Registration Decision RD2026-03

Isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST

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Under the authority of the *Pest Control Products Act*, pesticides must be assessed before they are sold or used in Canada in order to determine that they do not pose unacceptable risks to humans or the environment and have value when used according to the label instructions. The pre-market assessment considers available data and information[1] from pesticide registrants, published scientific reports, other governments, and international regulatory agencies, as well as written comments directly related to the proposed decision, such as comments directed to the science evaluation, if received during public consultations. Health Canada applies internationally accepted current risk assessment methods as well as risk management approaches and policies. More details, on the legislative requirements, risk assessment and risk management approach, are provided under the section of Evaluation Approach of this document.

Registration decision statement[2] for Isocycloseram

Health Canada's Pest Management Regulatory Agency (PMRA), pursuant to subsection 8(1) of the *Pest Control Products Act*, is granting registration for the sale and use of Isocycloseram Technical, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST, containing the active ingredient isocycloseram. VANECTO COCKROACH GEL BAIT is for the control of cockroaches in commercial, industrial and residential buildings and other listed structures. EQUENTO is a seed treatment product for the control of insect pests on wheat, oat, barley, rye and triticale. A23128 ST, also containing active ingredients difenoconazole, sedaxane, metalaxyl-M (and S-isomer) and fludioxonil, is another seed treatment product for the control of insect pests and the control or suppression of seed-borne and soil-borne diseases on wheat, oat, barley, rye and triticale.

The Proposed Registration Decision PRD2025-11, *Isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST,* containing the detailed evaluation of the information submitted in support of this registration, underwent a 30-day consultation period ending on November 8, 2025. The evaluation found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable. Health Canada received written comments relating to the health, environmental and value assessments during the public consultation period conducted in accordance with section 28 of the *Pest Control Products Act*.

Comments and responses

Health Canada received comments from a non-governmental organization (noted as "commenter") on the health, environmental and value assessments of isocycloseram and its associated end-use products. The responses are provided below.

1. Comment related to waiving the requirement for a developmental neurotoxicity study

The commenter stated that Health Canada allowed a waiver for developmental neurotoxicity testing despite a finding of a serious developmental effect.

[1] Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*.
[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act.*

Health Canada response:

According to Health Canada's Guidance for Developing Datasets for Conventional Pest Control Product Applications[3], a developmental neurotoxicity study (DACO 4.5.14) is required if neurological effects are observed in other studies and should be considered if a test substance: i) causes neuropathology or neurotoxicity in adults, ii) is hormonally active in vivo, or iii) causes other types of nervous system involvement at a developmental stage. As stated in the PRD2025-11, there was no evidence of selective neurotoxicity and no neurohistopathological findings observed in the acute oral neurotoxicity study or the subchronic oral neurotoxicity study with isocycloseram, all of which were conducted in adult rats. The effects noted in the acute and 90-day neurotoxicity studies were found to be either within the pre-test range results, not statistically significant, showed no dose-response or were at one time point only and were considered incidental in nature. The decreased motor activity that was noted at the high dose in the acute neurotoxicity study was present at a dose level where body weight loss was evident. Therefore, the decreased motor activity was considered to be secondary to the systemic effect of body weight loss and not indicative of selective neurotoxicity. There were no signs of neurotoxicity noted in either sex at any dose level in the 90-day neurotoxicity study. While thyroid weight was increased in the 28-day oral toxicity study in the mouse, there was no noted observation with respect to thyroid hormones and no reported incidences of perturbation of hormone homeostasis. Although there was evidence of sensitivity of the young and the presence of malformations in the rat developmental toxicity study, these findings were related to skeletal effects and did not involve the nervous system. Overall, it was concluded that there was no concern for neurotoxic effects in the database and that a developmental neurotoxicity study would not be required.

2. Comment related to waiving the requirement for an immunotoxicity study

The commenter stated that Health Canada waived an immunotoxicity study, without legitimate grounds, contending that the toxicological data on isocycloseram suggested a possible toxicity to the immune system.

Health Canada response:

An immunotoxicity study is not a standard data requirement for the registration of pesticides in Canada. According to Health Canada's Guidance for Developing Datasets for Conventional Pest Control Product Applications, "The potential of the pest control product to affect the immune system may be discerned from hematology, blood chemistry, organ weights and histopathology, routinely investigated in short-term repeated exposure studies." In addition, an analysis of parameters related to immune function using the United States Environmental Protection Agency's (US EPA's) weight of evidence approach guidance was also conducted in order to assess the requirement for an immunotoxicity study[4].

[3] Health Canada (2021). PMRA - Guidance for Developing Datasets for Conventional Pest Control Product Applications: Data Codes for Parts 1, 2, 3, 4, 5, 6, 7 and 10. February 12, 2021.

[4] US EPA (2013). Part 158 Toxicology Data Requirements: Guidance for Neurotoxicity Battery, Subchronic Inhalation, Subchronic Dermal and Immunotoxicity Studies. United States Environmental Protection Agency, May 1, 2013.

It is noted that there were some effects observed in the database that involve the immune system, including increases in white blood cell counts, changes in total protein and globulins, increased lymphoid cellularity in the spleen and thymus, increased spleen and thymus weights, and plasmacytosis in the lymph nodes, spleen and thymus. However, these findings are not representative of immunosuppression but rather immunostimulation. Additionally, any effects observed in relation to potential immune system dysregulation were noted at dose levels that were already at or above those used for establishing toxicology reference values for use in the human health risk assessment, and consequently immunotoxicity effects were not more sensitive than the systemic toxicity endpoints used for regulation. It was concluded that requesting an immunotoxicity study would not provide critical information for the assessment of risks to human health, and therefore there was sufficient information to determine that an immunotoxicity study would not be necessary.

3. Comment related to the cancer risk assessment for isocycloseram being based on equivocal evidence

The commenter stated that since the cancer risk assessment for isocycloseram was based on equivocal evidence, there is no reasonable certainty that is does not cause cancer and that the significance of the finding cannot be diminished based on irrelevant factors considered in a weight of evidence approach.

Health Canada response:

The designation of "equivocal" is used by Health Canada if the findings are ambiguous, not clearly attributable to treatment or where the overall weight of evidence supports a non-treatment-related etiology, despite some remaining uncertainty. In its evaluation of the available studies with isocycloseram, Health Canada concluded that the ovarian luteomas observed in female mice and the Leydig cell (LC) adenomas observed in male rats were equivocally related to treatment.

Health Canada performed an extensive review of the available data on ovarian luteomas, a benign tumour type. Several factors were taken into consideration when reviewing the tumours. The incidence of ovarian luteomas at the low- and mid-doses was the same as or below the concurrent control incidence; however, incidences were above concurrent controls at the high dose. Additionally, the slightly elevated incidences of these tumours in high-dose females were not statistically significantly different from the control incidence by pair-wise or trend test analysis. Secondly, there was no evidence of pre-neoplastic lesions or other effects in the ovary of the mouse. Overall, the weight of evidence suggested that the tumours were equivocally related to treatment and that the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of isocycloseram.

With respect to LC adenomas in male rats, this tumour type is of low concern to humans. It is commonly recognized that human LCs are quantitatively less sensitive than those in rats in their proliferative response to luteinizing hormone (LH), mostly due to physiological and endocrine differences between rats and humans, including the presence of an increased number of LH receptors in rat LCs versus the number in human LCs, and the absence or low expression of

certain receptors on rat LCs versus those in humans.[5] The incidence of LC adenomas at the low- and mid-doses was the same as the concurrent control incidence; however, incidences were above concurrent controls at the high dose. Additionally, the slightly elevated incidences of these tumours in high-dose males were not statistically significantly different from the control incidence by pair-wise or trend test analysis. Overall, the weight of evidence suggested that the tumours equivocally related to treatment and that the toxicology reference values selected for the non-cancer risk assessment are protective of any residual concerns regarding the carcinogenic potential of isocycloseram.

