based and protein-based detection methods (Table 3). DNA-based polymerase chain reaction (PCR) is one powerful technique that has been used for detection of new constructs in the environment. There are three main PCR strategies used with GE microorganisms: multiplex PCR, quantitative competitive PCR (QC-PCR), and real-time PCR (RT-PCR).

Microarray technology has been proposed for several applications in DNA analysis for detection of different nucleic acid

Table 1: Phenotypic characteristics of a microorganism to be identified in a NSN package[a]

Characteristics	Observation (Examples)	Methodologies
Morphological: Colony morphology Cell and spore morphology	• Color, shape, presence of halo, fruiting bodies, mycelia type, hyphal structures, etc. • Shape, cluster type, type of cell wall, cell staining (i.e., Gram stain), motility (i.e., via pili, fimbria, flagella) and their quantity, presence or absence of envelope structures (i.e., capsule or slime layer), etc.	Microbial growth on specific media with or without supplements, plating, staining, and microscopic observation
Physiological and biochemical	• Range of growth temperature (optimum maximum and minimum • pH optimum and range • Requirement for nutrients and growth supplements • Enzymatic activities • Carbohydrate utilization • Acid production from carbohydrates • Utilization of sources of carbon, nitrogen, etc. • Oxygen requirement • Salt tolerance • Growth on selective, differential or enriched media • Susceptibility/resistance to antibiotics, antifungal or antiviral agents • Susceptibility/resistance to heavy metals or other substances • Pigment production	Standard testing
Serological	• Agglutination • Immunodiffusion • ELISA • Detection of specific proteins (Western blotting)	Determination of microbial antigens against specific antibodies
Toxin/Primary and secondary metabolite production	• Endotoxins • Mycotoxins • Other metabolites	Molecular methods, Gas chromatography, (GC), GC-Mass spectrometry (GC-MS), High-performance Liquid Chromatography (HPLC), HPLC-MS, Matrix-assisted Laser Desorption/Ionization Time-of-Flight spectrometry (MALDI-TOF), Enzyme-linked Immuno-sorbent Assay (ELISA)
Chemotaxonomic	• Fatty Acid Methyl Ester (FAME) • Lipopolysaccharides, type of peptidoglycan, whole cell sugar, cell wall sugars, mycolic acids, diamino-acids, quinone system, polyamine content, cell wall amino acids, etc. • Cellular proteome, metabolome, etc.	Extract analysis from micro-organisms (fatty acid, protein, etc.); Cellular proteome can be determined using 2D gel electrophoresis, MALDI–TOF, etc.; Cellular metabolome can be determined using methods listed under section toxin/ primary and secondary metabolite production

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targets at once [16]. These protein-based methods are mostly based on immunoassays. Enzyme-linked immunosorbent assay (ELISA) and immuno-chromatographic assay (lateral flow strip testing) methods have been used to detect site-specific proteins [25]. Some other methods, such as chromatography, mass spectrometry, and near infrared (NIR) spectroscopy, may be used for the detection of GE microorganisms, but their sensitivity and reliability depends on many factors if the sample is acquired from an environmental site.

(C) Biological and ecological characteristics

Regardless of the microbial modification, the NSN package must contain a detailed methodology to track the environmental release of the microorganism, and the following biological and ecological characteristics of the organism must be discussed:

- Life cycle
- Microbial ability to cause infection, pathogenicity, toxicity, and toxigenicity in the environment
- Microbial tolerance to metals and pesticides, including

Table 2: Genotypic characteristics of a microorganism to be identified in NSN package[a]

Characteristics	Observation (Examples)	Methodologies
a) Conserved genes or hypervariable regions in the conserved gene sequence	• 16S rRNA, chaperonin-60 (cpn60) for bacteria; 16S rRNA, type II chaperonin for archaea • 18S, 5.8S, 28S rRNA operon (along with ITS1, ITS2, D1/D2 regions) for eukaryotes • Multi-Locus Sequence Alignment (MLSA) or Typing (MLST) using house-keeping genes (i.e., gyrase A, gyrase B, translation initiation factor 1, translation initiation factor 2, transcription elongation factor 1, recombinase A, recombinase B, cytochrome C oxidase, β-subunit of ATP-synthase, etc.)	DNA sequencing and DNA alignment
b) Whole Genome Sequence (WGS)	• Full genome analysis	DNA sequencing, DNA alignment and genome annotation (i.e., useful in the detection of specific genes that may contribute to the identification, such as virulence factors)
c) DNA polymorphism	• DNA base ratio (G+C content) • Random Amplification of Polymorphic DNA (RAPD) • Restriction Fragment Length Polymorphism (RFLP) • Pulsed-field gel electrophoresis (PGFE) • Southern and northern blotting • Cellular transcriptome	PCR and DNA-based typing and hybridization
d) DNA hybridization	• DNA:DNA hybridization or DNA:RNA hybridization	Hybridization

