New substances: risk assessment summary, new substances notification 21722

Official title: New substances: risk assessment summary, New Substances Notification 21722 – Schedule 1 of the *New Substances Notification Regulations (Organisms)*

Notified organism: Live Vaccinia Virus Acambis clone 2000

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

Organism type: Virus

Use: Import of the notified organism to establish a stockpile under the control of the Government of Canada limited to the Public Health Agency of Canada (PHAC) for vaccination of individuals who are determined to be at high risk for smallpox infection.

Anticipated quantity: confidential and not for disclosure.

Assessment level of concern:

- Human health hazard: Low for general population; medium for children of ≤16 years of age, pregnant and/or breast-feeding individuals, and immunocompromised individuals
- Human exposure: Low
- Environmental hazard: Low for aquatic species and terrestrial plant and invertebrate species; medium for terrestrial vertebrate species, specifically livestock
- Environmental exposure: Low

Assessment conclusion under section 64 of the *Canadian Environmental Protection Act, 1999*: Suspected to be toxic

Category: Ministerial Condition published on March 16, 2024

Risk management action: Ministerial Condition

Waiver: Waiver 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)*, were granted under paragraph 106(8)(a) of the *Canadian Environmental Protection Act, 1999* (CEPA) for aquatic plants, invertebrate and vertebrate and terrestrial plants and invertebrate species, respectively, for the following reasons:

- Long history of safe use of its parental strain in smallpox vaccines in Canada and internationally.
- Vaccinia virus as a genus is not commonly known to infect plants or aquatic vertebrates and invertebrates.

Synopsis

The notified organism is considered a laboratory adapted and selected virus and is not genetically modified. It was notified to the New Substances program for use in a smallpox vaccine.

There is 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 toxic or capable of becoming toxic according to the criteria under section 64 of CEPA as there is 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, and
- constitute or may constitute a danger in Canada to human life or health.

Ministerial Condition provisions were recommended to protect the environment and the general population in Canada, including children of ≤16 years of age, pregnant and/or breast-feeding individuals, and immunocompromised individuals from exposure to the notified organism.

Background information

The notified organism is a naturally occurring microorganism of unknown origin and hence is not known to be indigenous to any Canadian ecozone. It was imported into Canada to establish a vaccine stockpile under the control of the Government of Canada (currently limited to PHAC) for vaccination of individuals who are determined to be at high risk for smallpox infection. Other potential uses could include its manufacture in Canada, or use in commercial vaccine product for vaccination programs for Canadians in case of smallpox or other disease outbreaks in Canada against which ACAM2000® Smallpox (Vaccinia) vaccine would be required

Hazard

The environmental hazard potential of the notified organism is determined to be low for aquatic species and terrestrial plant and invertebrate species and medium for terrestrial vertebrate species, specifically livestock, because:

1) The notified organism is a laboratory adapted andselected vaccinia virus (VACV) strain derived from the parental strain New York Board of Health (NYCBH). It is a well-studied virus and its entire genome has been sequenced.
2) The information provided by the notifier and an updated search of the scientific literature by the New Substances program yielded no results for potential negative impacts (pathogenicity or toxicity) of the notified organism or its parental strain, on aquatic plant, invertebrate or

vertebrate species. In addition, there are no reports of infections caused by VACV in terrestrial plants and invertebrates.

3) The notified organism was classified as a Risk Group (RG) 2[1] terrestrial animal pathogen by PHAC. This classification is based partly on the data available from comparable VACV species, such as Bovine VACV (BV). Studies on BV have shown that it can cause severe lesions on the teats and udders of infected livestock (i.e., cattle, buffalo, and water buffalo) leading to mastitis and other secondary infections. About 40% of infected animals were reported to have developed severe disease. In addition, BV has been found to be highly contagious in cattle herds with infection rates of up to 100%.
4) Despite the widespread smallpox vaccination of Canadians decades ago, the parental strain of the notified organism is not known to be present in Canadian cattle, and no infections were reported from earlier vaccination efforts in Canada.
5) Animal studies in mice, rabbits, and non-human primates showed that the vaccine containing the notified organism, at doses 40 times or higher than the human dose, is less harmful to the nervous system and skin than the parental strain used in the previous smallpox vaccine.

The human hazard potential of the notified organism is determined to be low for the general population and medium for children of ≤16 years of age, pregnant and/or breast-feeding individuals, and immunocompromised individuals because:

1) The notified organism has been classified as a RG 2 human pathogen by PHAC. Furthermore, results from human clinical studies in otherwise healthy individuals indicate that the most common adverse effects ranged from mild effects at the vaccination site (e.g., redness of the skin, itching) to flu-like symptoms. The notified organism may also cause more severe adverse effects in humans. However, such events are less common compared to those caused by older generations of the VACV strain NYCBH.
2) The notifier stated that the safety of the notified organism has not been studied in children of ≤16 years of age, in pregnant and/or breast-feeding individuals, or in persons aged ≥65 years old. However, severe adverse effects in these groups have been reported for other live VACV based vaccines.
3) The notified organism belongs to the *orthopoxvirus* family, and genetic recombination events amongst different members of this family have been commonly reported. . For such events to occur, different viruses must be present and replicating within the same infected host cell. In that situation, however, there are further physical constraints within any host cell that can further limit recombination between those co-infecting viruses.
4) In the event of complications occurring in an individual following an injection of the smallpox vaccine, there are two available antiviral agents (i.e., TEMBEXA® and TPoxx®) and a polyclonal

[1] RG2 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.

antibody product (i.e., Vaccinia Immune Globulin Intravenous (Human)) that are effective against VACV.