4. Comment related to potential genotoxic effects of metabolite SYN548569

The commenter stated that no detailed explanation or scientific justification was provided for discounting the positive in vitro genotoxicity result for metabolite SYN548569.

Health Canada response:

As stated in PRD2025-11, although metabolite SYN548569 showed positive results in one in vitro micronucleus assay, the concern for potential mutagenicity is low because there was no evidence of mutagenicity in the bacterial reverse mutation assay and there was no evidence of genotoxicity in the in vivo micronucleus assay using SYN548569 as the test material. In a weight of evidence assessment of the three available studies using SYN548569 as the test material, the negative results of the in vivo micronucleus study were considered more relevant than the results of the in vitro micronucleus study. Both assays are assessing chromosomal damage and the in vivo study takes into account absorption, distribution and excretion, which are not factors in in vitro tests, and in vivo metabolism is likely to be more relevant than the systems normally used in vitro[6]. Therefore, metabolite SYN548569 was considered overall to be negative for genotoxicity.

5. Comment related to the serious effects in the young observed in the developmental toxicity study in rats and the retention of the 100-fold PCPA factor

The commenter stated that the serious effects in the young observed in the rat developmental toxicity study point to a high level of concern in accordance with SPN2008-01, therefore justifying retention of the "100-fold PCPA Factor."

Health Canada response:

It should be noted that contrary to what is stated in the comment, the default magnitude of the PCPA factor, as outlined in the *Pest Control Products Act*, is 10-fold and not 100-fold. As outlined in section 3.1.2 of PRD2025-11, *Pest Control Products Act* Hazard Characterization, the database for isocycloseram was complete as it pertains to the toxicity to infants and children. It was identified that in the rat developmental toxicity study, an increased incidence of skeletal variations and malformations was observed in the absence of maternal toxicity. The overall

[5] Cook, J. C., Klinefelter, G. R., Hardisty, J. F., Sharpe, R. M., & Foster, P. M. D. (1999). Rodent Leydig Cell Tumorigenesis: A Review of the Physiology, Pathology, Mechanisms, and Relevance to Humans. *Critical Reviews in Toxicology*, *29*(2), 169–261. https://doi.org/10.1080/10408449991349203

[6] European Medicines Agency (2012). ICH Guideline S2 (R1) on genotoxicity testing and data interpretation for pharmaceuticals intended for human use. EMA/CHMP/ICH/126642/2008. June 2012.

conclusion was that there was a high level of concern for prenatal toxicity and sensitivity of the young based on the presence of the serious endpoint of malformations in the absence of maternal toxicity. Therefore, in accordance with SPN2008-01, the full 10-fold PCPA factor was retained for scenarios in which the endpoint of malformations in rats was used to establish the point of departure for assessing risk to women of reproductive age.

6. Comment related to the serious endpoints in the 2-generation reproductive toxicity study

The commenter stated that qualitative sensitivity of the young appeared to be evident in the dietary 2-generation reproductive toxicity study in rats as the types of effects on the young differed from those noted in parental animals. Additionally, the commenter indicated that the conclusion that the concern for the serious endpoints in young can be tempered by the presence of parental toxicity is not adequately justified.

Health Canada response:

As outlined in SPN2008-01[7], Health Canada must apply a default 10-fold factor (the PCPA factor) for the protection of infants and children, unless Health Canada concludes, based on reliable data, that a different factor is appropriate. Determination of the magnitude of the factor involves evaluating the completeness of the data with respect to exposure of and toxicity to infants and children as well as potential for prenatal or postnatal toxicity. Incomplete toxicology databases are not equally incomplete and all prenatal and postnatal toxicities are not of equal concern. For these reasons, Health Canada makes specific case-by-case determinations as to the magnitude of the PCPA factor if reliable data permit. An integrative approach is taken to optimize the use of all available information. A PCPA factor less than or equal to 10-fold or, in very rare circumstances, greater than 10-fold may be employed in an assessment.

With respect to the completeness of the toxicity database, as discussed in PRD2025-11, the database for isocycloseram contains the full complement of required studies in order to characterize the potential for toxicity to infants and children, including gavage developmental toxicity studies in rats and rabbits, an enhanced 1-generation gavage reproductive toxicity study in rats, and a dietary 2-generation reproductive toxicity study in rats. Dose range-finding studies were also available to support dose level selection in the main developmental toxicity studies.

In the dietary 2-generation reproductive toxicity study in rats, a decreased viability index was observed in both sexes of the F1 generation offspring at the same dose level that resulted in vacuolation of the liver and small intestine, and increased weight of the adrenals and liver in parental animals. Additionally, at the same dose level, decreased live birth index and fertility index were noted, along with altered reproductive parameters (increased abnormal sperm, decreased sperm count, decreased number of ovarian follicles) and histopathological changes to reproductive organs (testicular tubular degeneration/atrophy). The effects in the young are different than those observed in the parental animals and are considered to be serious in nature, thus representing by definition a qualitative sensitivity as outlined in SPN2008-01. However, the effects in the young are well characterized and concern was tempered by the lack of quantitative sensitivity of young as these effects were observed at the same dose level where parental toxicity

[7] SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

was evident. As such, it was determined that the PCPA factor would be reduced to 3-fold when using the 2-generation rat reproductive toxicity study to establish the point of departure for assessing risk to children.

7. Comment related to the toxicity assessment of all metabolites

The commenter stated that a toxicity assessment for all metabolites was not conducted.

Health Canada response:

Generally, Health Canada assumes that transformation products are of equal toxicity to the parent compound in the absence of sufficient toxicological information. Limited toxicological information is available for only a subset of characterized metabolites of isocycloseram. As a result, potential exposure to several transformation products was taken into consideration in the human health risk assessment by including them in the residue definition for drinking water (see section 3.5.2 of PRD2025-11) and assuming their toxicity to be equal to that of isocycloseram.

8. Comment related to the lack of clarity surrounding the establishment of the target margin of exposure (MOE) of 1000 for occupational scenarios

The commenter stated that Health Canada did not provide a clear justification for the value of 1000 that was determined as the target margin of exposure (MOE) for occupational scenarios.

Health Canada response:

As outlined in section 3.2.2 of PRD2025-11, Occupational and Residential Toxicology Reference Values, the target margin of exposure (MOE) for short-, intermediate-, and long-term dermal inhalation occupational exposures was determined to be 1000, which includes the standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a 10-fold factor to afford additional protection for the serious endpoints observed in the young, as outlined in the *Pest Control Products Act* Hazard Characterization Section (Section 3.1.2).

In SPN2008-01[8], it is explained that the PCPA specifies the use of the PCPA factor for the protection of infants and children in the dietary risk assessment as well as in the risk assessment for products used residentially (that is, used in or around homes or schools). The PCPA factor is also applied to protect fetuses and nursing infants that may be exposed indirectly as a result of placental or lactational transfer from women who receive dietary or residential exposure. The PCPA does not specifically require the application of the PCPA factor in occupational risk assessment. Regardless, those exposed occupationally could include pregnant or lactating women; therefore, there is the potential for indirect exposure of their offspring to a pesticide. In keeping with the spirit of the legislation, it is necessary to protect these indirectly exposed young to a similar degree as their counterparts that are afforded protection through the application of the PCPA factor. Consequently, where warranted, an additional uncertainty factor will be applied

[8] Health Canada (2008). Science Policy Note SPN2008-01. The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides.

to worker exposure scenarios if available data identify concerns for potential effects on the young or if appropriate data are not available to adequately address the concerns.

