Risk Assessment Summary
for
EAU 829, NSNs 18525 and 18526:
Listeria monocytogenes strains
CRS-207, JNJ-64041809 and JNJ-64041757

(Investigational use as immunotherapy in humans with advanced cancer)

Introduction

Under the Canadian Environmental Protection Act, 1999 (CEPA), animate products of biotechnology (i.e. “living organisms”) not listed on the Domestic Substances List (DSL) are considered “new” to Canada. Information and data prescribed by the New Substances Notification Regulations (Organisms) [NSNR(O)] must be submitted before they are manufactured or imported, and Environment and Climate Change Canada (ECCC) and Health Canada (HC) must assess their potential to harm human health and the environment.

Listeria monocytogenes strains CRS-207, JNJ-64041757 and JNJ-64041809, bacteria that were proposed to be imported for use in human clinical trials of an investigational immunotherapy, were assessed according to the requirements of Schedule 1 of the NSNR(O), which applies to manufacture or import of new micro-organisms for introduction anywhere in Canada (which is the appropriate Schedule for human clinical trials). Living organisms notified under this schedule may be eligible for addition to the DSL.

Regulatory Decision

Based on the assessment described below, L. monocytogenes CRS-207, L. monocytogenes JNJ-64041757 and L. monocytogenes JNJ-64041809 are not considered to be harmful to human health or the environment for their intended use as investigational immunotherapy treatment in humans with advanced cancer. As L. monocytogenes CRS-207, L. monocytogenes JNJ-64041757 and L. monocytogenes JNJ-64041809 are not anticipated to enter the environment in a quantity or under
conditions that pose a danger to the environment or human health, no further action is recommended as a result of this assessment.

After January 2, 2015, the manufacture or import of *L. monocytogenes* CRS-207 could proceed in Canada. After April 22, 2016, the manufacture or import of *L. monocytogenes* strains JNJ-64041757 and JNJ-64041809 could also proceed in Canada. These three strains are eligible to be added to the DSL.

**Background**

*L. monocytogenes* CRS-207, *L. monocytogenes* JNJ-64041757 and *L. monocytogenes* JNJ-64041809 are genetically modified bacteria that are derived from the same parental organism. They are intended for use as immunotherapy in humans with advanced cancer. While one set of the modifications (gene deletions) renders these bacteria incapable of causing disease, the other set of modifications (gene additions) enables them to produce cancer-specific antigens. By producing large amounts of antigens in the human body, *L. monocytogenes* CRS-207, *L. monocytogenes* JNJ-64041757 and *L. monocytogenes* JNJ-64041809 are designed to stimulate an improved immune response against cancer cells that also produce those antigens. As a result, the patient’s own immune system is thought to more effectively attack the cancer cells, helping to treat advanced cancers.

**Hazard Considerations**

**With respect to the environment**

The environmental hazard potential of strains CRS-207, JNJ-64041757 and JNJ-64041809 is considered to be low for the following reasons:

- There is no evidence to suggest that naturally occurring *L. monocytogenes* can infect aquatic or terrestrial invertebrates, or aquatic vertebrates.

- Naturally occurring *L. monocytogenes* is known to cause different diseases (listeriosis) exhibiting as encephalitis, abortion and septicemia in ruminants (Freitag et al., 2009) and other terrestrial vertebrates. However, CRS-207, JNJ-64041757 and JNJ-64041809 are modified in a manner that renders them incapable of causing the diseases of naturally occurring *L. monocytogenes*. The effectiveness of these modifications in reducing virulence was shown in an animal study using mice (Brockstedt et al., 2004).
Although it is found on dead or decaying terrestrial plants, there is no evidence to suggest that *L. monocytogenes* causes disease in terrestrial or aquatic plants.

**With respect to human health**

The human hazard potential of strains CRS-207, JNJ-64041757 and JNJ-64041809 is considered to be low for the general population and low to medium for pregnant women, neonates, the elderly and immune-compromised individuals, for the following reasons:

- Despite its widespread presence in the environment, naturally occurring *L. monocytogenes* rarely infects healthy individuals in the general population, with infection rates ranging from 0.1 to 11.3 per million people. Infection with *L. monocytogenes* occurs and has a high mortality rate (20-60%) in immunocompromised individuals, neonates, and the elderly and in pregnant women (Liang et al., 2014). However, CRS-207, JNJ-64041757 and JNJ-64041809 are modified in a manner that renders them incapable of causing the diseases of naturally occurring *L. monocytogenes*. The effectiveness of these modifications in reducing virulence was shown in an animal study using mice (Brockstedt et al., 2004).

