Proposed Registration Decision PRD2021-01

Indole-3-butyric acid, Calcium Disodium EDTA hydrate, VNT MFG, and VNT Selective Herbicide Ready-to-Use

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Overview

Proposed registration decision for Indole-3-Butyric Acid and Calcium Disodium EDTA Hydrate

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Intelligro IBA Technical, containing the technical grade active ingredient indole-3-butyric acid, Intelligro Calcium Disodium EDTA Technical, containing the technical grade active ingredient calcium disodium ethylenediaminetetraacetic acid (EDTA) hydrate, the manufacturing concentrate VNT MFG and the end-use product VNT Selective Herbicide Ready-to-Use, containing the technical grade active ingredients indole-3-butyric acid and calcium disodium EDTA hydrate for control of broadleaf weeds and moss on turf.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of indole-3-butyric acid, calcium disodium EDTA hydrate, VNT MFG and VNT Selective Herbicide Ready-to-Use.

What does Health Canada consider when making a registration decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "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."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the Health Canada regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

Before making a final registration decision on indole-3-butyric acid, calcium disodium EDTA hydrate, VNT MFG and VNT Selective Herbicide Ready-to-Use, Health Canada's PMRA will consider any comments received from the public in response to this consultation document.[3] Health Canada will then publish a Registration Decision[4] on indole-3-butyric acid, calcium disodium EDTA hydrate, VNT MFG and VNT Selective Herbicide Ready-to-Use, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Health Canada's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What is Indole-3-butyric Acid and Calcium Disodium EDTA Hydrate?

Indole-3-butyric acid (IBA) is a naturally occurring auxin, which is a plant hormone. IBA primarily promotes lateral/adventitious root formation in the plants. When IBA is administered to plants at higher concentrations, it causes uncontrolled cell division and abnormal growth, which may lead to death of susceptible plants.

Calcium disodium EDTA hydrate ($CaNa_2$ EDTA) is a chelating agent, which may act both as a penetrant to improve uptake of IBA and to counteract the destruction of IBA during auxin conjugation and transport in the plant cells.

Health considerations

Can approved uses of Indole-3-Butyric Acid and Calcium Disodium EDTA Hydrate affect human health?

Indole-3-butyric acid and calcium disodium EDTA hydrate, are unlikely to affect your health when used according to label directions.

Potential exposure to indole-3-butyric acid (IBA) and calcium disodium ethylenediaminetetraacetic acid (EDTA) hydrate ($CaNa_2$ EDTA) may occur when handling or applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The levels used to assess risks are established to protect the most sensitive human population (for example, children

[3] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[4] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed.

In laboratory animals, the technical grade active ingredient, indole-3-butyric acid, was of low acute toxicity by the oral and dermal routes of exposure and moderately irritating to eyes. A request to waive dermal irritation testing was accepted based on the lack of irritation noted in the short-term dermal toxicity study. Acute inhalation toxicity testing demonstrated that indole-3-butyric acid cannot be generated into particles that could be inhaled, and as a result, acute inhalation toxicity is considered to be low. A waiver for dermal sensitization testing was accepted based on published scientific literature and Quantitative Structure Activity Relationship [(Q)SAR] model predictions. Indole-3-butyric acid is not considered to be a dermal sensitizer.

Short-term dermal toxicity testing, prenatal developmental toxicity testing, and information from published scientific literature were assessed for the potential of indole-3-butyric acid to cause short-term toxicity, developmental toxicity, genotoxicity, and various other effects. Treatment related adverse effects in animals administered repeated high doses of indole-3-butyric acid were not observed. In pregnant animals, exposure to indole-3-butyric acid resulted in reduced fetal body weight and increased incidence of skeletal variations. There was an indication that the young were more sensitive than the adult animal. There was no indication of genotoxicity or mutagenicity for indole-3-butyric acid.

In laboratory animals, the technical grade active ingredient, calcium disodium EDTA hydrate, was of low acute toxicity by the oral, dermal and inhalation routes and slightly irritating to skin. Publicly available information and published scientific literature were considered acceptable to waive eye irritation and dermal sensitization testing. Calcium disodium EDTA hydrate is considered to be severely irritating to the eyes and a potential dermal sensitizer.

Short-term dermal toxicity testing, prenatal developmental toxicity testing as well as information from published scientific literature were assessed for the potential of calcium disodium EDTA hydrate to cause short-term toxicity, developmental toxicity, genotoxicity, and various other effects. Adverse effects in animals given repeated high doses of calcium disodium EDTA hydrate included damage to coronary blood vessels and lesions in esophagus, trachea, and pharynx, and effects in the kidneys of males. However, these effects were not seen in other published repeat dose studies with EDTA and related compounds. In pregnant animals, exposure to calcium disodium EDTA hydrate resulted in an increase in skeletal variations in the fetus consistent with effects expected from the zinc-chelating effects of EDTA. Based on surrogate studies from published scientific literature on calcium disodium EDTA, trisodium EDTA and disodium EDTA, calcium disodium EDTA hydrate is not considered genotoxic or mutagenic.

In laboratory animals, the end-use product, VNT Selective Herbicide Ready-to-Use, was of low toxicity by the oral, dermal and inhalation routes, minimally irritating to eyes, non-irritating to skin and not a dermal sensitizer. The toxicological profile of the manufacturing concentrate, VNT MFG, is equivalent to the toxicological profile of the end-use product.

The risk assessment protects against the findings noted above as well as any other potential effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occur in animal studies.

Residues in water and food

Dietary risks from food and water are acceptable.