Exposure

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

1) A predetermined quantity of the smallpox vaccine containing the notified organism will be imported from the United States into Canada to establish stockpile(s) under the control of the Government of Canada (limited to PHAC) for vaccination of individuals who are determined to be at high risk for smallpox infection.
2) Secure transportation, handling and administration of the vaccine will be under the purview of relevant provincial regulations in the recipient provinces.
3) The vaccine is securely packaged and stored frozen solid at -15°C during transportation. In addition, the notifier has described the procedures in place to mitigate spills and handle waste, should a transportation accident occur.
4) When subjected to higher temperatures (≥20°C) and moisture, the concentration of the viable notified organism will drop. No viable virus is expected to remain after nine days.
5) The notified organism will be administered under controlled conditions in hospital centre(s) by properly trained health care professionals. Each individual will receive a predetermined dose administered under the skin by the percutaneous route (scarification) using a bifurcated needle.
6) The notifier provided guidance that vaccinated individuals should cover the skin injection site with an adequate bandage and keep the site covered until the scab falls off on its own. This provides a physical barrier to protect against direct contact. Additional guidance was given to both healthcare providers and patients to limit release of virus to the environment and indirect exposure to bystanders, including those at high risk of serious adverse effects of VACV.
7) Studies have shown that VACV transmission between humans and animals occurs primarily through direct contact with wet lesions or small breaks in skin. Human-to-human transmission of VACV can occur through contact with VACV-contaminated objects or materials which are likely to carry infection, including contaminated bandages, clothing, towels, and bedding.
8) In cattle, transmission of VACV is observed to occur commonly from teats of lactating cows to the mouths of suckling calves. In addition, both cattle and house pets can become infected following exposure to infected humans.
9) Results from human clinical studies have shown that the notified organism can be shed from the site of vaccination from the third day after vaccination to up to six weeks post-vaccination. Maximal viral shedding following vaccination, as measured at the vaccination site, occurs between 7 to 15 days post vaccination. Cell-bound viral particles (i.e., in the scabs) have been shown to remain viable in the environment for over eight weeks. Limited historical data suggests that virus released through blood, urine, and pharyngeal shedding occurred in the case

of the parental strain. However, such events involved more virulent strains used for vaccinations in Europe and Asia.

10) At the time of notification, the notifier indicated that they did not intend to manufacture the notified organism in Canada. However, other potential uses could include manufacturing of the vaccine product in Canada in the future, or use of the vaccine product for vaccination programs for Canadians in case of smallpox or other disease outbreaks in Canada against which the smallpox vaccine containing the notified organism would be required. In case of such potential uses, the release of the notified organism into the environment could increase.

Risk characterization

The notified organism has a low hazard potential for aquatic species and terrestrial plant and invertebrate species. However, given the medium hazard potential for terrestrial vertebrates, specifically livestock, the notified organism is suspected to meet criteria in paragraph 64(a) of CEPA.

The notified organism has a low potential for hazard in the general population. However, given the medium hazard for children of ≤16 years of age, pregnant and/or breast-feeding individuals and immunocompromised individuals, the notified organism is suspected to meet the criteria in paragraph 64(c) of CEPA.

Due to the identified risk to the environment for terrestrial vertebrates, specifically livestock, and to human health for children of ≤16 years of age, pregnant and/or breastfeeding women and immunocompromised individuals, Ministerial Conditions were imposed to restrict the manner in which the notifier may manufacture, import or administer the substance with conditions on its use, handling and disposal in order to mitigate these potential risks. *Ministerial Condition No. 21722* was published in the Canada Gazette Part I, Vol. 158, No. 11 on March 16, 2024.

Risk assessment conclusion

There is evidence to suggest a risk of adverse environmental effects at the exposure levels predicted for the environment should pre- or post-administration, handling or disposal procedures be altered from those described by the notifier. These risks are associated with the import of the notified organism for use in a smallpox vaccine or in vaccination programs for the general population in Canada in case of smallpox or other disease outbreaks in Canada. The risk to the environment associated with the notified organism is suspected to meet the criteria in paragraph 64(a) of CEPA for these activities in Canada. To protect the environment from this strain, Ministerial Condition provisions were recommended.

There is evidence to suggest a risk of adverse human health effects at the exposure levels predicted for the general population in Canada (safety has not been tested in specific subpopulations) should pre- or post-administration, handling or disposal procedures be altered from those described by the notifier. These risks are associated with the use of the notified organism in a smallpox vaccine or in vaccination programs for Canadians in case of smallpox or other disease outbreaks in Canada. The risk to human

health associated with the notified organism is suspected to meet the criteria in paragraph 64(c) of CEPA for these activities in Canada. To protect children of ≤16 years of age, pregnant and/or breast-feeding individuals, and immunocompromised individuals from exposure to this strain, Ministerial Condition provisions were recommended.