The toxicology reference values selected for use in the occupational risk assessment was based on the increased incidences of fetal and litter variations and malformations observed in the absence of maternal toxicity in the rat developmental toxicity study. Since worker populations could include pregnant women, these endpoints were considered appropriate for the occupational risk assessment. As noted above, where warranted, an additional uncertainty factor will be applied to worker exposure scenarios if available data identify concerns for potential effects on the young. As such, the target MOE of 1000 includes a 10-fold factor to afford additional protection against the serious effects observed in the young, and the standard 100-fold factor to account for interspecies extrapolation and intraspecies variability.

9. Comment that isocycloseram belongs to the PFAS (per- and polyfluoroalkyl substance) class of chemicals and is a "forever" chemical

The commenter stated that isocycloseram is classified as a PFAS chemical and summarized information related to the PFAS exposure and contamination in the United States. The commenter also stated that isocycloseram is a forever chemical and therefore this runs afoul of sustainability for future generations which is a requirement of the "no harm" standard under the Pest Control Products Act.

Health Canada response:

It is noted that isocycloseram contains at least one fully fluorinated methyl or methylene carbon atom (without any hydrogen, chlorine, bromine, or iodine atom attached to it). However, Health Canada has undertaken a thorough and complex scientific risk assessment of this new active ingredient in order to determine whether there is any risk to human health and the environment, and if that risk is acceptable. The health and environmental effects of an active ingredient in a pest control product are well characterized and form part of the risk assessment. A pest control product would not be registered for use in Canada unless it was determined that that there is no unacceptable risk to human health or the environment when the product is used according to label directions.

10. Comment related to the common mechanism of toxicity considered in the cumulative health assessment

The commenter stated that the cumulative assessment did not consider all potential modes of toxicity that isocycloseram may have in common with other pesticides, such as mitochondrial dysfunction, oxidative stress, and endocrine disruption, or those that may disrupt toxicokinetic processes.

Health Canada response:

The database of animal toxicity studies conducted with isocycloseram evaluated a variety of apical effects, target organs, and life stages, and the results of these studies would address any concerns for downstream effects from mitochondrial damage, oxidative stress, or disruption of

the endocrine system or toxicokinetic processes. As per SPN2018-02[9], a common mechanism of toxicity pertains to two or more chemicals that share a common toxic effect that results from the same, or essentially the same, sequence of major biochemical events. Health Canada follows a "weight-of-evidence" approach to support the development of hypotheses pertaining to mechanisms of toxicity. The totality of the evidence is assessed to ensure that the mechanism is consistent with current toxicological theory and knowledge and deemed scientifically plausible by Health Canada for these purposes. Grouping of pesticides that might cause a common toxic effect by a common mechanism of toxicity is based on structural similarity, common mechanism of action, and similarity of toxic effect. However, not all toxic effects can be used as a preliminary basis for grouping pesticides. Toxic effects that have many possible unrelated causes, or that could be defined as nonspecific in origin, are not appropriate as the primary basis for the initial grouping of pesticides. In the case of isocycloseram, the initial grouping was based on the known pesticidal mode of action. Following the initial grouping of pesticides, a detailed evaluation of available toxicology data for each pesticide within the group is undertaken to identify and characterize the toxic effects caused by each, and to determine which of the pesticides cause toxic effects that are common with other pesticides (that is, toxic effects that are concordant in both site and nature). Although the mammalian mode of action for isocycloseram has not been elucidated, the available toxicity information demonstrated common toxicological effects between isocycloseram and other pesticides in the group, such as effects on the adrenal cortex, small intestine, and effects on sperm function. As such, it was concluded that those pesticides (isocycloseram, broflanilide, and fluxametamide) would form a common assessment group in the cumulative health assessment.

11. Comment related to dietary exposure

The commenter stated that the consumption data is based on National Health and Nutrition Examination Survey/What We Eat in America (NHANES/WWEIA) for the years 2005–2010, which measures what Americans, not Canadians consume, which is not relevant and is outdated.

Health Canada response:

Health Canada has conducted a detailed analysis of the consumption datasets available for North America (in other words, the United States National Health and Nutrition Examination Survey – NHANES and the Canadian Community Health Survey – CCHS) and published an Information Note on comparing food and drink consumption data from Canada and the United States to explain why Health Canada uses NHANES data.

Based on this analysis, the total consumption levels determined for NHANES and CCHS show a very similar pattern between the USA and Canada. Further, Health Canada selected NHANES data for use in dietary risk assessments for pesticides over the CCHS after carefully considering several factors (as noted in SPN2014-01, General Exposure Factor Inputs for Dietary, Occupational, and Residential Exposure Assessments) including relevance for people in Canada and the need to have foods "as eaten" converted to the raw agricultural commodity (RAC). Both NHANES and the CCHS collect consumption data "as eaten" foods, but only NHANES data is broken down further to RACs within the Dietary Exposure Evaluation Model – Food Commodity Intake Database™ program (DEEM-FCID™, Version 4.02, 05-10-c). This is

[9] Health Canada (2018). Science Policy Note SPN2018-02. Cumulative Health Risk Assessment and Framework

extremely important because both the consumption data and pesticide residue concentration must be based on RACs to most accurately estimate dietary exposure for a pesticide.

Based on the above, Health Canada has determined that using the NHANES data is most appropriate for determining exposure levels to pesticides in the diets of Canadians. The Agency continues to monitor this area to ensure that the data used in the dietary exposure and risk assessments for pesticides are appropriate, reflective of modern day dietary trends, and protective of people in Canada.

The 2015 CCHS consumption data is more recent than the NHANES 2005-2010 data. However, the NHANES data provides greater confidence because it has more data points: it covers multiple years and captures consumption patterns over a longer period of time. More recent NHANES consumption data are available (up to March 2020). This will replace the current version once converted to RACs and Health Canada has determined that it continues to meet the requirements for dietary exposure and risk assessments for pesticides.

12. Comment related to the OECD MRL Calculator

The commenter stated that the OECD MRL Calculator is a statistical tool that can yield misleadingly high values when limited or heterogeneous residue trials are used. PMRA must demonstrate the MRL was not inflated by the calculator's algorithmic rounding or statistical treatment of small datasets. It appears from the PRD that there were 5 field trials conducted for each of oats, barley, rye and triticale. The OECD Calculator White Paper warns that for trials numbered between 3 and 7, there is a "High uncertainty of MRL estimate. [Small dataset]". Accordingly, it appears that the MRL estimate used for the dietary risk assessment is highly uncertain.

Health Canada response:

Up to 28 independent field trials were conducted on wheat and barley, in locations representative of growing conditions for small cereal grains. The number of trials provided exceeds the field trial requirements as outlined in Science Policy Note (SPN) 2017-02, Joint Canada/United States Field Trial Requirements. Residues of isocycloseram measured in all barley and wheat samples were below the limit of quantitation (LOQ) of the proposed enforcement method (<0.01 ppm), therefore the OECD calculator could not be used, as prescribed in the OECD Calculator User Guide and White Paper. The data for wheat and barley were extended to oats, rye and triticale, as a similar residue profile is expected in all small grains. As a result, an MRL of 0.01 ppm was established for isocycloseram on small cereal grains.

13. Comment related to occupational exposure

The commenter stated that dermal absorption values are based on in vitro studies, which may not fully represent real-world conditions. Certain dose groups were not assessed, which presents further uncertainty.

