Summary of Risk Assessment Conducted Pursuant to subsection 83(1) of the *Canadian Environmental Protection Act, 1999*

New Substances Notification 21127: α-D-Glucopyranoside, 4-hydroxyphenyl (Chemical Abstracts Service Registry Number 84380-01-8)

Regulatory decisions

Under the provisions for Substances and Activities New to Canada in Part 5 of the *Canadian Environmental Protection Act, 1999* (CEPA), and pursuant to section 83 of the Act, the Minister of the Environment and the Minister of Health have assessed information in respect of the substance and determined that the substance is anticipated to enter the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

In order to ensure that the substance does not cause harm to the Canadian environment or human health, its manufacture and import are authorized subject to conditions as described in Ministerial Condition No. 21127 published in the *Canada Gazette* Part I, Vol. 156, No. 28 on July 9, 2022.

Substance identity

The notified chemical is α-D-glucopyranoside, 4-hydroxyphenyl (Chemical Abstracts Service Registry Number[1] 84380-01-8).

Notified uses

The substance is proposed to be imported into Canada in quantities greater than 1000 kg/yr for the notified use in cosmetic skin care products.

Environmental fate and behaviour

Based on its physical and chemical properties, if the substance is released to the environment, it will tend to partition to water. The substance is not expected to be persistent in this compartment based on high biodegradability (60-85% over 28 days). The substance is not expected to bioaccumulate based on a very high water solubility (> 10 000 mg/L), very low octanol-water partition coefficient (log K_{ow} < 0) and low predicted bioconcentration factor (< 250 L/kg).

1 The Chemical Abstracts Service Registry Number is the property of the American Chemical Society and any use or redistribution, except as required in supporting regulatory requirements and/or for reports to the Government of Canada when the information and the reports are required by law or administrative policy, is not permitted without the prior, written permission of the American Chemical Society.

Environmental risk assessment

Based on the available hazard information, the substance has low acute toxicity to aquatic invertebrates (median effective concentration > 100 mg/L; no-observed-effect-concentration (NOEC) > 10 mg/L). Using the NOEC from the most sensitive organism (aquatic invertebrates) and by applying an assessment factor of 10 to account for acute to chronic extrapolation, species sensitivity variation and mode of action, the predicted no-effect concentration (PNEC) was calculated to be in the range of 1-10 mg/L, which was used to estimate the risk to the environment.

The notified activities in Canada were assessed to estimate the environmental exposure potential of the substance throughout its life cycle. Environmental exposure from the notified activities is expected to be mainly from processing (i.e. formulation and blending) and use in cosmetic products by release of the substance to water resulting in a predicted environmental concentration (PEC) of 0.01-0.1 µg/L.

Comparing the PEC with the PNEC, the ratio is less than 1. This, along with other lines of evidence including environmental fate, hazard, and exposure, indicates that the substance is unlikely to cause harm to the environment in Canada.

Human health risk assessment

Based on the available hazard information, the substance has a moderate acute toxicity by the oral route (median lethal dose 300-2000 mg/kg body weight). The substance is expected to have a moderate developmental toxicity following repeated subcutaneous doses in mammalian test animals (no-observed-adverse-effect level (NOAEL) 60-600 mg/kg-bw/day). It is a mild skin sensitizer (9-28% response in guinea pig maximization test) and is not phototoxic or photoallergenic. It is not mutagenic *in vitro* or clastogenic *in vivo*. Therefore, the substance is unlikely to cause genetic damage. The point of departure (POD) for the notified substance is in the range of 10-100 mg/kg-bw/day based on reduced foetal body and ovary weights observed in the test animals of the subcutaneous developmental toxicity study.