VNT Selective Herbicide Ready-to-Use is not proposed for food or feed uses. In addition, the likelihood of residues of indole-3-butyric acid and calcium disodium EDTA hydrate in drinking water will be low. Consequently, health risks from dietary exposure are acceptable for all segments of the population, including infants, children, adults and seniors.

Risks in residential and other non-occupational environments

Estimated risk for residential and other non-occupational exposure is acceptable.

VNT Selective Herbicide Ready-to-Use is proposed for use as a domestic, spot treatment herbicide to control weeds in residential lawns. The product label for VNT Selective Herbicide Ready-to-Use will include measures to minimize bystander exposure such as not applying when people are present, reducing spray drift, not allowing access to the treated area until after sprays have dried, and ensuring that applicators limit non-target application.

Residential and non-occupational exposure to VNT Selective Herbicide Ready-to-Use is therefore expected to be low when label directions are observed. Consequently, the risk to residents and the general public is acceptable.

Occupational risks from handling VNT Selective Herbicide Ready-to-Use

Occupational risks are not applicable when VNT Selective Herbicide Ready-to-Use is used according to the label directions, which includes protective measures.

Since VNT Selective Herbicide Ready-to-Use is a domestic product, occupational risks are not applicable.

Environmental Considerations

What happens when indole-3-butyric acid and calcium disodium EDTA hydrate are introduced into the environment?

When used according to label directions, risks associated with indole-3-butyric acid and calcium disodium EDTA hydrate and associated end-use product are acceptable from the viewpoint of environmental protection.

The product containing indole-3-butyric acid and calcium disodium EDTA hydrate is formulated as a ready-to-use product and is applied as a spot treatment for direct application using a handheld application equipment (plastic jug fitted with a spray trigger) to target weeds and moss on residential lawns, until foliage is thoroughly wetted, or just to the point of runoff, while minimizing contact with the surrounding turf. As such, environmental releases are expected to be minimal and a quantitative risk assessment was not conducted. The environmental risks associated with the end-use product are acceptable when used according to label directions.

Value considerations

What is the value of VNT Selective Herbicide?

VNT Selective Herbicide provides control, suppression, or partial suppression of several broadleaf weeds and moss on residential lawns.

VNT Selective Herbicide, containing 1.25% IBA and 2% $CaNa_2$ EDTA, is formulated as a ready-to-use product for spot treatment on lawns. Application of VNT Selective Herbicide provides control, suppression, or partial suppression of numerous broadleaf weeds and moss.

VNT Selective Herbicide is a non-conventional herbicide that will serve as an alternative option for broadleaf weed and moss management on residential lawns.

Measures to minimize risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Intelligro IBA Technical, Intelligro Calcium Disodium EDTA Technical, VNT MFG, and VNT Selective Herbicide Ready-to-Use to address the potential risks identified in this assessment are as follows.

Key risk-reduction measures

Human health

People and pets are not allowed to enter lawns that have been treated with VNT Selective Herbicide Ready-to-Use until the sprays have dried.

The signal words “WARNING- EYE IRRITANT” are required on the principal display panel of the label for Intelligro IBA Technical. Standard hazard and precautionary statements are also required on the technical grade active ingredient label to inform workers of the eye irritation potential of the product.

The signal words “DANGER- EYE IRRITANT” and “POTENTIAL SENSTIZER” are required on the principal display panel of the label for Intelligro Calcium Disodium EDTA Technical. Standard hazard and precautionary statements are also required on the technical grade active ingredient label to inform workers of the eye irritation and potential for sensitization of the product.

Standard hazard and precautionary statements are required on the end-use product label to address exposure to individuals in residential areas.

Environment

Precautionary label statements will be required to direct users to avoid contact with non-target terrestrial plants and when rain is forecast. Direct application of indole-3-butyric acid and calcium disodium EDTA hydrate to water is not allowed.

Next steps

Before making a final registration decision on indole-3-butyric acid, calcium disodium EDTA hydrate, VNT MFG and VNT Selective Herbicide Ready-to-Use, Health Canada’s PMRA will consider any comments received from the public in response to this consultation document. Health Canada will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). Health Canada will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Health Canada’s response to these comments.

Other information

When the Health Canada makes its registration decision, it will publish a Registration Decision on indole-3-butyric acid, calcium disodium EDTA hydrate, VNT MFG and VNT Selective Herbicide Ready-to-Use (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA’s Reading Room (located in Ottawa).

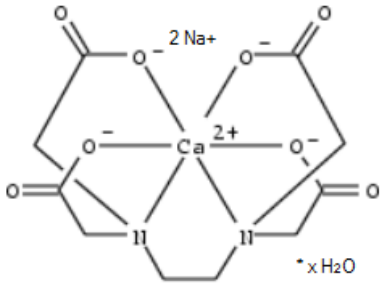
Science Evaluation

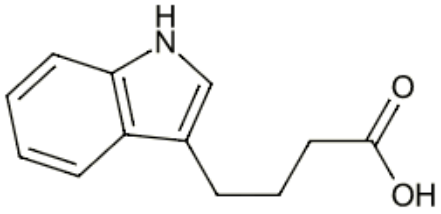
Indole-3-Butyric Acid, Calcium Disodium EDTA Hydrate, VNT MFG and VNT Selective Herbicide Ready-to-Use

Calcium Disodium EDTA Hydrate and Indole-3-Butryic Acid

1.0 The Active Ingredients, Its Properties and Uses

1.1 Identity of the Active Ingredients

Active substance	Calcium Disodium EDTA Hydrate
Function	Herbicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Disodium ((ethylenedinitrilo)tetraacetato)calciate(2-) hydrate
2. Chemical Abstracts Service (CAS)	Calciate(2-), [[N,N'-1,2-ethanediylbis[N-[(carboxy-κ-O)methyl]glycinato-κ-N-κ-O]](4-)]-, sodium, hydrate (1:2:?), (OC-6-21)-
CAS number	23411-34-9
Molecular formula	$C_{10}H_{12}CaN_2Na_2O_8*xH_2O$
Molecular weight	374.3 – 410.3
Structural formula	
Purity of the active ingredient	99.94