Health Canada response:

For isocycloseram, a comprehensive database of dermal absorption data was available. This included a triple pack (rat in vivo, rat in vitro, human in vitro) and two human in vitro dermal

absorption studies that were conducted on different products and tested a wide range of doses (3-4 doses/study). The triple pack of studies indicated that the in vitro model using excised skin is a conservative estimate of absorption in vivo (in a living organism). Therefore, it was considered acceptable to select dermal absorption values from human in vitro studies.

The dermal absorption value was selected from the lowest dose group in the human in vitro study conducted with the test material (A21708 E) and used for all exposure scenarios. This low dose group was representative of the lowest estimated in-field spray dilution of VANECTO COCKROACH GEL BAIT, EQUENTO, and A23128 ST. As the absorption of isocycloseram in the dermal absorption studies generally increased with decreasing dose, selection of a dermal absorption value from the lowest dose group is considered conservative for scenarios where a more concentrated dilution or the concentrated end-use products are handled. In addition, for in vitro studies, all residues in the skin are included in the dermal absorption value; this is conservative as some of those residues are bound to the skin and will not be absorbed systemically.

14. Comment related to personal protective equipment (PPE)

The commenter stated that the recommended PPE, clothing and vehicles shows a high degree of concern for workers. It is unreasonable to dictate what type of vehicle a grower must use and to expect people to be completely protected from all potential bodily exposure as described. The commenter expressed concern that label requirements could not reasonably be expected to be followed at all times, given human nature, financial constraints and the potential for error. There can be no reasonable certainty of no harm to human health to the extent such certainty is premised on label compliance.

Health Canada response:

Workers in commercial facilities and farmers are trained in reading and following label instructions and in properly using personal protective equipment. For EQUENTO and A23128 ST, the PPE are based on the worker exposure studies used to conduct the risk assessments for each scenario (treater, bagger/sewer/stacker and planter) as well as the risk assessment outcomes.

Based on this, the proposed PPE are considered adequate to protect workers. Therefore, health risks to workers are not of concern when EQUENTO and A23128 ST are used according to the label directions.

All pesticide handlers (applicators, mixers/loaders) have a legal obligation to follow all PPE requirements and engineering controls that appear on pesticide labels.

Lastly, the regulatory oversight function is delivered by Health Canada's Regulatory Operations and Enforcement Branch (ROEB). ROEB's Pesticide Compliance Program is responsible for promoting, verifying and enforcing compliance with the *Pest Control Products Act* (PCPA) and its Regulations. It provides oversight on all parties regulated by the PCPA, including pesticide registrants, importers, retailers, and users. To that effect, Health Canada's Pesticide Compliance Program conducts compliance promotion, compliance verifications (including inspections, sampling, and verifying records) and enforcement activities.

15. Comment related to the cumulative assessment

The commenter stated that the cumulative health risk assessment (CHRA) associated with isocycloseram was limited in scope as a result of excluding cyproflanilide, focusing on dietary exposure only, not assessing acute risk, and taking a qualitative approach. They claimed that the assessment did not speak to sensitive subpopulations. They also commented that the approach of conducting the cumulative assessment was not explained as it did not set out the specific data sources, models or assumptions used; as such, the validity of the assessment cannot be verified.

Health Canada response:

As stated in the Cumulative Health Risk Assessment Framework (SPN2018-02), "cumulative assessment is aimed at identifying the human health risks associated with co-exposures to two or more pesticides that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (that is, a common mechanism of toxicity)." In addition, "cumulative assessment is focused on non-occupational sources of exposure."

Assessment of Canadian non-occupational exposure of pesticides with common mechanism of toxicity

Accordingly, an assessment of a potential common mechanism of toxicity with other pesticides was undertaken for isocycloseram. Isocycloseram, along with broflanilide, cyproflanilide and fluxametamide, belong to a common pesticidal mode of action (MOA) group (Group 30) as determined by the Insecticide Resistance Action Committee (IRAC) that act as GABA-gated chloride channel allosteric modulators. Of this group of pesticides, exposure to cyproflanilide is not expected for Canadians, as there are no registered uses in Canada or the US, and there are no American tolerances or Codex MRLs. As such, no CHRA is required with cyproflanilide.

In addition, the PRD2025-11 determined that only the dietary exposure pathway is relevant for cumulative assessment as residential co-exposure is not expected. Exposure to fluxametamide is expected only through dietary exposure of imported commodities, as it is not registered in Canada and it has an American tolerance for imported tea from Japan. Broflanilide is registered in Canada on agricultural crops only; therefore, no residential exposure is expected. With the restrictions for the cockroach bait product, residential exposure to isocycloseram is negligible. As such, the cumulative assessment focused on dietary exposure only.

Although acute exposure to isocycloseram may result in adverse effects, an acute reference dose was not considered necessary and hence not established for either fluxametamide or broflanilide as no adverse effect could be attributed to a single dose. In addition, the common endpoints of the GABA-gated chloride channel allosteric modulators are not relevant to acute exposures. Therefore, the CHRA was for repeated exposure scenarios only.

Qualitative cumulative assessment approach

As outlined in SPN2018-02, Health Canada uses a tiered approach in conducting CHRAs, with each tier being more refined (that is, less conservative and uncertain) than the previous tier. Based on this tiered approach, a more refined quantitative risk assessment was not required, since based on the less refined qualitative risk assessment conducted in PRD2025-11, the

cumulative health risks from the potential co-exposure to GABA-gated chloride channel allosteric modulators through food and drinking water are acceptable.

While a qualitative cumulative assessment can be applied to any scenario, it is particularly suitable when the cumulative assessment group (CAG) contains few active ingredients, when single-chemical risk assessments are not highly refined, and for pesticides that have been registered more recently, which was the case for the GABA-gated chloride channel allosteric modulators.

For qualitative risk assessments that involve dietary exposures only, the single-chemical dietary exposure assessment (DEA) for each active ingredient in the CAG is reviewed. If there is sufficient margin in the risk cup of all the active ingredients to allow for the simple addition of individual dietary risk contributions while remaining below 100%, cumulative risks are considered acceptable, and no further assessment is necessary. This approach is equivalent to the Hazard Index Method as described in SPN2018-02, section 3.1. It uses existing dietary risk assessments, which addresses sensitive subpopulations.

For the GABA-gated chloride channel allosteric modulators, based on common toxicological effects between isocycloseram and other pesticides in the group, isocycloseram was assessed with fluxametamide for their common effects on the small intestine and sperm function. Then separately, isocycloseram was assessed with broflanilide, which both target the adrenal cortex.

For fluxametamide, the potential exposure to Canadians through imported tea from Japan was considered. The US EPA concluded that risk from chronic exposure to fluxametamide from food only is less than 1% of the acceptable daily intake (ADI) for all population subgroups (US EPA, 2020). As such, the contribution of fluxametamide to the cumulative risk with isocycloseram is minimal.

For broflanilide, the most recent dietary risk assessment was conducted in 2023 (PMRL2024-08). No other expansion of use has been approved for broflanilide since then. The refined chronic dietary exposure from all supported food uses for the representative population subgroups were less than 2% of the ADI.

When considering the estimated risks from the individual dietary exposure assessments (food + drinking water), exposure represented less than 8% of the ADI in the basic chronic dietary exposure assessment for isocycloseram (as described in section 3.5.3.2 of PRD2025-11) and less than 2% in the refined chronic dietary exposure assessment for broflanilide. These risk estimates from the individual dietary exposure assessments were calculated using the most conservative points of departure, that are not necessarily based on common effects on the adrenal cortex. As a result, the summing of these individual risk estimates (less than 10% of the risk cup) overestimates the cumulative risk of isocycloseram and broflanilide.

