New substances: risk assessment summary, new substances notification 22095

Official title: New substances: risk assessment summary, New Substances Notification 22095 – Schedule 1 of the *New Substances Notification Regulations (Organisms)*

Notified organism: Recombinant and replicative human Herpes Simplex Virus encoding human derived genes for FMS like tyrosine kinase 3 ligand, single chain interleukin-12, cluster of differentiation 40 agonist, and antibody to human cytotoxic T-lymphocyte associated protein 4 (JNJ-87704916)

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

Organism type: Virus

Use: Import of JNJ-87704916 for use in human clinical trials to treat adult patients with advanced solid tumours

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

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 as the information is not needed in order to determine whether the living organism is toxic or capable of becoming toxic.

Synopsis:

JNJ-87704916 is a genetically modified human Herpes Simplex Virus type 1, notified for use in human clinical trials to treat adult patients with advanced solid tumours. Other potential uses could include its manufacture and use in a commercialized gene therapy drug product. There is no evidence to suggest a potential risk of adverse effects to the environment and for the general population in Canada from the notified or potential uses. Owing to the low potential for hazard and the low potential for exposure to the environment and the general Canadian population, JNJ-87704916 is 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

The notified substance, JNJ-87704916, is a genetically modified oncolytic herpes simplex virus type 1 (HSV-1). As a result of the genetic modifications JNJ-87704916 has selective replication in human tumor cells along with an increased oncolytic capacity to preferentially kill cancerous tumour cells.

Hazard

The environmental and human hazard potential of JNJ-87704916 is determined to be low because:

1. Similar to wild-type (WT) HSV-1, the only reservoir for JNJ-87704916 is humans. Additionally, JNJ-87704916 cannot remain viable outside the host for prolonged periods as it requires specific physiological conditions of the human body to survive.
2. JNJ-87704916 is a genetically modified, attenuated strain of HSV-1 which will preferentially infect and kill cancerous tumor cells. The genetic modifications are well-defined and stably integrated. The introduced genetic modifications are not known to confer any pathogenic or toxic properties.
3. The literature reports a limited number of HSV-1 infections in certain terrestrial animals such as primates, pet rabbits, chinchilla and hedgehog. However, there are no reports of JNJ-87704916 or WT HSV-1 infections in aquatic plants, invertebrates or vertebrates, nor in terrestrial plants or invertebrates.
4. Recombination between JNJ-87704916 and WT HSV-1 or WT HSV-2 is theoretically possible. However, it is unlikely considering that a WT virus replicates in normal tissues while the notified JNJ-87704916 is directly injected into tumour cells and cannot spread effectively into normal tissue, Furthermore, due to the large genome size of such resultant recombinant virus as compared to WT HSV-1 or WT HSV-2, the recombinant virus would likely be eliminated.
5. The notifier provided data from published preclinical studies using JNJ-87704916 on terrestrial vertebrates. Those studies indicate that treatment was well-tolerated and no adverse neurological or pathological effects were reported.
6. There is limited human clinical study data available with JNJ-87704916. However, data from clinical studies with a commercialized product containing a surrogate organism (i.e., an

attenuated HSV-1 modified to preferentially replicate in human tumour cells) has shown an acceptable safety profile in humans. Therefore, JNJ-87704916 is expected to have a comparable safety profile.

7. In the unlikely case of pathogenicity caused by JNJ-87704916, available antiviral agents against WT HSV-1, such as acyclovir or valacyclovir, could be used.

Hazards related to micro-organisms used in the workplace should be classified accordingly under the Workplace Hazardous Materials Information System (WHMIS)[1].

Exposure

The environmental and human exposure potential of JNJ-87704916 is determined to be low because:

1. JNJ-87704916 will be imported into Canada in secure containers during the course of the clinical trial to treat a maximum of eighty adult patients with advanced solid tumors.
2. JNJ-87704916 will be administered intratumorally to patients under controlled conditions in healthcare centers by properly trained health care professionals.
3. General biosafety measures in healthcare settings, contingency plans for accidental spills and procedures for treatment of contaminated wastes were adequately described by the notifier. The general population will therefore not be exposed to JNJ-87704916.
4. Infection and replication in the host and subsequent human to human transmission is unlikely given that JNJ-87704916 is unable to replicate in non-tumor cells. Furthermore, if JNJ-87704916 is released into the environment it is not expected to survive outside of the human body. Taken together, exposure of the general population and the environment to JNJ-87704916 is unlikely.
5. JNJ-87704916 is intended for use in human clinical trials to treat adult patients with advanced solid tumors. No other potential use has been identified beyond commercialization as a human drug for similar therapeutic uses. Given that JNJ-87704916 cannot survive outside of the human body, exposure of the environment and general population is not expected as a result of any potential uses.
6. The notifier does not intend to manufacture JNJ-87704916 in Canada. Should it be manufactured in Canada, environmental and human exposure would not be expected to significantly increase, as JNJ-87704916 is not expected to survive in the environment, outside the bodies of treated patients.

Risk Characterization

[1] 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.

Given the low potential hazard and the low potential for exposure, the environmental and human health risks associated with the use of JNJ-87704916 as an immunotherapy product in human clinical trials or as a potential commercial immunotherapy product for use in adult patients with advanced solid tumors is considered to be low.

Risk Assessment Conclusion

Available evidence does not indicate a potential risk of adverse environmental or human health effects from the use of JNJ-87704916 as an immunotherapy product in human clinical trials or as a potential commercial immunotherapy product for use in adult patients with advanced solid tumors. The risk to the environment and human health associated with JNJ-87704916 is not suspected to meet criteria in paragraphs 64(a) or (b) or (c) of CEPA.