

New substances: risk assessment summary, new substances notifications 22052 and 22053

Official title: New substances: risk assessment summary, New Substances Notifications 22052 and 22053 – Schedule 1 of the *New Substances Notification Regulations (Organisms)*

Notified organisms:

- Unmodified *Pseudomonas* bacteriophage 1 for treating infections in humans
- Unmodified *Pseudomonas* bacteriophage 2 for treating infections in humans

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

Organism type: Bacteriophage

Use: Manufacture of Unmodified *Pseudomonas* bacteriophages 1 and 2 as components of the QDP-PSA-011 bacteriophage cocktail for use in one designated patient for the control of the active and recurrent multidrug resistant (MDR) *Pseudomonas aeruginosa* periprosthetic joint infection in an 82-year-old female.

Anticipated quantity: confidential and not for disclosure

Assessment level of concern:

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

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

Recommended action: None.

Waiver: Requested for information elements 5(a)(i), 5(a)(ii), and 6(b) of Schedule 1 of the NSNR(Organisms), under paragraph 106(8)(a) of CEPA.

Synopsis

Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans are naturally-occurring lytic bacteriophages infecting *Pseudomonas aeruginosa*. They have not been genetically modified. They are classified as risk group 1 (RG1) pathogens for humans and animals by the Public Health Agency of Canada (PHAC). They were notified for their manufacture and use in Canada for the treatment of MDR *P. aeruginosa* infection in one designated patient. Other potential uses could include their manufacture and use in Canada to treat any *P. aeruginosa* infection in human patients wherein their clinical sample is sensitive to them. There is no evidence to suggest a potential risk of adverse effects for the environment and for the general population in Canada from the manufacture and use of Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans for the treatment of *P. aeruginosa* infections in humans. The risk assessment considered the low potential for hazard and the medium potential for exposure to the environment and the general population in Canada (due to the possibility of future commercial uses). Based on that assessment, Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans are not suspected to meet criteria in paragraphs 64(a), (b), or (c) of CEPA. It was recommended that a waiver of information requirements under subparagraphs 5(a)(i), 5(a)(ii), and 6(b) of the NSNR (Organisms) be accepted under CEPA 106(8)(a).

Background information

Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans are naturally occurring lytic bacteriophages infecting *Pseudomonas aeruginosa*, an opportunistic human and animal pathogen. They were notified for their manufacture in a single contained facility in Canada and subsequently used as a mixture to treat active and recurrent multidrug resistant (MDR) *P. aeruginosa* infection in humans. Upon administration, the bacteriophage mixture is expected to kill the targeted *P. aeruginosa* via its lytic activity, thereby controlling the infection in the treated patient.

Hazard

The environmental and human health hazard potential of Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans is determined to be low because:

1. The bacteriophages are naturally occurring lytic bacteriophages. The notifier verified the identity of the bacteriophages using whole genome sequence analysis.
2. The notifier did not determine the host range of the bacteriophages, however, indicated that they are able to infect multiple *P. aeruginosa* strains. It is not known if the bacteriophages can infect other *Pseudomonas* species or other bacteria.
3. The results of the in-house literature search indicated that the bacteriophages are not expected to replicate or cause infections in eukaryotic cells. Although the interactions between phages and eukaryotic cells could lead to inflammatory responses in phage-

treated patients, these responses are not expected to occur in the untreated general population. Therefore, the bacteriophages are not anticipated to cause infections on terrestrial or aquatic plants, invertebrates or vertebrates, including humans.

4. As lytic and non-transducing phages, they lack the ability to integrate their genetic material into the genome of host bacteria, or to package bacterial genes for use in the phages themselves or to transfer it to another bacterium. This non-transducing feature limits their involvement in phage-mediated horizontal gene transfer.
5. The bacteriophages are classified as a RG1 pathogens for animals and humans by the Public Health Agency of Canada. Based on the genome sequence analyses provided by the notifier, the bacteriophages do not carry any toxin, virulence, or antibiotic resistance genes, which further limits the potential of harmful gene transfers.
6. An *in vivo* study performed on rats with skin wounds showed that the dermal application of the bacteriophage cocktail did not induce treatment-related health effects.
7. No study reports are available for human clinical studies using the bacteriophages¹. Information on surrogate lytic *P. aeruginosa* phages provided by the notifier, and published information on other clinical uses of *P. aeruginosa* targeting phages, did not indicate serious side effects in treated patients.
8. Currently there is no antiviral treatment available against the bacteriophages. However, they are non-transducing phages lacking the capability to induce infection in both animals and humans, and adverse effects are not expected in the general population.

Exposure

The environmental and indirect human exposure potential of Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans is determined to be low for the notified use and medium for potential uses because:

1. The bacteriophages will be manufactured, dispensed, and formulated as a drug product under GMP-like conditions in a facility at Qeen Biotechnologies Inc.
2. The bacteriophages will be manufactured and transported in a refrigerated state in properly labelled, secured containers to the clinical site for the purposes of treating a single patient with an MDR *P. aeruginosa* periprosthetic joint infection.
3. The transportation and handling of the bacteriophages from the manufacture facility to the clinical site will be under the purview of relevant provincial regulations pertaining to the transportation and storage of RG1 microorganisms.
4. The phage cocktail will be administered to the designated patient by a health care provider under the controlled health care conditions at the clinical site.
5. The patient will receive a single dose of the bacteriophages.
6. The notifier indicated that materials used to dilute, transfer, or contain the bacteriophages at the clinical site will be autoclaved and disposed of. Since the bacteriophages are

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

intended only for use in a single patient over a limited course of treatment, the exposure of the bacteriophages to the environment and general population is expected to be minimal from the intended use.

7. Bacteriophages are susceptible to extreme temperatures and pH in the environment, as well as antibacterial agents affecting its bacterial host, as the bacteriophages cannot replicate without its host.
8. Other potential uses of the bacteriophages could include their use as a commercial drug product for treatment of any *P. aeruginosa* infections in humans where the clinical sample is sensitive to them. Their release into the environment or exposure of the general population could likely increase from potential large scale commercial use of the bacteriophages for treatment of *Pseudomonas* infections in humans.
9. However, as naturally occurring phages, they could already be abundant in the natural environments where its host bacteria can thrive regardless of the potential release of the bacteriophages from the intended or potential uses.

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

Risk Characterization

The risk assessment considered the low potential for hazard and the medium potential for exposure to the environment and the general population in Canada (due to the possibility of future commercial uses). Based on that assessment, the environmental and human health risks associated with the manufacture and use of Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans as part of a bacteriophage cocktail for the treatment of *P. aeruginosa* infections in humans in Canada are both assessed to be low.

Risk Assessment Conclusion

There is no evidence to suggest a risk of adverse effects for the environment or for the general population in Canada from manufacture and use of Unmodified *Pseudomonas* bacteriophages 1 and 2 for treating infections in humans as part of a bacteriophage cocktail for the treatment of *P. aeruginosa* infections in humans in Canada. The risk to the environment and human health associated with the bacteriophages is not suspected to meet criteria in paragraphs 64(a), (b), or (c) of CEPA. No further action is recommended.

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.