Therefore, based on this qualitative assessment, the cumulative risks from potential co-exposure to GABA-gated chloride channel allosteric modulators through food and drinking water, where relevant, are acceptable.

16. Comment related to the assessment of nanoparticles in seed treatments

The commenter stated that an assessment of potential harms and risks requires an assessment of the interaction of the products with constituents of the seed treatment. The commenter cited several articles to infer that harm to the environment from nanomaterials in seed treatments could occur.

Health Canada response:

Isocycloseram Technical and its end-use products, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST do not contain nanomaterials. As such, the references cited by the commenter are not applicable to the assessment of isocycloseram. The formulations of pest control products are confidential business information, and as such, are not published by Health Canada. However, a review of the proposed product formulations was conducted. Health Canada concluded that isocycloseram and its end-use products, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*. More information on the List can be found in Science Policy Note SPN2020-01, *Policy on the List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under paragraph 43(5)(b) of the Pest Control Products Act*.

17. Comment related to the Toxic Substances Management Policy evaluation

The commenter stated that there was not empirically measured data for all TSMP Track 1 criteria for isocycloseram and its transformation products. They stated that the conclusions made under the TSMP assessment are not valid as it is not clear whether or not some of the TSMP criteria were met given that the information was not available. The commenter also indicated that transformation product SYN549107 met all the TSMP criteria except for the criterion of bioaccumulation, which was evaluated based on a modelled BCF instead of an empirically measured BCF, and that the model used was not appropriate. The commenter cited an article by Arnot and Gobas in support of the used model being inappropriate.

Health Canada response:

Health Canada's strategy for implementing the Toxic Substances Management Policy (TSMP) is published under DIR99-03[10]. Details of the TSMP key management objectives are in Appendix I on page 9. For a substance to be deemed Track 1, all four TSMP Track 1 criteria must be met. When less than four of the criteria are met, the substance is not classified as TSMP Track 1.

It is standard practice for Health Canada to review substances under TSMP without having empirical data on all of the TSMP criteria. In the case of isocycloseram, empirical data was available for all criteria with the exception of persistence in air and in sediment. Based on empirical data, it was determined that isocycloseram does not meet the TSMP criteria for bioaccumulation. As such, isocycloseram does not meet all four TSMP criteria; therefore, it is

[10] Regulatory Directive DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy

not classified as a TSMP Track 1 substance. This approach is consistent with DIR99-03 and the *Canadian Environmental Protection Act*.

With regards to the model used for the determination of the bioconcentration factors (BCFs) for the transformation products SYN549107 and SYN550738, the models used were proposed by the same author cited by the commenter, Dr. Jon Arnot. A detailed report by Dr. Arnot recommending the use of the selected models used for the determination of the BCF factors for SYN549107 and SYN550738 was prepared and submitted to Health Canada in support of this review. In his report, which Health Canada has reviewed and is in agreement with the approach, Dr. Arnot demonstrated that the use of these models are a scientifically sound and appropriate method for reliably estimating the BCFs of SYN549107 and SYN550738. As reported in the footnotes of Table 29 in PRD2025-11, "Modelled BCF values were derived from BCFBAF v3.01 (EPISUITE) using both the regression-based estimate and the Arnot-Gobas BCF (including biotransformation) for lower trophic (96 g; 5.98% lipid content) fish or from Exposure and Safety Estimation (EAS-E) Suite."

18. Comment related to the environmental risk assessment

The commenter stated that the assessment of isocycloseram shows that the risks are unacceptable and that isocycloseram causes toxic effects in some species. The commenter added that it must be shown that unacceptable risk has to be rendered acceptable by the conditions of registration before registration, amendment or approval can occur, and that this has not been shown using a scientifically based approach, and therefore the onus for considering the risks acceptable has not been met.

Health Canada response:

Health Canada completed the environmental risk assessment as described in PMRA Guidance Document (2023) Health Canada's Approach to Environmental Risk Assessment for Pest Control Products, and considered both environmental exposure and ecotoxicology information. The environmental risk assessment presented in PRD2025-11 determined that the risks to the environment from the use of isocycloseram as a seed treatment and as a cockroach gel bait are acceptable when directions for use and risk mitigation measures are followed. Health Canada considers the proposed conditions of use of a pest control product, including mitigation measures, when determining the acceptability of risk. Risks to the environment were determined to be acceptable when considering the proposed use pattern, the conditions of use, the fate of isocycloseram in the environment, and the protection goals for non-target species.

19. Comments related to persistence in soil, soil bound residues, risk to soil organisms and soil impacts of seed treatment use

The commenter indicated that isocycloseram is moderately persistent to persistent in aerobic soil and that because of this persistence, residues may remain in the soil for a long time, potentially exposing soil organisms repeatedly or over extended periods. The commenter also pointed out that some portion of the radioactive residues in the degradation studies was "unextractable" (soil bound) and that this would suggest that there may be long-term non-bioavailable residues that could slowly become bioavailable over time. The commenter indicated that these bound residues represent a reservoir that could potentially be remobilized or affect soil over time, depending on

environmental conditions, and that this presents potential exposure. The commenter noted that the constituents of the seed treatment were not described and that it appears that an assessment was not conducted. The commenter believes that at a minimum, field trial data are required to assess the impacts of seed treatments on soil and ecosystems.

Health Canada response:

Health Canada completed a risk assessment on various species of soil dwelling organisms, which included both short-term (acute) exposure and long-term (chronic) exposure scenarios. Table 18 of PRD2025-11 summarizes the outcome of the risk assessment for soil dwelling organisms. It should be noted that for the seed treatment risk assessment of isocycloseram, estimated environmental concentrations in soil account for total residues and do not differentiate between bound and unbound residues. It was determined that the level of concern of 1 was not exceeded for soil dwelling organisms for both acute and chronic exposure scenarios. Health Canada agrees with the commenter that it is possible for bound residues to become unbound overtime. A bound residue also does not necessarily mean that the chemical is not bioavailable. However, the exposure to non-target organisms from bound residues is expected to be significantly lower than the exposure from unbound residues based on the concentrations observed in the laboratory studies. As the exposure is expected to be significantly lower, and since the risks from the unbound residues were determined to be acceptable, then the risks to non-target organisms from bound residues would be significantly lower and therefore also acceptable.

The constituents of the seed treatment were not described as the product formulation is protected under Canadian law as confidential business information. Health Canada has reviewed the product formulation constituents, and an environmental risk assessment was conducted on the entire product formulation. Please refer to section 6.2 of PRD2025-11, page 46.

20. Comment related to modelling mobility of transformation products

The commenter stated that some of the transformation products are of concern, that the transformation products vary in mobility and persistence and that they could move through runoff into adjacent water bodies. The commenter goes on to say that there is not sufficient data to evaluate the environmental risk of the transformation products and that appropriate data should be requested.

Health Canada response:

Not all of the transformation products identified under laboratory conditions are anticipated to be formed in significant quantities under environmental conditions. For example, some transformation products were only formed at temperatures and pH levels not relevant to Canadian environmental conditions. Fate and ecotoxicology studies, as well as scientific rationales for several transformation products, were available for the review of isocycloseram. In addition, Health Canada uses highly conservative assumptions to conduct the environmental risk assessment. For example, for the screening level risk assessment of a transformation product, Health Canada assumes that 100% of isocycloseram is instantaneously transformed into that transformation product. For ecological water modelling, in the absence of data on degradation, and if the transformation product is not shown to decline in the fate studies, Health Canada assumes that the transformation product is stable.