Active substance	Indole-3-butyric acid
Function	Herbicide, plant growth regulator
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	4-(1*H*-indol-3-yl)butyric acid
2. Chemical Abstracts Service (CAS)	1*H*-indole-3-butanoic acid
CAS number	133-32-4
Molecular formula	$C_{12}H_{13}NO_2$
Molecular weight	203.24
Structural formula	
Purity of the active ingredient	98.5%

1.2 Physical and chemical properties of the active ingredients and end-use product

Technical product—Calcium Disodium EDTA Technical

Property	Result
Colour and physical state	White solid
Odour	Odourless
Melting range	Decomposes at 166°C before melting.
Boiling point or range	N/A
Density	1.45 g/mL
Vapour pressure at 50°C	$<8.62 \times 10^{-5}$ Pa at 50°C
Ultraviolet (UV)-visible spectrum	N/A
Solubility in water at 20°C	14.47 g/100 mL
Solubility in organic solvents at 20°C	Practically insoluble in organic solvents.
n-Octanol-water partition coefficient (K_{ow})	$\underline{\log K_{ow}}$ = -5.01 (calculated for EDTA)

Property	Result
Dissociation constant (pK_a)	pK_{a1} 2.35, pK_{a2} 7.73
Stability (temperature, metal)	Stable for 14 days at 54°C.

Technical Product—Indole-3-Butyric Acid Technical

Property	Result
Colour and physical state	Colourless to pale yellow solid
Odour	Odourless
Melting range	123–125°C
Boiling point or range	N/A
Density	1.35 g/mL
Vapour pressure at 25°C	<0.01 mPa
Ultraviolet (UV)-visible spectrum	Media / λ_{max} (nm) / absorbance Neutral / 220 / 1.29 Basic / 281 / 0.54 Acidic / 222 / 1.30
Solubility in water at 20-25°C	0.346 g/L (pH 4), 14.7 g/L (pH 7)
Solubility in organic solvents at 20–25°C	Solvent / Solubility (g/L) Acetone / 500 Dichloromethane / 24.5 Ethyl acetate / 159 Methanol / 334 n-heptane / 0.00008
n-Octanol-water partition coefficient (K_{ow})	pH / log K_{ow} 10 / -0.83 7 / 0.36 4 / 2.3
Dissociation constant (pK_a)	4.80
Stability (temperature, metal)	Stable in neutral, acidic and alkaline media.

End-use product and manufacturing concentrate — VNT Selective Herbicide Ready-to-Use / VNT MFG

Property	Result
Colour	Green (F1 and F3) and colourless (F2)
Odour	Odourless
Physical state	Liquid
Formulation type	Solution (SN)
Label concentration	Calcium disodium EDTA hydrate … 2.0% Indole-3-butyric acid, present as potassium salt … 1.25%

Property	Result
Container material and description	Plastic jugs, 700 mL to 6 L, fitted with a spray trigger.
Specific gravity	1.0218 at 20°C
pH of 1% dispersion in water	6.81
Oxidizing or reducing action	Not an oxidizing or reducing agent
Storage stability	Stable for 1 year when stored in commercial containers at 20°C.
Corrosion characteristics	No corrosion to HDPE material was observed during 1 year storage at 20°C.
Explodability	Not explosive

1.3 Directions for use

VNT Selective Herbicide Ready-to-Use is formulated with 1.25% indole-3-butyric acid (IBA) and 2.0% calcium disodium EDTA hydrate ($CaNa_2$ EDTA). Application of VNT Selective Herbicide Ready-to-Use provides control, suppression, or partial suppression of certain broadleaf weeds as well as moss. A repeat application should be made two or more weeks after the previous application if necessary.

VNT Selective Herbicide Ready-to-Use is applied as a spot treatment for direct application to target weeds until foliage is thoroughly wetted, or just to the point of runoff, while minimizing contact with the surrounding turf. The application should be made when the air temperature is between 10 and 26°C. When temperatures exceed 26°C, potential injury to turfgrass is increased.

1.4 Modes of action

The modes of action of IBA and $CaNa_2$ EDTA as herbicide active ingredients are not fully understood.

IBA is a naturally occurring auxin-type plant hormone that plays a role in promoting lateral root formation and development. It can also serve as a precursor for the synthesis of other auxins, such as indole-3-acetic acid (IAA). When it is administered to plants at higher concentrations, it unbalances auxin pools and causes uncontrolled cell division and abnormal growth, which may lead to death of susceptible plants.

$CaNa_2$ EDTA is a chelating agent, which may act both as a penetrant to improve uptake of IBA and to counteract the destruction of IBA during auxin conjugation and transport in the plant cells.

2.0 Methods of analysis

2.1 Methods for analysis of the active ingredient

Calcium disodium EDTA hydrate: Analytical methods/validation data for the active ingredient and impurities are not required as the proposed product meets the food grade criteria listed in the Food Chemicals Codex.

Indole-3-butyric acid: The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for formulation analysis

Calcium Disodium EDTA hydrate: The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

Indole-3-butyric acid: The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for residue analysis

No methods are required to quantify residues of indole-3-butyric acid and calcium disodium EDTA hydrate because there are no proposed food uses.

