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

New Substances Notification 21116: *Prevotella histicola* strain ES894

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 that is a living organism. It was determined that *Prevotella histicola* ES894 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, *Prevotella histicola* ES894 (hereafter, *P. histicola* ES894), is a naturally occurring bacterium that is isolated from the human gastrointestinal tract. Upon administration to humans in a clinical setting, this bacterium is anticipated to modulate the immune cells of the host leading to anti-inflammatory effects that could potentially help to treat atopic dermatitis.

Notified and potential uses

P. histicola ES894 was notified as an investigational immunomodulatory drug product for the treatment of atopic dermatitis in adult patients. Other potential uses include its use as a commercial drug product for the treatment of atopic dermatitis or other diseases.

Hazard assessment

The environmental and human health hazard potential of *P. histicola* ES894 is assessed to be low because:

1. *P. histicola* ES894 was derived from *P. histicola* strain NRRL B-50329 which was isolated from a human gut biopsy. *P. histicola* is a naturally-occurring commensal bacterium of the human gut and oral cavity.
2. *P. histicola* ES894 is an anaerobic bacterium that requires special nutrients for growth and it cannot survive in an aerobic environment.
3. Results of the whole genome sequencing analysis of *P. histicola* ES894 provided by the notifier did not indicate the presence of genes encoding toxins, phage or plasmid sequences.
4. The species is reported as a commensal of horse oral microbiome, there is one report of *P. histicola* associated dental infection in a horse, which was resolved using surgical intervention and antibiotic

therapy. The information provided by the notifier and an updated search of the scientific literature yielded no results for potential negative impacts (pathogenicity or toxicity) of *P. histicola* strains ES894 or NRRL B-50329 on aquatic plant, invertebrate or vertebrate species, or on terrestrial plant, invertebrate or non-equine vertebrate species.

5. *P. histicola* ES894 is designated a risk group 1 human and animal pathogen by the Public Health Agency of Canada (PHAC, 2023).
6. Data from animal studies conducted by the notifier in mice did not indicate any mortality or adverse effects.
7. Clinical studies conducted in several other countries indicated that treatment with *P. histicola* ES894 in healthy adults can cause occasional but non-serious adverse effects that are similar to those caused by the placebo[1].
8. *P. histicola* ES894 is susceptible to several members of the β-lactam family of antibiotics, which could be used as effective treatments in the unlikely event of human infection with the strain.

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 exposure and indirect human health exposure potential of *P. histicola* ES894 is assessed to be low because:

1. Only planned target doses of *P. histicola* ES894 will be imported into Canada and transported to nine clinical sites in secured containers during the clinical trial.
2. *P. histicola* ES894 will be administered to up to 36 subjects under controlled conditions in healthcare centres by properly trained healthcare professionals.
3. General biosafety measures in healthcare settings and contingency plans for accidental spills are expected to be in place to minimize any spread of the organism.
4. *P. histicola* ES894 in the drug product has a low viability. *P. histicola* ES894 could shed from treated patients, however, it is not expected to survive or multiply in the aerobic environment, since it is an anaerobic bacterium and requires special nutrients (heme) for growth and survival.
5. *P. histicola* ES894 is an investigational immunomodulatory drug product for the treatment of dermatitis in adults. Other potential uses included its use as a commercial drug product. Since *P. histicola* ES894 is not expected to remain viable in the aerobic environment, its release to the environment and exposure to the general population is not expected to significantly increase from its potential use as a commercial drug product.

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[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.

6. The notifier does not intend to manufacture *P. histicola* ES894 in Canada. Should it be manufactured in Canada in the future, the exposure to the environment is not expected to significantly increase considering the low viability of the notified organism in an aerobic environment and its special nutrient growth requirements.

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 will be imported and used as an investigational immunomodulatory drug product or as a commercial drug product for the treatment of atopic dermatitis or other diseases in adults.

Owing to the low potential for environmental hazard and the low potential for environmental exposure, the environmental risk associated with the use of *P. histicola* ES894 as an investigational or commercial immunomodulatory drug product for use in the treatment of atopic dermatitis or other diseases in adults 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 *P. histicola* ES894 as an investigational or commercial immunomodulatory drug product for use in the treatment of atopic dermatitis or other diseases in adults 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 *P. histicola* ES894 as an investigational or commercial immunomodulatory drug product to treat atopic dermatitis or other diseases in adults. The risk to the environment associated with *P. histicola* ES894 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 *P. histicola* ES894 as an investigational or a commercial immunomodulatory drug product to treat atopic dermatitis or other diseases in adults. This risk to human health associated with *P. histicola* ES894 is not suspected to meet the criteria in paragraph 64(c) of CEPA. No further action is recommended.

References:

Canada (1999). *Canadian Environmental Protection Act*, 1999. S.C. 1999, c.33. Part 6: Animate Products of Biotechnology. https://www.canada.ca/en/environment-climate-change/services/canadian-environmental-protection-act-registry/publications/canadian-environmental-protection-act-1999/part-6.html (viewed 2023-04-14).

[PHAC] Public Health Agency of Canada. (2023). ePATHogen - Risk Group Database. Available at: https://health.canada.ca/en/epathogen