New substances: risk assessment summary, new substances notification 21695

Official title: New substances: risk assessment summary, New Substances Notification 21695 – Schedule 1 of the *New Substances Notification Regulations (Organisms)*

Notified organism: Recombinant, chimeric vesicular stomatitis virus (VSV) carrying the envelope glycoprotein of the visceral non-neurotropic WE-HPI strain of the lymphocytic choriomeningitis virus, and a codon optimized human CD80 gene fused to the Fc IgG1 heavy chain constant region (VSV-GP-CD80Fc)

Schedule of the NSNR(O): Schedule 1 – Information Required in Respect of Micro-organisms

Organism type: Virus

Use: Import as an immunotherapy drug product for use in clinical trials to treat adult patients with advanced solid tumors

Anticipated quantity: confidential and not for disclosure.

Assessment level of concern:

- Human health hazard: Low
- Human exposure: Low
- Environmental hazard: Low
- Environmental exposure: Low

Assessment conclusion under section 64 of the *Canadian Environmental Protection Act, 1999* (CEPA): Low risk, not suspected to be toxic

Category: Added to the Domestic Substances List on May 22, 2024

Recommended action: None

Waivers: Waivers to submit the data from tests conducted to determine the pathogenicity and toxicity of the notified organism under subparagraphs 5(a)(i) and 5(a)(ii) of Schedule 1 of the *New Substances Notification Regulations (Organisms)* [NSNR(O)] were granted under paragraph 106(8)(a) of the *Canadian Environmental Protection Act, 1999* (CEPA) for aquatic and terrestrial plants, invertebrate and vertebrate species, respectively, for the following reasons:

- The genetic modifications made to the notified organism have weakened its virulence compared to that of the wild type VSV;
- Preclinical data in terrestrial vertebrates demonstrated negligible shedding from treated patients.

A waiver to submit the data from tests of antibiotic susceptibility under paragraph 6(b) of Schedule 1 of the NSNR(O) was granted under paragraph 106(8)(a) of CEPA because the notified organism is weakened and does not carry any antiviral resistance genes.

Synopsis

The notified organism is a genetically modified virus that was notified to the New Substances program for use in clinical trials to treat adult patients with advanced solid tumors. Other potential uses include its use as a commercial immunotherapy product for treatment of advanced solid tumors.

There is no evidence to suggest a potential risk of adverse environmental and indirect human health effects at the exposure levels predicted to the environment and general population in Canada from the import and use of the notified organism.

It is determined that the notified strain is not toxic or capable of becoming toxic according to the criteria under section 64 of CEPA as there is no evidence to suggest that the notified organism may enter the environment in a quantity or concentration or under conditions that:

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

No risk management is recommended.

Background information

The notified organism is a genetically modified virus that is live, attenuated, and replication-competent, and contains an optimized CD80-Fc fusion protein. It is derived from the parental VSV strain where its neurotoxic glycoprotein (GP) has been replaced with a nontoxic GP from a lymphocytic choriomeningitis virus (LCMV) resulting in the attenuation of the parental strain. Following intravenous infusion, the notified organism is expected to stimulate immune responses by replication and expression of CD80-Fc fusion protein in the infected tumor cells leading to the lysis of the tumor cells.

Hazard

The environmental and human health hazard potential of the notified organism is determined to be low because:

1) Like the parental strain, VSV-GP, the notified organism is also an attenuated strain, lacking the neurotoxic glycoprotein found in wild type VSV, because it has been replaced with a non-toxic glycoprotein of a lymphocytic choriomeningitis virus (LCMV)
2) The modifications to introduce the CD80-Fc fusion protein are well-defined, stable, and are not expected to alter its host range compared to wild type VSVs.
3) The notified organism has been classified by the Public Health agency of Canada as a Risk Group (RG) 2 human and terrestrial animal pathogen[1] because it is derived from the wild type vesicular stomatitis Indiana virus.
4) Results of animal studies in mice and swine showed that both the notified organism and its parental strain are safe. The introduced LCMV-GP and the CD80-Fc fusion protein were determined to be minimally ecotoxic. There was low or absent shedding of the infectious virus in mice, poor persistence in the environment, and no evidence of pathogenesis in treated swine.
5) Biting (sand) flies, midges, and possibly mosquitos are considered as biological vectors for wild type VSVs, meaning they can carry and transmit infectious pathogens from infected individuals to other individuals. It is theoretically possible that an individual treated with the notified organism could have enough virus present in the blood for a susceptible insect to become infected and transmit the notified organism. Although transmission between an infected host to a non-infected host via an active lesion is possible, it is unlikely to result in the widespread dissemination of the notified organism.
6) Recombination events between the notified organism and the wild type VSV leading to formation of virulent strains would be extremely rare since the notified organisms are expected to be present only in treatment settings and in patients who receive it. In addition, the notified organism rarely recombines with other viruses. There is no other information specific to the notified organism to indicate that it has or would be able to recombine to acquire virulent properties exhibited by the wild type virus.
7) Results of earlier human clinical studies indicate that the notified organism was well tolerated. Patients reported a range of symptoms including but not limited to tumor pain, fatigue and flu-like symptoms, as well as a single case of cytokine release syndrome. Similar to infection with the wild type strain, these symptoms resolved on their own and only symptom management measures were required.
8) Although the antiviral medications ribavirin and interferon have been described in the scientific literature as being efficient against VSV in pre-clinical studies, there are no approved antiviral treatments for treating humans with VSV infections. In the case of infection or adverse immune reaction, it is recommended that symptomatic treatment be provided, given that infection usually goes away on its own with no need for any therapeutic agents or additional interventions.