3.0 Impact on human and animal health

3.1 Toxicology summary

A detailed review of the toxicological information was conducted in support of Intelligro IBA Technical, Intelligro Calcium Disodium EDTA Technical, VNT MFG, and VNT Selective Herbicide Ready-to-Use. The data package for Intelligro IBA Technical, Intelligro Calcium Disodium EDTA Technical, VNT MFG, and VNT Selective Herbicide Ready-to-Use is considered acceptable (Appendix I, Tables 1–3) to assess the toxic affects that may result from exposure to indole-3-butyric acid and calcium disodium EDTA hydrate.

The data package consisted of acute toxicity studies for Intelligro IBA Technical (acute oral, dermal, and inhalation toxicity, eye irritation), Intelligro Calcium Disodium EDTA Technical (acute oral, dermal, and inhalation toxicity, primary skin irritation) and VNT Selective Herbicide Ready-to-Use (acute oral, dermal and inhalation toxicity, skin and eye irritation, and dermal sensitization); in vitro mammalian cell mutagenicity studies, a short-term dermal toxicity study, a prenatal developmental toxicity study, and published scientific literature on dermal sensitization and genotoxicity in bacterial systems for Intelligro IBA Technical; and a short-term dermal toxicity study, a prenatal developmental toxicity study, and rationales supported by published

scientific literature and publicly available information to address eye irritation, dermal sensitization, genotoxicity and mutagenicity for Intelligro Calcium Disodium EDTA Technical.

Intelligro IBA Technical is considered to be of low acute toxicity by the oral, dermal and inhalation routes, moderately irritating to eyes, not irritating to skin and not a dermal sensitizer. Acute inhalation toxicity testing with IBA demonstrated that it could not be aerosolized into particles of a sufficient size to be inhaled. As a result, acute inhalation toxicity for IBA is considered to be low. A request to waive dermal irritation testing was accepted based on a lack of irritation noted in the short-term dermal toxicity study. Intelligro IBA Technical is, therefore, considered to be non-irritating to the skin.

Scientific literature, as well as Quantitative-Structure Activity Relationship [(Q)SAR] model predictions, which indicated no skin sensitization reactivity domain alerts for indole-3-butyric acid, were considered acceptable to waive dermal sensitization testing. This technical grade active ingredient is considered to be non-sensitizing.

Short-term dermal toxicity testing, prenatal developmental toxicity testing and information from published scientific literature were assessed for the potential of IBA to cause short-term toxicity, developmental toxicity, genotoxicity, and various other effects.

Treatment related adverse effects in animals administered repeated high doses of indole-3-butyric acid by the dermal route were not observed. In pregnant animals, oral exposure to indole-3-butyric acid resulted in maternal toxicity at the highest dose, with one unscheduled sacrifice and one dam found dead, with 100% postimplantation loss and complete litter losses, respectively. A reduction in body weight, body weight gain, gravid uterine weight, as well as a reduction in food consumption and efficiency was also noted in high dose dams. Clinical signs of toxicity included hunched posture, hypo-activity, irregular respiration, thin appearance, and dehydration. The maternal NOAEL was determined to be 500 mg/kg bw/day. Developmental effects were observed as lower litter weight, reduced fetal body weight, and skeletal variations (unossified and incompletely ossified sites) that were in excess of both concurrent and historical control values. The reduced fetal body weight and skeletal variations occurred at a dose level lower than that producing maternal toxicity. The developmental NOAEL was 100 mg/kg bw/day.

Based on information from published genotoxicity and mutagenicity studies in bacterial and mammalian cell lines, there was no indication of genotoxicity or mutagenicity for indole-3-butyric acid. Furthermore (Q)SAR model predictions indicated no alerts for the micronucleus assay for indole-3-butyric acid.

Intelligro Calcium Disodium EDTA Technical is considered to be of low acute toxicity by the oral, dermal and inhalation routes, and is slightly irritating to skin. Eye irritation testing for Intelligro Calcium Disodium EDTA Technical was waived based on publicly available information that indicated calcium disodium EDTA hydrate is severely irritating to eyes. A request to waive dermal sensitization testing for Intelligro Calcium Disodium EDTA Technical was supported by published scientific literature indicating that EDTA and related compounds are weakly sensitizing, and therefore, this technical grade active ingredient is considered to be a potential dermal sensitizer.

Short-term dermal toxicity testing, prenatal developmental toxicity testing and information from published scientific literature were assessed for the potential of calcium disodium EDTA hydrate to cause short-term toxicity, developmental toxicity, genotoxicity, and mutagenicity effects.

Test-substance related adverse effects in animals given repeated high doses of calcium disodium EDTA hydrate by the dermal route consisted of damage to the coronary vasculature, specifically arterial fibrinoid necrosis in the mid and high dose group. Other effects at the high dose included myofiber mineralization of the esophagus and trachea; myofiber degeneration/regeneration in the pharynx; and chronic progressive nephropathy in kidneys (males animals only). The NOAEL determined in this study was 250 mg/kg bw/day. The findings at the mid and high dose in this dermal repeat-dose study were unexpected given the very low dermal absorption expected of EDTA compounds, and that no such effects were seen in longer-term studies conducted with EDTA compounds via the dietary route, where a greater degree of toxicity would be expected. This included a three-month dietary study of disodium EDTA (NOAEL = 500 mg/kg/day, LOAEL = 2500 mg/kg bw/day) and a one year dietary study in dogs with calcium disodium EDTA (NOAEL = 338 mg/kg bw/day), among others. Nor were these effects seen in a chronic toxicity study in mice and rats which reported a NOAEL of 7500 ppm trisodium EDTA.