- Strain CRS-207 was determined to have an acceptable safety profile after being administered to monkeys (notifiers’ internal studies). Strains JNJ-64041757 and JNJ-64041809 would be expected to have similar safety profiles.

- In human studies, strain CRS-207 has been administered to more than 400 subjects with advanced cancer. As of February 2017, there have been fourteen reports of unexpected serious adverse events that could be related to treatment with the micro-organism at doses as high as $1 \times 10^{10}$ colony forming units of the strain per treatment. However, all reported adverse events were resolved. Overall, CRS-207 was well tolerated and did not cause any deaths or long-term effects. Strains JNJ-64041757 and JNJ-64041809 would be expected to have similar safety profiles.

- Certain subpopulations that are especially susceptible to wild type *L. monocytogenes* (pregnant women and children) were excluded from clinical trials to date, as the safety of strains CRS-207, JNJ-64041757 and JNJ-64041809 in these groups has not been assessed.

The following considerations were also taken into account in the assessment of human health and environmental hazard:
• The modifications enabling the strains CRS-207, JNJ-64041757 and JNJ-64041809 to produce cancer specific antigens do not reverse the attenuation that renders these bacteria incapable of causing disease, as shown in animal studies using mice (Brockstedt et al., 2004) and monkeys (notifiers’ internal studies).

• Strains CRS-207, JNJ-64041757 and JNJ-64041809 are susceptible to antibiotics of clinical and veterinary importance. Therefore, in the unlikely event of infection with strains CRS-207, JNJ-64041757 and JNJ-64041809, effective antibiotic treatments are available.

Exposure Considerations

With respect to the environment and humans

The environmental and human exposure potential of *L. monocytogenes* CRS-207, *L. monocytogenes* JNJ-64041757 and *L. monocytogenes* JNJ-64041809 are considered to be low for the following reasons:

• Strain CRS-207, JNJ-64041757 and JNJ-64041809 are securely transported in small quantities and administered by trained personnel to up to 20 patients under controlled conditions in each of two Canadian cancer clinics.

• Strains CRS-207, JNJ-64041757 and JNJ-64041809 have no observed shedding from treated subjects and are usually cleared from the blood within 24 hours of administration. To ensure that the tested subjects are free of the micro-organism, patients receive antibiotics for a period of seven days following the end of each treatment period.

• Clinical study procedures and emergency plans to deal with accidental spills are expected to effectively contain the micro-organisms.

• In the unlikely event that CRS-207, JNJ-64041757 and JNJ-64041809 are released into the general environment, their genetic modifications are not expected to provide any survival advantages over naturally occurring microbial populations.

• Future possible uses are limited to the treatment (under similar supervised conditions) of a small group of patients with particular types of cancer. Therefore, future uses are not expected to significantly increase environmental exposure to CRS-207, JNJ-64041757 and JNJ-64041809.
- Strain CRS-207, JNJ-64041757 and JNJ-64041809 have not been tested in pregnant women, breast feeding women or individuals with a weakened immune system. Patients who participate in human studies are advised to avoid close contact with pregnant women, newborn infants and individuals with weakened immunity.

**Risk assessment conclusion**

Risk is typically described as the probability of an adverse effect occurring based on hazards and a particular scenario of exposure (Environment Canada and Health Canada, 2011). Different exposure scenarios can be described based on intended and any potential uses. In the present case, *L. monocytogenes* CRS-207, *L. monocytogenes* JNJ-64041757 and *L. monocytogenes* JNJ-64041809 will be used as investigational immunotherapy agents or as approved and commercialized drugs.

**With respect to environment (as an investigational immunotherapy)**
Given the low potential environmental hazard and the low potential environmental exposure, the environmental risk associated with the use of *L. monocytogenes* CRS-207, *L. monocytogenes* JNJ-64041757 and *L. monocytogenes* JNJ-64041809 as investigational immunotherapy agents is assessed to be low.

**With respect to human health (as an investigational immunotherapy)**
Given the low potential human health hazard to the general population, the low potential human exposure, and specific measures in place to prevent exposure to vulnerable subpopulations, the human health risks associated with the use of *L. monocytogenes* CRS-207, *L. monocytogenes* JNJ-64041757 and *L. monocytogenes* JNJ-64041809 as investigational immunotherapy agents is assessed to be low.

**With respect to environment and human health (as a commercialized immunotherapy)**
Should the notified strains be approved and commercialized for use in Canada in the treatment of cancer, the environmental and indirect human exposure is not expected to change significantly, and so would not significantly increase environmental or human health risks.
References
(excluding proprietary information or references provided by the notifier)