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resistance to antibiotics

- Microbial role in biogeochemical cycling
- Environmental factors limiting microbial growth, survival, replication, etc.
- Factors of microbial dispersal/spread and interaction with the dispersal agent

It is not uncommon for genetic elements inserted into recipient microorganisms to reveal different biological and ecological characteristics under different environmental conditions and through interaction with unknown species. Therefore, mechanisms of gene transfer within and between the microorganisms should be described in the NSN package. Data on the organism's capability to transfer genetic material into other organisms must be provided, and applicants must discuss the genetic basis for the new substance's pathogenicity to nonhuman species, along with its toxigenicity and resistance to antibiotics.

(D) Mode of action in relation to the intended use

Microorganisms can be employed for various commercial uses, but physical, chemical, and biological conditions play key roles in their intended use. Classically, microbial modes of action have shown different sets of biochemical pathways and by-products under different environmental conditions. Therefore, applicants must identify the intended use based on the mode of action of the microorganism under optimized conditions. It is equally important to predict the role of the end products after the proposed intended use, such as the formation of recalcitrant compounds at the end of biodegradation during bioremediation processes, which may be more toxic than the parent compound.

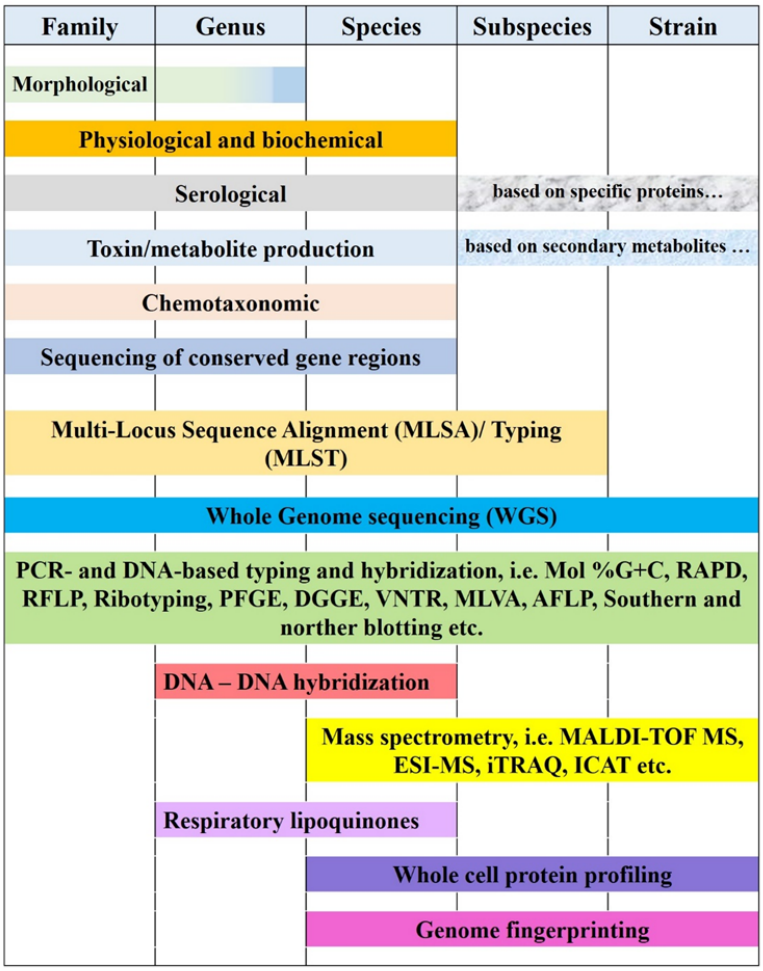
(E) Patent or any application for patent

A patent is an exclusive right granted by the state to an inventor or their assignee for a certain period of time in return for the full disclosure of the invention. This right excludes others from making, using, and commercializing the invention for the term of the patent, generally for 20 years from the filing date [20]. If an NSN applicant has applied for a patent and/or been granted one, they must provide the patent number or application number.