In pregnant animals, exposure to calcium disodium EDTA hydrate did not result in maternal toxicity. However, skeletal variations (unossified or incompletely ossified sites) in the fetus were observed at the mid and high doses. It has been reported in the literature that the pattern of variations observed after exposure of pregnant female rats to EDTA, EDTA salts or calcium EDTA is similar to that observed when dams were held on zinc depleted diets during either short intervals or for the whole period of gestation. This mechanism has also been reported for malformations resulting from EDTA treatment near or exceeding the limit dose. In short, the embryo/fetal impairment and the inductions of variations and malformations arise as a result of a depletion of zinc in the diet, or in this case the depletion of endogenous zinc tissue concentrations, caused by the zinc-chelating effect of EDTA. Essentially, the teratogenic effect of EDTA has been shown to be attributable to an interference with zinc homeostasis in the dams and fetuses.

Based on data from published genotoxicity and mutagenicity studies in bacterial and mammalian cell lines with calcium disodium EDTA hydrate or related compounds, Intelligro Calcium Disodium EDTA Technical is not genotoxic or mutagenic.

VNT Selective Herbicide Ready-to-Use is considered to be of low acute toxicity by the oral, dermal and inhalation routes, minimally irritating to eyes, non-irritating to skin and not a dermal sensitizer. The toxicological profile of the manufacturing concentrate, VNT MFG, is equivalent to the toxicological profile of the end-use product.

Incident reports

Calcium disodium EDTA hydrate (and related forms), indole-3-butryric acid (as well as indole-3-butryric acid, present as potassium salt) are new active ingredients pending registration for use in Canada, and as of 27 October 2020, no human or domestic animal incident reports had been submitted to the PMRA.

3.2 Occupational, residential and bystander exposure and risk assessment

3.2.1 Dermal absorption

No information was submitted on the potential dermal absorption of indole-3-butyric acid nor calcium disodium EDTA hydrate. Indole-3-butyric acid is an aromatic compound with low molecular weight (203 Da) and a relatively low Log K_{ow} (2.3) and p*K*a value (4.8). The potential for dermal absorption is relatively low.

Published literature reports that EDTA and its salts are poorly absorbed following dermal exposure (Environment and Climate Change Canada and Health Canada, 2018. *Final Screening Assessment of EDTA and its salts*), therefore, the potential for dermal absorption of calcium disodium EDTA hydrate is considered to be low.

3.2.2 Use description

VNT Selective Herbicide Ready-to-Use is a domestic class herbicide product. The ready-to-use liquid formulation is contained in a trigger spray bottle and is manually sprayed by homeowners as a spot treatment on actively growing weeds in lawns. The product can be re-applied, as necessary, every 2–3 weeks when weeds are actively growing.

3.2.3 Mixer, loader, and applicator exposure and risk

There is no potential for occupational exposure since the product is for domestic use.

3.2.4 Postapplication exposure and risk

As the end-use product is for domestic use, no postapplication exposure and risk assessment is required.

3.2.5 Residential and bystander exposure and risk

VNT Selective Herbicide Ready-to-Use is proposed for domestic uses only. There are no mixing and loading activities for the end-use product because it is a ready-to-use product.

Based on estimates of area treated per day and the estimated application rate of 25–100 g VNT/acre for spot treatments, homeowners could handle between 0.05–900 mg indole-3-butyric acid and between 0.09–1000 mg calcium disodium EDTA hydrate per day depending on the size of their lawn, the degree to which the weed is sprayed (in other words, application rate) and weed severity.

When VNT Selective Herbicide Ready-to-Use is used according to label directions, exposure to residential users is characterized as acute in duration and is primarily by the dermal route, mainly through contact with the spray solution. Ocular and inhalation exposure may occur to a lesser extent from exposure to spills or spray mist.

Precautionary statements on the end-use product label aimed at mitigating exposure are adequate to protect individuals from any risk due to user exposure. Overall, risks to residential users are acceptable when the precautionary statements on the label are followed.

Residential exposure following application may occur for adults and young adults from lawn care maintenance activities, and for adults, children, and pets from high contact recreational activities on treated lawns. The likely route of exposure is dermal (acute or short-term), via contact of the hands and feet with treated lawns. For toddlers, incidental oral exposure may also occur (hand-to-mouth, object-to-mouth or ingestion of treated grass).

Bystander and residential exposure will be mitigated by the inclusion of a statement on the label of VNT Selective Herbicide Ready-to-Use that specifies people and pets are not permitted to enter the treated area until sprays have dried, and by the inclusion of a spray drift statement advising against application to areas of human habitation unless consideration has been given to the wind speed, wind direction, temperature inversions, application equipment, and sprayer settings. In addition, bystander exposure to humans and pets is expected to be low since the product is sprayed directly to weeds.

Given that recreational and other users could repeatedly come into direct contact with treated lawns, and that a NOAEL value was identified from the developmental toxicity study of indole-3-butyric acid, Health Canada determined that margin of exposure estimates (MOEs) should be generated for residential exposures following application. The MOE estimates were calculated by dividing the NOAEL to applicant-generated postapplication exposure estimates, and assumed 100% dermal absorption for indole-3-butyric acid. The dermal MOEs for indole-3-butyric acid ranged from greater than 49000 for toddlers engaged in high contact lawn activities three hours after application, to greater than 10^6 for adult females mowing treated lawns 24 hours after application. For incidental oral exposure (toddlers), the MOEs for all time points were greater than 10^6 for hand to mouth, object to mouth and accidental soil ingestion. Given the margins for indole-3-butyric acid, it is expected to be protective for recreational and other users of treated lawns.

As no toxicological endpoint of concern was identified for calcium disodium EDTA hydrate, a qualitative residential and bystanders exposure assessment was considered appropriate. Considering the toxicity profiles of calcium disodium EDTA hydrate and the end-use product, the status of this active as a food additive, the spot treatment pattern of use, and the precautionary statements on the end-use product label aimed at mitigating exposure, residential and bystander exposures and risks from calcium disodium EDTA hydrate are acceptable.

