Summary Report of Risk Assessment Conducted Pursuant to subsection 108(1) of the *Canadian Environmental Protection Act, 1999*

New Substances Notification 20417: Recombinant replication-defective human adenovirus type 5 expressing Spike protein (S protein) of SARS-CoV-2 (Ad5-nCoV)

Regulatory decision

Under the provisions for Animate Products of Biotechnology in Part 6 of the Canadian Environmental *Protection Act, 1999* (CEPA), and pursuant to section 108 of the Act, the Minister of the Environment and the Minister of Health have assessed information in respect of the substance, Ad5-nCoV, that is a living organism. It was determined that Ad5-nCoV is not suspected to be toxic and not anticipated to 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 to human life or health in Canada. Therefore, no further action is recommended as a result of this assessment.

Identity

The notified organism (Ad5-nCoV) is a genetically modified human adenovirus containing the gene encoding the Spike (S) protein of SARS-CoV-2. The genetic modifications render the virus incapable of replication. Upon administration as a vaccine to humans, the notified organism expresses the S protein of SARS-CoV-2, leading to the production of antigens in the human body. These antigens are expected to trigger immune response and offer protection against SARS-CoV-2 infection and COVID-19 disease.

Notified and potential uses

Ad5-nCoV was originally notified for import into Canada as a vaccine product for use in phase I/II human clinical trials in healthy adults against SARS-CoV-2 infection. Ultimately, the organism was not imported into Canada as the clinical trial was conducted elsewhere. Other potential uses include its use as a non-commercial vaccine for emergency pandemic situations.

Hazard assessment

The environmental and human health hazard potential of Ad5-nCoV is assessed to be low because:

1. Wild-type human Ad5 is ubiquitous in the environment and its host range is limited to humans and non-human primates (Pond, 2005; Lion and Wold, 2021). Human Ad5 virus is not known to infect aquatic plants, invertebrates or vertebrates, or terrestrial plants or invertebrates.
2. Ad5-nCoV is incapable of replication and it needs specific cell culture lines that support its replication during manufacture. The likelihood of Ad5-nCoV reverting to a functionally competent viral vector in the environment is low.

3. The genetic changes made in the construction of Ad5-nCoV are not expected to alter its original host tropism and it is unlikely to cause productive infections in aquatic or terrestrial plants, invertebrates and non-host vertebrates.
4. Data from animal studies conducted by the notifier in rodents and non-human primates showed no observable adverse effects or treatment-induced toxicity in treated animals.
5. The genetic modifications made in Ad5-nCoV are well-defined and the introduced genetic materials are stably integrated. Despite the introduction of the gene encoding the SARS-CoV-2 S protein, Ad5-nCoV was demonstrated to be safe and well-tolerated in animal studies and clinical trials. Therefore, Ad5-nCoV is not expected to cause adverse effects such as pathogenicity or productive infection in animals or humans.
6. Wild-type human Ad5 is ubiquitous in the environment and has been implicated in respiratory tract infections in humans. However, these are usually mild and self-limiting with no reports of secondary transmission (PHAC, 2014).
7. Preliminary results from Phase I and ongoing Phase II clinical trials with Ad5-nCoV indicate that fever is the most common adverse reaction, but otherwise, no severe adverse effects were reported. Preliminary safety data to date has indicated a good safety profile.[1]

Hazards related to micro-organisms used in the workplace should be classified accordingly under the Workplace Hazardous Materials Information System (WHMIS)[2].

Exposure assessment

The environmental and indirect human exposure potential of Ad5-nCoV is assessed to be low because:

1. Planned target doses of Ad5-nCoV will be imported into Canada for use in Phase I/II adaptive clinical trials and administered to a maximum of 696 study participants/healthy adults under controlled conditions in healthcare centre(s) by properly trained healthcare professionals. General biosafety procedures and contingency plans for accidental spills are well established. These procedures are expected to minimize the spread of the notified organism.
2. No shedding of Ad5-nCoV is anticipated following administration to study participants.
3. Ad5-nCoV is replication-defective and therefore is not expected to remain viable, persist or proliferate in the environment outside the body of the vaccinated study participant, and therefore aquatic and terrestrial plants, invertebrates and vertebrates are unlikely to be exposed. In addition, exposure of Ad5-nCoV to the general population through the environment is not expected.
4. Ad5-nCoV will be used as a drug product in human clinical trials to prevent SARS-CoV-2 infection in adults. Potential uses include its use as a non-commercial vaccine for emergency pandemic

[1] In Canada, biologic drugs are assessed for safety, quality and efficacy under the *Food and Drugs Act* and Regulations, administered by the Biologic and Radiopharmaceutical Drugs Directorate of Health Canada.

[2] A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon 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 is not relevant to, nor does it preclude, an assessment against the criteria 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.

situations. It could also be used for commercial product manufacture of the vaccine drug but this use in Canada would require a new notification prior to this activity. Ad5-nCoV is not expected to remain viable in the environment outside of the body of vaccinated individuals and therefore exposure to the environment is not expected to significantly increase from such potential uses.

5. The notifier intends to manufacture Ad5-nCoV in Canada in the future for other clinical trials or large-scale production of vaccine for emergency pandemic use or commercialized vaccine for widespread use. A new notification must be submitted prior to engaging in any of these activities with Ad5-nCoV in Canada.

Risk characterization

Risk is typically described as the probability of an adverse effect occurring based on hazards and a particular scenario of exposure. Different exposure scenarios can be described based on the intended and/or potential uses (if any) involved. In the present case, the organism was proposed to be imported and used as a vaccine in human clinical trials for the prevention of SARS-CoV-2 infection.

Owing to the low potential for environmental hazard and the low potential for environmental exposure, the environmental risk associated with the use of Ad5-nCoV as a vaccine in human clinical trials, or from its potential uses is assessed to be low.

Owing to the low potential for human health hazard and the low potential for human exposure, the human health risk associated with the use of Ad5-nCoV as a vaccine in human clinical trials, or from its potential uses is assessed to be low.

The assumptions made in the assessment are adequately protective for the general population as well as for subpopulations who may be more susceptible or highly exposed.

Risk assessment conclusion

There is no evidence to suggest a potential risk of adverse environmental effects at the exposure levels predicted for the Canadian environment from the use of Ad5-nCoV as a vaccine in human clinical trials, or from its potential uses. The risk to the environment associated with Ad5-nCoV is not suspected to meet the criteria in paragraphs 64(a) or (b) of CEPA. No further action is recommended.

Similarly, there is no evidence to suggest a potential risk of adverse human health effects at the exposure levels predicted for the general Canadian population from the use of Ad5-nCoV as a vaccine in human clinical trials, or from its potential uses. This risk to human health associated with Ad5-nCoV is not suspected to meet the criteria in paragraph 64(c) of CEPA. No further action is recommended.

References:

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