The notified substance is expected to degrade to hydroquinone (1,4-benzenediol, Chemical Abstracts Service Registry Number 123-31-9) in and on skin during use in cosmetics. Hydroquinone is a strong skin sensitizer (65-80% response in guinea pig maximization test). It has moderate developmental toxicity following repeated oral doses in mammalian test animals (NOAEL 30-300 mg/kg-bw/day based on external, visceral and skeletal malformations), although this may be secondary to maternal toxicity. Hydroquinone has high subchronic toxicity by the oral route (90-day lowest-observed-adverse-effect level 10-100 mg/kg-bw/day) and is carcinogenic in mammalian test animals. *In vitro* and *in vivo* genotoxicity data are inconclusive. The POD for hydroquinone is in the range of 10-100 mg/kg-bw/day based on liver weight increases and central nervous system effects observed in test animals of the 90-day study.

When the notified substance is used in cosmetic skin care products for the body at a concentration at or below 0.5% and for the face at a concentration at or below 2%, direct exposure of the general population is expected to be mainly by contact with the skin at levels in the range of 1-10 µg/kg-bw/day for both the notified substance and hydroquinone. Indirect exposure of the general population from environmental media such as drinking water is conservatively estimated to be at levels in the range of 0.001-0.01 µg/kg-bw/day for children and adults.

The target margin of exposure (MOE_T) was calculated to be 1000 for the notified substance and 3000 for hydroquinone based on the available information. The MOE_T is the level of exposure at or above which there is no expected risk in the exposed population. The derived margin of exposure (MOE_D) is the ratio of the POD value to the available exposure doses and is compared to the MOE_T. The MOE_D was calculated to be greater than 10 000 for the notified substance based on the POD, the NOAEL of the subcutaneous developmental toxicity study in mammalian test animals. The MOE_D was calculated to be in the range of 3000-4000 for hydroquinone based on the POD, the NOAEL of the oral subchronic toxicity study in mammalian test animals. The MOE_D resulting from the maximum approved use levels of the notified substance (0.5% in cosmetics applied to the body and 2% in cosmetics applied to the face) remains at or above the MOE_T, and is not anticipated to be harmful to human health. However, at higher concentrations in cosmetic skin care products, the substance is anticipated to be harmful to human health.

The assumptions made in the assessment and the risk management measures applied are considered to be adequately protective for the general population as well as for subpopulations who may be more susceptible or highly exposed.

Other considerations

This substance is controlled in Australia. The notified substance has been included in Schedule 6 (Poison) under the Standard for the Uniform Scheduling of Medicines and Poisons in a final decision by Australia's Therapeutic Goods Administration, except in preparations containing the notified substance at ≤ 2% intended for application to the face and at ≤ 0.5% intended for application to the body.

The degradation product of the notified substance (hydroquinone) has been concluded to be "toxic" to human health, but is not toxic to the environment as defined under CEPA and is subject to a Significant New Activity Order. Hydroquinone is prohibited from use in cosmetic products with intended dermal application, but is permitted at maximum levels of 0.3% in hair dyes, 0.02% (post-mix) in two-component acrylic artificial nail systems and 0.1% in cyanoacrylate adhesive products.

Assessment conclusion

The substance is suspected to constitute a danger to human health according to the criteria under paragraph 64 (*c*), but is not suspected to have a harmful effect on the environment according to the criteria under paragraph 64 (*a*) or (*b*) of the Act.

Due to the identified risk to human health related to carcinogenicity, subchronic toxicity and developmental toxicity as a result of hydroquinone release during use of the notified substance, a ministerial condition was issued to restrict the manner in which the notifier may manufacture or import the substance with conditions on its use (i.e., limiting concentration to a maximum of 0.5% in cosmetics applied to the body and 2% in cosmetics applied to the face) in order to mitigate these potential risks. Ministerial Condition No. 21127 was published in the *Canada Gazette* Part I, Vol. 156, No. 28 on July 9, 2022.

A conclusion under CEPA, on this substance, is not relevant to, nor does it preclude an assessment against the hazard criteria for Workplace Hazardous Materials Information System that are specified in the *Controlled Products Regulations* or the *Hazardous Products Regulations* for products intended for the workplace.