Overall, the health risks to individuals in residential areas from exposure to indole-3-butyric acid and calcium disodium EDTA hydrate in VNT Selective Herbicide Ready-to-Use are considered acceptable.

3.3 Food residue exposure assessment

3.3.1 Food

VNT Selective Herbicide Ready-to-Use is not proposed for food or feed use. Consequently, dietary exposure to indole-3-butyric acid and calcium disodium EDTA hydrate from the proposed use is not of concern.

3.3.2 Drinking water

Dietary exposure from drinking water is expected to be negligible as the label has the necessary mitigative measures to limit contamination of drinking water from the proposed uses of VNT Selective Herbicide Ready-to-Use. Consequently, health risks from residues of indole-3-butyric acid and calcium disodium EDTA hydrate in drinking water are acceptable.

3.3.3 Acute and chronic dietary risks for sensitive subpopulations

Establishment of an acute reference dose (ARfD) or acceptable daily intake (ADI) is not required as there are no food or feed uses and contamination of drinking water sources is not expected.

3.3.4 Aggregate exposure and risk

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

The use pattern of VNT Selective Herbicide Ready-to-Use is limited to use as a spot treatment on residential lawns and thus, exposure from the diet (food and water) is considered to be negligible. When the end-use product is used as labelled, there is reasonable certainty that no harm will result from aggregate exposure of residues of indole-3-butyric acid and calcium disodium EDTA hydrate to the general population in Canada, including infants and children,. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information.

3.3.5 Cumulative assessment

The *Pest Control Products Act* requires that the PMRA consider the cumulative exposure to pesticides with a common mechanism of toxicity. Accordingly, assessments of potential common mechanisms of toxicity with other pesticides were undertaken for indole-3-butyric acid and calcium disodium ethylenediaminetetraacetic acid (EDTA) hydrate.

Indole-3-butyric acid is structurally related to another registered auxin phytohormone pest control product, 4-chloroindole-3-acetic acid. However, the observed effects in the available toxicity studies for these compounds were indicative of more generalized toxicity, and a common mechanism of toxicity has not been identified. Therefore, a cumulative assessment for indole-3-butyric acid is not required at this time.

Calcium disodium EDTA hydrate shares a common chemical moiety with other registered pesticide active ingredients: iron HEDTA and ferric sodium EDTA. However, given that calcium disodium EDTA and other EDTA-based chemicals are used as food additives and have low toxicity to mammalian systems, the potential health risks from cumulative exposure to EDTA-based pest control products are acceptable when these products are used as directed on the label.

3.3.6 Maximum residue limits

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure the food Canadians eat is safe.

Maximum residue limits for indole-3-butyric acid and calcium disodium EDTA hydrate were not required for the proposed non-food use of VNT Selective Herbicide Ready-to-Use.

4.0 Impact on the environment

4.1 Fate and behaviour in the environment

Indole-3-butyric acid

Indole-3-butyric acid (IBA) is a naturally occurring auxin-type plant hormone that plays a role in promoting lateral root formation and development. It has very high solubility, low volatility and is not expected to undergo hydrolysis in the environment due to the lack of hydrolyzable functional groups. Indole-3-butyric acid has low potential for phototransformation. If released to soil, indole-3-butyric acid is estimated to have moderate to low mobility in soil. However, based on limited environmental exposure through the proposed use pattern as spot treatment, and given its non-persistence, indole-3-butyric acid is not expected to move through soil to groundwater. If released into water, indole-3-butyric acid is not expected to adsorb to suspended solids and sediment. Its potential for bioconcentration in aquatic organisms is estimated to be low.

Similar to other natural plant hormones and substances, IBA may be present in the environment from plant sources and concentrations found in the soil from herbicide application would not be distinguishable from naturally occurring sources.

Calcium disodium EDTA hydrate

Calcium disodium EDTA hydrate ($CaNa_2$ EDTA) is one of the several EDTA salts produced for use as a chelating agent to sequester metal ions in multiple industries (for example, textile, pulp and paper, food, medicine, personal care products). The function of $CaNa_2$ EDTA used in combination with IBA as a herbicide may be both as a penetrant to improve uptake of IBA and to counteract the destruction of IBA during auxin conjugation and transport in the plant cells.

Publicly available environmental fate data for EDTA indicate that these compounds are slow to degrade under typical environmental conditions but are not expected to bioconcentrate. The EDTA salts are soluble in water, have low sorption to soil and sediments, have no significant vapour pressure, and have a biodegradation half-life of weeks to months.

Environmental exposure of IBA and $CaNa_2$ EDTA is expected to be limited due to the following factors:

1. The end-use product, VNT Selective Herbicide Ready-to-Use, is formulated as a ready-to-use product and is proposed as spot treatment on residential lawns using handheld spraying equipment. The direct targeting of weeds with spot treatments is expected to limit spray drift.
2. Target weeds are to be sprayed directly until foliage is thoroughly wetted, just to the point of runoff. Hand-held application equipment gives the user good control of the amount applied and minimizes off-target exposure.
3. One application is recommended when target weeds are young and actively growing (i.e., in the fall, in the spring, or early summer) and if needed, a repeat application two or more weeks later, is not expected to result in significant deposition on soil, adjacent water bodies, or non-target plants.
4. Label instructions advise avoiding application during rainfall or if rain is forecast within a few hours to ensure treatment effectiveness. In addition, irrigation is to be avoided for at least 8 hours after application. Following these instructions should help minimize off-target movement through runoff immediately after application.