[1] RG2 human pathogens pose a moderate risk to the health of individuals or animals, and a low risk to public health and the animal population. These pathogens are able to cause serious disease in a human or animal but are unlikely to do so. Effective treatment and preventive measures are available and the risk of spread of diseases caused by these pathogens is low.

Exposure

The environmental and indirect human health exposure potential of the notified organism is determined to be low because:

1) Only limited quantities of VSV-GP-CD80Fc will be imported into Canada in secure containers to treat maximum 10 adult patients with advanced solid tumors during the course of clinical trial. It will be administered to the patients under controlled conditions in healthcare centers by properly trained healthcare professionals.
2) The class II Biosafety measures will be applied for the preparation, handling and administration of the notified organism at healthcare center(s). The contingency plans for accidental spills and procedures for treatment of contaminated wastes to minimize release of the notified organism were adequately described by the notifier.
3) Following administration of the notified organism, the patients will be required to cover the injected site and remain in a private room at the health center until discharge. For the duration of the clinical trial, patients with respiratory syndromes will be advised to avoid crowded or poorly ventilated public places and avoid contact with susceptible animals (e.g., farm animals) or pets.
4) Similar to wild type VSV, the notified organism is susceptible to extremes of temperature and dryness. Therefore, if released into the environment, the notified organism can only survive for a limited time in the excretions of an infected host and/or in the natural environment.
5) Data from animal studies using the notified organism indicate that shedding is expected to be limited. Other animal studies using a similar organism have shown that horizontal transmission of the notified organism to the animals is highly unlikely and thus limits the likelihood of spreading. Taken together with the limited use of the notified organism exclusively for treating adult patients with advanced solid tumors, followed by the subsequent moving of the treated individuals to different locations post-discharge, the exposure of the environment and the general public to the notified organism is further reduced and is therefore expected to be negligible.
6) The notifier does not intend to manufacture the notified organism in Canada. Should it be manufactured in Canada in the future, the exposure to the environment is not expected to significantly increase. Other potential uses include its use as a commercial immunotherapy product for treatment of advanced solid tumors. However, similar to the case for the intended use, the overall exposure from the potential uses would still remain negligible.

Risks from workplace exposure to the notified strain are not considered in this assessment[2]**.**

[2] A determination of whether one or more criteria of section 64 of CEPA are met is based on an assessment of potential risks to the environment and/or to human health associated with exposure in the general environment. For humans, this includes, but is not limited to, exposure from air, water and the use of products containing the substances. A conclusion under CEPA may not be relevant to, nor does it preclude, an assessment against the criteria specified in the *Hazardous Products Regulations*, which is part of the regulatory framework for the Workplace Hazardous Materials Information System (WHMIS) for products intended for workplace use.

Risk characterization

Owing to the low potential hazard and the low potential exposure, the environmental and human health risk associated with the import and use of the notified organism as an immunotherapy drug product in human clinical trials or as a potential commercial immunotherapy product to treat adult patients with advanced solid tumors is assessed to be low.

Risk assessment conclusion

There is no evidence to suggest a potential risk of adverse environmental and human health effects at the exposure levels predicted to the environment and general population from the import and use of the notified organism as an immunotherapy drug product in human clinical trials or as a potential commercial immunotherapy product to treat adult patients with advanced solid tumors. The risk to the environment and human health associated with the notified organism is not suspected to meet the criteria in paragraphs 64(a), (b), or (c) of CEPA. No further action is recommended.