(F) Dispersal of traits by gene transfer

Any movement of individual microorganisms that has potential consequences for gene flow across the area is referred as "dispersal". The dispersal of any organism includes departure (initiation to leave the natural habitat), transfer (movement), and settlement (establishment) in the novel habitat where they can thrive. All three elements of dispersal often involve multiple morphological, physiological, and behavioral traits [2]. In the NSN package, each element must be described based on the following criteria:

- The microbial potential for dispersal must be provided based on the genetic basis for pathogenicity to nonhuman



[a]RAPD: Random Amplified Polymorphic DNA; RFLP: Restriction Fragment Length Polymorphism; PFGE: Pulse-field Gel Electrophoresis; DGGE: Denaturing Gradient Gel Electrophoresis; VNTR: Variable Number of Tandem Repeats; MLVA: Multiple-Locus Variable-number of tandem–repeats Analysis; AFLP: Amplified Fragment Length Polymorphism; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization-Time Of Flight mass spectrometry; ESI MS: Electrospray Ionization Mass Spectrometry; iTRAQ: Isobaric Tag for Relative and Absolute Quantitation; ICAT: Isotope-Coded Affinity Tags

Figure 1: Relative taxonomic resolution of various techniques for microbial identification[a]

Table 3: Detection and sensitivity of laboratory methods to track the GE microorganisms in the environment

Method	Sensitivity	Type of Measurement	References
DNA-based methods:			
RT-PCR[a]	0.005 ng	Qualitative and quantitative	Ding et al. [3]
RTi-PCR[b]	2.595 ng	Qualitative and quantitative	Hernandez et al. [11]
MQDA-PCR[c]	1.1-0.2 for GE constructs	Qualitative	Rudi et al. [23]
Protein-based methods:			
C- ELISA[d]	4 ng	Qualitative and quantitative	Jennings et al. [16]
Lateral flow strip	High	Qualitative	Stave, J. W. [25]

[a]RT-PCR = real time polymerase chain reaction
[b]RTi-PCR = real time immuno-capture polymerase chain reaction
[c]MQDA-PCR = multiplex quantitative DNA-based polymerase chain reaction
[d]C-ELISA = competitive enzyme-linked immunosorbent assay

species, toxigenicity, and resistance to antibiotics. The genetic exchange of characteristics should be described using the number of genes coding for the trait and their location (i.e., chromosomal or extrachromosomal).

- Applicants must cite information regarding the nature of extrachromosomal genetic elements (i.e., plasmid born or organelle based), and transposable elements, and lysogenic viruses associated with the microorganism, if any. Detailed information is required on genetic elements such as copy number, host range, mobilization ability, size, insertion specificity, transduction potential, transposition potential, and any resulting phenotypic changes.
- It is possible that environmental conditions may influence the gene transfer capability of the microorganism. Therefore, growth and tolerance conditions for the subject microorganism should be described to evaluate the environmental influence.

(G) Geographic distribution of subject microorganism

Many microorganisms are ubiquitous in nature, but some found in selective environmental sites are called extremophiles (i.e., microorganisms living under adverse environmental conditions) [24]. The application must include a literature-based description of the known geographical distribution of the subject microorganism that includes its distribution within North America. Microorganisms with global occurrence can be noted as "ubiquitous in nature".

3.2. Manufacturing or importation information

The regulations require applicants to provide the following information on their products: trade names, location of manufacturing or importation, containment level for each facility to which the microorganism will be imported, formulated and physical state of formulation, active and total ingredients in the formulation, viability of the microorganism, requirements of storage and disposal, quantity to be imported, quality control procedures and checkpoints, procedure for release of the microorganism, treatment of waste containing the microorganism, and data demonstrating the microbial occurrence from the site of introduction.

The final finished product may be vulnerable to contamination; therefore, it is important to identify the other ingredients and contaminants in the formulation. The viability of the microorganism in the formulation must be demonstrated. Any ingredient intended to promote microbial metabolic activity must be identified in the formulation. The description of the manufacturing process should include the quality control measures and assurance procedures that can maintain microbial viability up to the proposed concentration throughout the product's shelf life. The quality assurance procedures must include procedures for measurement, frequency, limits, extent, range, and duration of testing.

3.3. Onsite introduction of the microorganism

The intended functions and/or uses of the microorganism should be provided with sufficient description of environmental safety. The NSN package requires that applicants inform the agency about the ecozone where the subject microorganism will be released, along with its history in the same or different ecozones. The historical data should reveal that the microorganism either was isolated from the same ecozone where it was introduced or is taxonomically identical to resident microorganisms. A side-by-side comparison of the natural habitat of the subject organism and the potential site would help to determine its adaptability to the site of introduction.

The procedure for applying the substance must be documented, not limited to the method of application, quantity of subject organism, and frequency and duration of application, along with activities performed during the application, such as supply of additional nutrients, mixing, tilling, and aeration or venting of oxygen. Applicants are required to provide information on predicted or accidental release of the subject microorganism, along with the effective termination and confinement procedures.