4.2 Environmental risk characterization

A quantitative risk characterization was not conducted for the environmental assessments of IBA and $CaNa_2$ EDTA as the proposed use pattern is expected to result in limited environmental exposure. The estimated environmental concentrations in soil and water cannot be quantified as the spray solution is to be directed to targeted weeds in turf over small areas. Users are instructed not to over-apply to the point of runoff to soil and not apply during rainfall or if rain is forecast. As it is a ready-to-use spot treatment product for residential lawns using handheld application equipment (use of trigger spray bottle), potential for exposure of non-target organisms is low and spray drift and runoff of IBA and $CaNa_2$ EDTA are expected to be limited.

Further information on the environmental fate and toxicology of IBA and $CaNa_2$ EDTA may be required should the use be expanded to other sites, hosts, application methods and/or pests.

4.2.1 Risks to terrestrial organisms

Indole-3-butyric acid is practically non-toxic to honey bees, birds and mammals (Appendix 1, Table 6). However, based on the reported mode of action of IBA and the proposed claims for use as a non-conventional herbicide, IBA is expected to be toxic to non-target terrestrial vascular plants. Therefore, a label statement will be required to inform users to avoid direct application to non-target terrestrial plants.

No environmental toxicity studies were provided specifically on the level of effects of $CaNa_2$ EDTA to terrestrial organisms (PMRA# 2822385). However, it was determined that $CaNa_2$ EDTA was non-toxic to rats. No other data were provided to assess the toxicity of $CaNa_2$ EDTA to terrestrial organisms. Based on the widespread use of $CaNa_2$ EDTA in various industries, risks to terrestrial organisms are not expected.

4.2.2 Risks to aquatic organisms

Publicly available environmental toxicity data indicate that indole-3-butyric acid is slightly toxic to *Daphnia magna* and *Oncorhynchus mykiss* (Appendix I, Table 6). However, based on the proposed use pattern (spot treatment, handheld application equipment), spray drift and runoff to adjacent bodies of water is not expected. Therefore, risks to aquatic fish and aquatic invertebrates are acceptable. Aquatic vascular plant toxicity data were not provided. Based on its mode of action, IBA is assumed to be toxic to aquatic vascular plants. A label statement indicating direct application to water is not allowed will be required.

No environmental toxicity studies were provided specifically on the levels of effects of $CaNa_2$ EDTA to aquatic organisms. Based on the widespread use of $CaNa_2$ EDTA in various industries, risks to aquatic organisms are not expected.

4.2.3 Incident reports

As of 27 October 2020, no environmental incident reports involving IBA and $CaNa_2$ EDTA were found in a search of available databases (PMRA incident reporting and the United States Ecological Incident Information System).

5.0 Value

In the past few years, several non-conventional herbicides have been registered for domestic weed management on turfgrass. The availability of VNT Selective Herbicide Ready-to-Use would provide homeowners and lawn care professionals with an additional option for control of broadleaf weeds and moss in situations where the use of conventional chemicals is not desirable or available due to provincial or municipal restrictions.

Since IBA is a naturally occurring plant hormone, the development of weed resistance to VNT Selective Herbicide Ready-to-Use is unlikely. The use of VNT Selective Herbicide Ready-to-Use may reduce the potential for the development of weed resistance to other herbicide modes of action.

Information submitted demonstrated that when applied as a spot treatment, control of annual sow-thistle, black medic, Canada thistle (season-long control), broadleaf plantain, dandelion, ground ivy, and common groundsel, suppression of moss and white clover, and partial suppression of narrow-leaf plantain and common ragweed can be expected. The efficacy of VNT Selective Herbicide Ready-to-Use is maximized when it is applied to young and actively growing weeds, and with complete coverage of the weed foliage. A repeat application should be made two or more weeks after the previous application, if necessary.

Injury may occur if there is any contact with the surrounding turfgrass but the observed injury was typically outgrown overtime.

6.0 Pest control product policy considerations

6.1 Toxic substances management policy considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, in other words, those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control Products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, indole-3-butyric acid, calcium disodium EDTA hydrate and their transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the conclusion that indole-3-butyric acid, calcium disodium EDTA hydrate and their transformation products do not meet all of the Track 1 criteria.

6.2 Formulants and contaminants of health or environmental concern

During the review process, contaminants in the technical as well as formulants and contaminants in the end-use products are compared against Parts 1 and 3 of the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*[6] The list is used as described in the PMRA Notice of Intent NOI2005-01[7] and is based on existing policies and regulations, including the *Toxic Substances Management Policy* and *Formulants Policy*,[8] and taking into consideration the *Ozone-depleting Substance Regulations*, 1998, of the *Canadian Environmental Protection Act* (substances designated under the *Montreal Protocol*).

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 SI/2005-114, last amended on June 25, 2008. See Justice Laws website, Consolidated Regulations, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*

7 PMRA's Notice of Intent NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act*

8 DIR2006-02, *Formulants Policy and Implementation Guidance Document.*

The PMRA has reached the following conclusions:

- Intelligro IBA Technical and Intelligro Calcium Disodium EDTA Technical and their end-use product, VNT Selective Herbicide Ready-to-Use, do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Proposed regulatory decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing registration for the sale and use of Intelligro IBA Technical, containing the technical grade active ingredient indole-3-butyric acid, Intelligro Calcium Disodium EDTA Technical, containing the technical grade active ingredient calcium disodium EDTA hydrate, the manufacturing concentrate VNT MFG and VNT Selective Herbicide Ready-to-Use, containing the technical grade active ingredients indole-3-butyric acid and calcium disodium EDTA hydrate for control of broadleaf weeds and moss on turf.

An evaluation of available scientific information found that, under the approved conditions of use, the health and environmental risks and the value of the pest control products are acceptable.