With respect to ecotoxicity, scientific data were submitted along with scientific rationales showing that certain transformation products are less toxic than isocycloseram.

When considering available information on degradation of the parent, formation of transformation products and their mobility and ecotoxicity, it was determined that measures put in place to mitigate the risk from isocycloseram would also be protective from exposure to any of the transformation products.

Using conservative assumptions in the risk assessment ensures that the environmental risk assessment for the transformation products is protective. The risk assessment concluded that the risk to the environment from exposure to the transformation products was acceptable.

21. Comment related to the potential for runoff and off-site movement

The commenter stated that although isocycloseram has limited ability to move downward in soil in some scenarios, the risk assessment highlighted the potential for runoff or erosion to transport residues into adjacent aquatic systems and that, regardless of the mobility of isocycloseram in soil, wind and water, erosion can carry contaminated soil particles containing isocycloseram off-site presenting potential harm. Additionally, the commenter stated that best management practice label statements to reduce leaching to groundwater and runoff are insufficient to mitigate risk and that detailed, enforceable standards are needed.

Health Canada response:

Health Canada agrees with the commenter that there is the potential for movement of isocycloseram through the movement of soil particles down-slope through runoff. To mitigate the potential for runoff, Health Canada is requiring best management practice label statements on seed treatment products to reduce runoff entering sensitive aquatic habitats. When the directions for use are followed, the risks to the environment from runoff of isocycloseram were determined to be acceptable without additional risk mitigation measures. As such, mandatory risk mitigation measures to reduce runoff and off-site movement were not required for isocycloseram based on the proposed use pattern as a seed treatment on wheat, barley, oats, rye and triticale. The following wording represents Health Canada's required best management practice label statements that must appear on the labels of all products used outdoors in a manner where runoff could occur as well as bags or containers containing treated seed:

> "To reduce runoff from treated areas into aquatic habitats, avoid application to areas with a moderate to steep slope, compacted soil, or clay. Avoid application when heavy rain is forecast. Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative filter strip between the treated area and the edge of the water body. Additional guidance can be found on the Runoff Mitigation portion of the Canada.ca website."

22. Comments related to the toxicity of isocycloseram towards soil and aquatic organisms, birds, mammals and bees

The commenter noted that the RQs exceeded the level of concern for several organisms including, but not limited to, daphnia, chironomus, mysid shrimp, birds and mammals. The

commenter also noted that isocycloseram is highly toxic to bees and indicated that the use of isocycloseram as a seed treatment on wheat, barley, oats, rye and triticale seed cannot ensure a reasonable certainty of no harm and that isocycloseram should, therefore, not be approved for use and that the registration is therefore unlawful.

Health Canada response:

Health Canada agrees with the commenter that the screening level RQs exceeded the level of concern for several non-target organisms.

Health Canada uses a tiered risk assessment approach, as described in the PMRA Guidance Document (2023) Health Canada's Approach to Environmental Risk Assessment for Pest Control Products.

As reported on page 36 of PRD2025-11:

> "Initially, a screening-level risk assessment was performed using simple methods, conservative exposure scenarios and sensitive effects metrics. A risk quotient (RQ) was calculated by dividing the EEC by the effects metric and was then compared to the level of concern (LOC). When the screening level RQ was below the LOC, the risk was considered to be acceptable, and no further risk characterization was necessary. When the screening level RQ was equal to or greater than the LOC, a refined risk assessment was performed to further characterize the risk.
>
> The refined risk assessment considered additional effects metrics as well as more realistic exposure scenarios, including runoff. Refinements to the risk assessment continued until the risk was adequately characterized or the available data did not permit further refinements."

Following further risk characterization, the risks to all non-target organisms from isocycloseram were found to be acceptable when directions for use are followed and in accordance with the required risk mitigation measures.

Environmental risk reduction measures are outlined on pages 7 and 8 of PRD2025-11.

23. Comment related to bioaccumulation

The commenter noted that Table 29 of the PRD shows isocycloseram has a relatively high log K_{ow} (≈ 4.89), which suggests potential for bioaccumulation in some systems.

Health Canada response:

Health Canada agrees with the commenter that log K_{ow} values may be used to evaluate whether a chemical has the potential to bioaccumulate. However, a log K_{ow} value of 4.89 does not necessarily mean that the chemical will bioaccumulate. Health Canada uses the log K_{ow} as an indication to determine if further examination into the potential for bioaccumulation is required to make a definitive conclusion on whether the chemical has the potential for bioaccumulation. Accordingly, two laboratory bioconcentration studies conducted with bluegill sunfish were available for isocycloseram. The bioaccumulation studies, conducted in accordance with

international guidelines, showed that isocycloseram has limited potential for bioconcentration, with bioconcentration factors (BCF) ranging from 877 to 1082 L/kg.

24. Comment related to secondary ecological effects

The commenter stated that because isocycloseram is very toxic to aquatic invertebrates, any movement from soil to water (via runoff or erosion) could pose ecological risk off-site. There may also be indirect soil ecosystem effects if non-target soil organisms are impacted. For example, reduction in soil arthropods could disrupt soil food-webs, nutrient cycling, or predator-prey dynamics.

Health Canada response:

The environmental risk assessment conducted for isocycloseram included an assessment of risk to non-target soil organisms and aquatic invertebrates. The conclusions of the risk assessment are summarized on pages 37 to 44 of PRD2025-11. It was determined that risks to non-target soil dwelling organisms and non-target aquatic invertebrates were acceptable when directions for use and risk mitigation measures are followed.

25. Comment related to treated seed soil incorporation as a risk mitigation measure

The commenter stated that risk reduction measures for birds and mammals required on the label for seed treatments are problematic for soil dwelling organisms as they instruct the user to incorporate spilled or exposed seeds into the soil and that this would result in higher exposure of soil dwelling organisms to isocycloseram.

Health Canada response:

Treated seed is planted at known seeding rates, which are taken into consideration during the environmental risk assessment. The full risk mitigation statement that will appear on the product label is the following:

> "Toxic to birds and small wild mammals. Any spilled or exposed seeds must be incorporated into the soil or otherwise cleaned up from the soil surface.

Health Canada does not anticipate large quantities of spilled seed to be incorporated into a small area of soil as a method to dispose of spilled seed. The statement is designed to inform growers that seeding equipment that incorporates the seed into the soil must be used. The use of broadcast seeding equipment where a large number of seeds may remain on the soil surface would be considered a violation of the directions for use. For spilled seed, it is expected that the seed would be cleaned up from the soil surface and added to the seeding equipment.

26. Comment related to the efficacy of best management practices

The commenter stated that the proposed best management practices for reducing exposure to bees and to reduce runoff are not effective risk mitigation measures.

Health Canada response:

The risk to non-target aquatic organisms from runoff of isocycloseram when applied as a seed treatment was determined to be acceptable without risk mitigation measures such as a mandatory vegetative filter strip. All products applied outdoors that may be subject to runoff require best management practices for runoff control to be indicated on product labels. These best management practices are not mandatory. The risks to non-target organisms from runoff of isocycloseram are expected to be low when used as a seed treatment. Conservatisms related to the runoff risk assessment are discussed on page 43 of PRD2025-11. This includes the assumption that 100% of the active ingredient is instantaneously introduced to the surrounding soil from the treated seeds at the time of planting.

With respect to bees, isocycloseram is proposed for use as a seed treatment on wheat, barley, oats, rye and triticale seed. As isocycloseram is highly toxic to bees, exposure to dust generated during planting of treated seed was considered in the pollinator risk assessment. Planting methods and equipment associated with proposed types of seeds to be treated are not expected to result in high dust generation or require use of a dust-reducing fluency agent. However, for types of seeds that tend to be dusty (cereal and legume seeds), label statements are required to inform the user of the toxicity of isocycloseram towards bees and the best management practices to reduce exposure of bees to dust from treated seed during planting.