3.4. Experimental field release

If the organism will be introduced in an experimental field trial, the applicant should explain the experimental setup, including objectives of the field trial, location, map, size, distance from population and protected areas in the vicinity, method of application, tracking/monitoring, stability, etc. The NSN for a field trial organism requires information similar to that for commercial importation, with some additional information [9, 10].

3.5. Environmental fate of subject microorganism

Regardless of the organism's genetic makeup (i.e., wild type or GE), it is important to determine the fate of the subject organism in the environment with respect to its stability and influence on animal populations and human society. A literature-based study should justify the fate of the subject microorganism and whether genetic elements derived from its decomposition in the field would have adverse effects on environmental health. In the past, concerns were raised on the existing data of naked bacterial DNA in a defined soil [17] and in more complex environmental samples [1]; however, the data interpretations may vary depending on the DNA binding ability with the type of soil particles and related environmental factors.

It is important to show how the subject microorganism may affect plants and animals. Data should be provided on how the organism persists or proliferates under varying environmental conditions at the introduction site, such as survival, limitations on growth and survival, selection mechanism, and varying biological, physical, and chemical factors.

3.6. Ecological impact of the subject microorganism

Survivability of the microorganism on-site is crucial. Therefore, as stated in the above section, methods for detecting the subject microorganism are necessary in order to study its ecological impacts. The regulatory agency requires that the

NSN package include comprehensive data on experiments exposing plant and animal species to the organism. The agency recommends that applicants conduct six main tests: aquatic plant, vertebrate, and invertebrate species, as well as terrestrial plant, vertebrate, and invertebrate species. Test organisms should be exposed to a "maximum hazard" concentration or dose of the microorganism. Per guidance, this should be 10^6 cells/mL or 1,000 times the expected microorganism concentration in the environment, whichever is greater. Applicants are required to provide related test procedures, data, and conclusion to Environment Canada for their independent evaluation.

3.7. Effects on human health

Microbes are the oldest form of life on earth. Some coexist with humans without harming them, and others have mutually beneficial relationships with human hosts. However, even non-pathogenic microorganisms can harm human hosts via their metabolites, such as indole sulphate, trimethylamine, etc. A literature-based study should be provided to examine whether the subject organism has any adverse effect on human health. An online search of Medline, Embase, or Biosis previews is recommended to explore the human health effects of microorganisms. Data collection should focus on the number of cases reported, nature and severity of the effect, option of treatment, geographical locations where reported cases were prevalent, nature of exposure that led to adverse effects, and predisposing factors related to the effects.

It is equally important to provide data on antibiotic susceptibility in terms of minimal inhibitory concentration (MIC) for major antibiotic classes such as aminoglycoside, beta-lactam, macrolide, tetracycline, and fluoroquinolone. Data on pathogenicity and adverse immunological reactions would also help to determine if the subject organism is deleterious to human health.

3.8. Additional information

Environment Canada encourages applicants to provide additional information such as experimental data, literature reviews, database searches, and test studies on employees, customers, the public, and the environment. This information will further help the agency to evaluate whether the subject microorganism is a less toxic substitute for an existing substance or technology, and whether its use will generate less waste than the existing substance.

4. Waivers and regulatory interactions

In addition to the above stated requirements, the CEPA 1999 defines waivers from technical information under subsection 106(8). There are a few specific conditions for applicants to seek a waiver, and the waiver request delays the NSN decision from the agency. Applicants can only pursue their NSN application once they receive the response to their waiver request, which may or may not be granted after thorough review. The regulatory agency has a mechanism for applicants to request and obtain feedback in pre-notification consultation (PNC) meetings, although these meetings are limited to determining schedules for notification and the acceptability of waiver requests or test protocols, not the test results or interpretations of test results. However, the PNC meetings are encouraged and highly recommended to avoid potential pitfalls in the submission and the data package.

5. Conclusion

Under the CEPA 1999 toxicity risk assessments for new substances, manufacturers or importers need to comply with NSNR before their substance can be sold in Canada. It may be complicated to interpret the requirements for technical information in the NSN package. However, microbial characterization and valid justification of environmental and ecological impacts are critical for the clearance of new substances to be listed in the DSL. Since each new microorganism may impose different risks to the environment, risk assessment studies are unavoidable to ensure safety. Environment Canada provides assistance through PNC meetings, and greatly encourages applicants to seek their feedback on test reports and related tasks before submitting an NSN package for agency review.

6. Declaration of Conflicting Interest

The author declares no conflicts of interest.

7. Article Information

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