27. Comment related to the value assessment

The commenter stated that the value assessment was lacking in that there was no need for the pest control products provided, and the three criteria for value set out in the Act were not established. Under section 2(1) of the PCPA, “value” includes: (a) efficacy, (b) effect on host organisms, and (c) health, safety, environmental, social, and economic impacts. Value requires demonstration of tangible benefits, but these have not been shown.

Health Canada response:

The *Pest Control Products Act* recognizes a pest control product’s actual or potential contribution to pest management in its definition of value.

The detrimental socio-economic impact of the subject insects and diseases on Canadian growers is well documented and the expected contribution to the management of these pests from the new active ingredient formed the basis for the finding of acceptable value. Wireworm and white grub infestations result in reduced plant stand, poor seedling vigor and loss of yield in cereal crops and are found in cereal-growing regions across Canada. Additionally, cockroaches can infest indoor and outdoor areas populated by humans and may harbour organisms which are pathogenic to humans.

The value information described in PRD2025-11 established a reasonable expectation of isocycloseram product performance in managing the detrimental effects of these pests. Based on efficacy trial results, it is expected that these products would prevent significant losses and/or failures of wheat (spring, winter, durum), barley, rye, oats and triticale crops resulting from infestations of the targeted pests. No phytotoxicity was observed on tested crop plant seedlings in field trials when EQUENTO and A23128 ST were applied as a seed treatment at proposed rates. No negative effects on crop plant stand, vigour or yield were noted in field efficacy trials where

these parameters were assessed, leading to the conclusion that isocycloseram application as a seed treatment at proposed rates does not negatively affect crop development.

Based on efficacy trial results, it is expected that VANECTO COCKROACH GEL BAIT will control cockroaches in commercial, industrial and residential areas, which will reduce damage from the insects to structures and may reduce the spread of harboured pathogens. VANECTO COCKROACH GEL BAIT is considered to be compatible with current integrated pest management practices for the control of cockroaches.

Health Canada recognizes value in access to new pest control products that offer either a first solution to emerging pest problems or an addition to existing alternatives that increase grower options, which, among other benefits, enables rotation of effective pesticide products and facilitates responsible insecticide resistance management.

For wireworms, these products would provide an alternative Group 30 insecticide to broflanilide, which may result in more competitive prices for products in this Group for growers. EQUENTO and A23128 ST may facilitate resistance management of European chafers and June beetles on the host crops. EQUENTO and A23128 ST would serve as additional replacements for neonicotinoid-containing products. In contrast to neonicotinoids, which only stun wireworm larvae, isocycloseram is expected to reduce pest populations in treated fields as it is lethal to these pests. VANECTO COCKROACH GEL BAIT will also provide users with a new mode of action for management of cockroaches, which may reduce the risk of resistance development.

Further detail on the approach to value assessments of pesticides is provided in the PMRA guidance documents *Value Guidelines for New Plant Protection Products and Label Amendments* (2023) and *Value Assessment of Pest Control Products* (2022).

28. Comment related to the social and economic impacts of complying with label directions

The commenter stated that the social and economic impacts of complying with label directions were not considered, for instance, excessive PPE are required, must be purchased, and closed tractors. The value assessment information presented did not justify the environmental and health risks of adding isocycloseram to the environment.

Health Canada response:

The feasibility of the PPE requirements are not considered. PPE is based on acute hazards and risk assessment, within the health risk assessment.

An evaluation of available scientific information found that, under the approved conditions of use, the value of the pest control products EQUENTO, A23128 ST and VANECTO COCKROACH GEL BAIT and the environmental and health risks were shown to be acceptable.

29. Comment related to the PMRA's jurisdiction over seed treatments

The commenter stated that seed coatings are not pesticides. Seed coatings are prophylactic – they act to prevent pests, not control, destroy, attract or repel them, and therefore the PMRA does not have jurisdiction over seed coatings.

Health Canada response:

Under the *Pest Control Products Act* (PCPA), a pest control product (pesticide) includes anything that is made or used to control pests, or to reduce or prevent the harm that pests can cause. This includes products used to kill, repel or otherwise limit the effects of insects, weeds, fungi, or other pests. The PCPA also allows for certain items to be prescribed as pest control products through regulations. Treated seeds are one of those prescribed items under the *Pest Control Products Regulations* (PCPR) and are therefore subject to regulation as a pest control product under the PCPA and associated regulations. A treated seed is a seed that contains or is coated with a pesticide before planting. Once treated, the treated seed becomes the means by which pests are controlled or repelled or their harm is prevented or mitigated. The regulation of treated seeds is consistent with that of other pesticide-treated items (treated articles). Health Canada evaluates and registers the pesticide itself (the active ingredient that controls or targets the pest) and also regulates how that pesticide is used on a treated seed. In this case, isocycloseram is a new insecticide that affects the nervous system of insects and mites. When used as a seed treatment, it helps protect crops from pests after planting.

Comments in support of this registration

The Canadian Pest Management Association, Structural Pest Management Association of Ontario, Abell Pest Control, and Rentokil Terminix expressed support for the registration of VANECTO COCKROACH GEL BAIT, stating that this product would help pest control operators maintain control of cockroaches in settings where broad-spectrum liquid insecticides are impractical or undesirable, and would help combat insecticide resistance and support public health.

Other information

The relevant confidential test data on which the decision is based (as referenced in PRD2025-11, *Isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST)* are available for public inspection, upon application, in the PMRA's Reading Room. For more information, please contact the PMRA's Pest Management Information Service.

Any person may file a notice of objection,[11] which must be based on scientific grounds, regarding this registration decision on isocycloseram, VANECTO COCKROACH GEL BAIT, EQUENTO and A23128 ST within 60 days from the date of publication of this Registration Decision through the Public Engagement Portal (Public Engagement Portal forms – Notice of Objection). The request for reconsideration must include the Notice of Objection form, the scientific explanation of the objection and the supporting scientific evidence in possession of the requestor that would not already be in the PMRA's possession or cite specific PMRA documentation they wish to rely on as supporting evidence (for example, scientific reports) in the form of electronic copies of cited references. Each of the references provided or cited must be clearly associated with the objection it supports. Failure to provide a complete package may result in the Notice of Objection being considered ineligible for further consideration by the

[11] As per subsection 35(1) of the *Pest Control Products Act.*

PMRA. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of the Canada.ca website or contact the PMRA's Pest Management Information Service.

Evaluation approach

Legislative framework

The Minister of Health's primary objective under the *Pest Control Products Act* subsection 4(1) is to prevent unacceptable risks to individuals and the environment from the use of pest control products.

As noted in the preamble of the Act, it is in the national interest that the attainment of the objectives of the federal regulatory system continue to be pursued through a scientifically-based national registration system that addresses risks to human health, the environment and value both before and after registration and applies to the regulation of pest control products throughout Canada; and that pest control products with acceptable risk and value be registered for use only if it is shown that their use would be efficacious and if there is acceptable risk to human health and the environment, taking into account the conditions of registration.

For the purposes of the Act, the health or environmental risks of a pest control product are acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from exposure to or use of the product, taking into account its conditions of registration as per subsection 2(2) of the *Pest Control Products Act*.

Risk for the human health and environment, and value are defined under the Act subsection 2(1) as follows:

> **Health risk**, in respect of a pest control product, means the possibility of harm to human health resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Environmental risk**, in respect of a pest control product, means the possibility of harm to the environment, including its biological diversity, resulting from exposure to or use of the product, taking into account its conditions or proposed conditions of registration.
>
> **Value**, in respect of a pest control product, means the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact.

When evaluating the health and environmental risks of a pesticide and determining whether those risks are acceptable, subsection 19(2) of the *Pest Control Products Act* requires Health Canada to apply a scientifically-based approach. The science-based approach to assessing pesticides considers both the toxicity and the level of exposure of a pesticide in order to fully characterize risk.

Pre-market assessments are based on a required set of scientific data that must be provided by the applicants for pesticide registrations. Additional information from published scientific reports, other government departments and international regulatory agencies are also considered.[12]

Risk and value assessment framework

Health Canada uses a comprehensive body of modern scientific methods and evidence to determine the nature as well as the magnitude of potential risks posed by pesticides. This approach allows for the protection of human health and the environment through the application of appropriate and effective risk management strategies, consistent with the purpose described in the preambular text set out above.

Health Canada's approach to risk and value assessment is outlined in A Framework for Risk Assessment and Risk Management of Pest Control Products.[13] A high-level overview is provided below.

i) Assessing potential health risks

With respect to the evaluation and management of potential health risks, Health Canada's risk assessments follow a structured, predictable process that is consistent with international approaches and the Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks.[14]

The evaluation of potential health risks begins with a consideration of the toxicological profile of a pesticide to establish reference doses at which no adverse effect is expected and against which the expected exposure is assessed. This includes, where appropriate, the use of uncertainty (protection) factors to provide additional protection that accounts for the variation in sensitivity among members of human population and the uncertainty in extrapolating animal test data to humans. Under certain conditions, the *Pest Control Products Act* requires the use of another factor to provide additional protection to pregnant women, infants, and children. Other uncertainty factors, such as a database deficiency factor, are considered in specific cases. More details related to the application of the uncertainty factors are provided in SPN2008-01.[15]

Assessments estimate potential health risks to defined populations[16] under specific exposure conditions. They are conducted in the context of the proposed or registered conditions of use, such as the use of a pesticide on a particular field crop using specified application rates, methods and equipment. Potential exposure scenarios consider exposures during and after application of the pesticide in occupational or residential settings, food and drinking water exposure, or

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12 Information Note – *Determining Study Acceptability for use in Pesticide Risk Assessments*.

13 PMRA Guidance Document, *A Framework for Risk Assessment and Risk Management of Pest Control Products*.

14 Health Canada Decision-Making Framework for Identifying, Assessing, and Managing Health Risks - August 1, 2000.

15 Science Policy Note: *The Application of Uncertainty Factors and the Pest Control Products Act Factor in the Human Health Risk Assessment of Pesticides*.

16 Consideration of Sex and Gender in Pesticide Risk Assessment.

exposure when interacting with treated pets. Also considered are the anticipated durations (short-, intermediate- or long-term) and routes of exposure (oral, inhalation, or skin contact). In addition, an assessment of health risks must consider available information on aggregate exposure and cumulative effects.

ii) Assessing risks to the environment

With respect to the evaluation of environmental risks, Health Canada's environmental risk assessments follow a structured, tiered approach to determine the likelihood that exposure to a pesticide can cause adverse effects on individual organisms, populations, or ecological systems. This involves screening assessments starting with simple methods, conservative exposure scenarios and sensitive toxicity effects metrics, then moving on, where required, to more refined assessments that can include exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods.

The environmental assessment considers both the exposure (environmental fate, chemistry, and behaviour, along with the application rates and methods) and hazard (toxic effects on organisms) of a pesticide. The exposure assessment examines the movement of the pesticide in soil, water, sediments and air, as well as the potential for uptake by plants or animals and transfer through the food web. The possibility for the pesticide to move into sensitive environmental compartments such as groundwater or lakes and rivers, as well as the potential for atmospheric transport, is also examined. The hazard assessment examines effects on a large number of internationally recognized indicator species of plants and animals (terrestrial organisms include invertebrates such as bees, beneficial arthropods, and earthworms, birds, mammals, plants; aquatic organisms include invertebrates, amphibians, fish, plants and algae), and includes considering effects on biodiversity and the food chain. Acute and chronic effects endpoints are derived from laboratory and field studies that characterize the toxic response and the dose–effect relationship of the pesticide.

The characterization of environmental risk requires the integration of information on environmental exposure and effects to identify which, if any, organisms or environmental compartments may be at risk, as well as any uncertainties in characterizing the risk.

iii) Value assessment

Value assessments consist of two components: an assessment of the performance of a pest control product and its benefits.

Assessing pesticide performance involves an evaluation of the pesticide's efficacy in controlling the target pest and the potential for the pesticide to damage host crops or use sites. Where the efficacy of a pesticide is acceptable, the assessment serves to establish appropriate label claims and directions and an application rate (or rate range) that is effective without being excessive, and with no unacceptable damage to the use site or host organism/crop (and subsequent hosts or crops) under normal use conditions.

In many cases, proof of performance alone is sufficient to establish the value of the pesticide, so that an in-depth or extensive evaluation of benefits may not be required. However, a more thorough assessment of benefits may be undertaken in particular cases where performance alone does not sufficiently demonstrate value, or while developing risk management options.

Risk management

The outcomes of the assessments of risks to human health and the environment, and the assessment of value, form the basis for identifying risk management strategies. These include appropriate risk mitigation measures and are a key part of decision-making on whether health and environmental risks are acceptable. The development of risk management strategies take place within the context of the pesticide's conditions of registration. Conditions can relate to, among other things, the specific use (for example, application rates, timing and frequency of application, and method of application), personal protective equipment, pre-harvest intervals, restricted entry intervals, buffer zones, spray drift and runoff mitigation measures, handling, manufacture, storage or distribution of a pesticide. If feasible conditions of use that have acceptable risk and value cannot be identified, the pesticide use will not be eligible for registration.

The selected risk management strategy is then implemented as part of the registration decision. The pesticide registration conditions include legally-binding use directions on the label. Any use in contravention of the label or other specified conditions is illegal under the *Pest Control Products Act*.

Following a decision, continuous oversight activities such as post-market assessments, monitoring and surveillance, including incident reporting, all play an essential role to help ensure the continued acceptability of risks and value of registered pesticides.

List of abbreviations

%	percent
ADI	acceptable daily intake
BCF	bioconcentration factor
CAG	cumulative assessment group
CHRA	cumulative health risk assessment
DACO	Data Code
DEA	dietary exposure assessment
g	gram(s)
GABA	gamma-aminobutryric acid
IRAC	Insecticide Resistance Action Committee
LC	Leydig cell
LH	Luteinizing hormone
LOAEL	lowest observed adverse effect level
MOA	mode of action
MOE	margin of exposure
MRL	maximum residue level
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
PCPA	*Pest Control Products Act*
PMRA	Pest Management Regulatory Agency
PFAS	Per- and polyfluoroalkyl substances
PPE	personal protective equipment
ROEB	Regulatory Operations and Enforcement Branch
SPN	Science Policy Note
TSMP	Toxic Substances Management Policy
US EPA	United States Environmental Protection Agency

References

A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

None

B. ADDITIONAL INFORMATION CONSIDERED

PMRA Document Number	Reference
3789903	Cook, J. C., Klinefelter, G. R., Hardisty, J. F., Sharpe, R. M., & Foster, P. M. D., 1999, Rodent Leydig Cell Tumorigenesis: A Review of the Physiology, Pathology, Mechanisms, and Relevance to Humans, *Critical Reviews in Toxicology*, *29*(2), 169–261, DACO: 4.4.4