List of Abbreviations

µg	micrograms
°C	degrees Celsius
♀	female
♂	male
a.i.	active ingredient
ADI	acceptable daily intake
ARfD	acute reference dose
atm	atmosphere
bw	body weight
bwg	body weight gain
$CaNa_2$ EDTA	calcium disodium ethylenediaminetetraacetic acid hydrate
CAS	Chemical Abstracts Service
d	day
Da	dalton
EC_{50}	effective concentration on 50% of the population
EDTA	ethylenediaminetetraacetic acid
FDA	*Food and Drugs Act*
fc	food consumption
fe	food efficiency
g	gram
h	hour(s)
hprt	hypoxanthine phosphoribosyltransferase
IAA	Indole-3-acetic acid
IBA	indole-3-butyric acid
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
mg	milligram
mL	millilitre
MAS	maximum average score for 24, 48 and 72 hours
MFG	manufacturing grade
MIS	maximum irritation score
MOE	margin of exposure
MRL	maximum residue limit
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million

(Q)SAR	quantitative structure activity relationship
RTU	ready-to-use
TK	thymidine kinase
TSMP	Toxic Substances Management Policy
UV	ultraviolet

Appendix I Tables and figures

Table 1 Toxicity profile of Intelligro IBA Technical

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA#	Study Results
Acute Oral Toxicity Sprague-Dawley rat (♀) PMRA# 2822473	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Inhalation Toxicity PMRA# 3036931	IBA could not be aerosolized into sufficiently small particles to conduct valid inhalation testing. Low toxicity
Acute Dermal Toxicity Sprague-Dawley rat PMRA# 2822474	LD_{50} > 5050 mg/kg bw Low toxicity No signs of irritation
Eye Irritation New Zealand White rabbit PMRA# 2822477	MAS = 11.8/110 MIS = 28/110 (24 h) Moderately irritating to eyes
28-Day Dermal Toxicity Sprague-Dawley rat PMRA# 2822479	NOAEL = 1000 ppm No signs of irritation
Developmental Toxicity (gavage) Crl:CD® IGS BR rat PMRA# 2822483	Maternal NOAEL = 500 mg/kg/d 1000 mg/kg/d: ↓ bw, bwg, fc, fe Developmental NOAEL = 100 mg/kg/d 500 mg/kg/d: ↓fetal bw, ↑ skeletal variations 1000 mg/kg/d: ↓total litter wt and fetal bw, ↑ skeletal variations Sensitivity of the young

Study Type/Animal/PMRA#	Study Results
Bacterial Reverse Mutation Assay *Salmonella* Typhimurium (TA100, TA98, TA1535, TA1537 and TA1538) and *Escherichia coli* strain (WP2 *hcr*) PMRA# 2822486	Negative
Bacterial Reverse Mutation Assay *S.* Typhimurium (TA97a, TA98, TA100, TA1535, TA1537 and TA1538) PMRA# 2822487	Negative
In vitro Mammalian Chromosomal Aberration Test Chinese hamster ovary cells PMRA# 3001722	Negative
In vitro Mammalian Cell Mutagenicity Assay V-79 Chinese hamster lung fibroblasts hprt locus PMRA# 3001721	Negative
(Q)SAR for skin sensitization PMRA# 3006680	No skin sensitization domain alerts (ToxTree).
Dermal sensitization (Buehler) PMRA# 3006679	Negative. Not a dermal sensitizer.

Table 2 Toxicity profile of Intelligro Calcium Disodium EDTA Technical

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Sprague Dawley rat (♀) PMRA# 2822512	LD_{50} > 5000 mg/kg bw Low toxicity
Acute Dermal Toxicity Sprague Dawley rat PMRA# 2822513	LD_{50} > 5050 mg/kg bw Low toxicity No signs of irritation
Acute Inhalation Toxicity Sprague Dawley rat PMRA# 2822514	LC_{50} > 2.29 mg/L Low toxicity
Primary Skin Irritation New Zealand White rabbit PMRA# 2822516	MAS = 0/8 MIS = 0.33/8 (1h) Slightly irritating
28-Day Dermal Toxicity Sprague-Dawley rat PMRA# 2822518	LOAEL = 500 mg/kg bw/d NOAEL = 250 mg/kg bw/d 500 mg/kg bw/d: coronary vasculature histological findings (arterial fibrinoid necrosis) 1000 mg/kg bw/d: coronary vasculature histological findings (arterial fibrinoid necrosis), myofiber mineralization in the esophagus and trachea, myofiber degeneration/ regeneration in the pharynx, and chronic progressive nephropathy in the kidneys (males only)

Study Type/Animal/PMRA #	Study Results
Developmental Toxicity Crl:CD® IGS BR rat PMRA# 2822483	Maternal NOAEL = 1000 mg/kg bw/d Developmental NOAEL = 100 mg/kg bw/d ≥500 mg/kg bw/d: ↑ skeletal variations
Bacterial Reverse Mutation Assay *Salmonella* Typhimurium (TA97, TA102) PMRA# 2991917	Negative 0, 0.1, 0.5, 1, 5, and 10 µg/plate With and without metabolic activation
Bacterial Reverse Mutation Assay *S.* Typhimurium (TA98, TA100, TA1535, and TA1537) PMRA# 2991920	EDTA is Negative 10, 100, and 500 or 1000 µg, with and without metabolic activation
L5178Y TK +/- mouse lymphoma assay PMRA# 3154795	Na_3EDTA is Negative No evidence of mutagenicity neither with metabolic activation (0, 250, 500, 1000, 1500, 2000 and 4000 µg/mL) nor without metabolic activation (0, 250, 500, 1000, 1500 and 2000 µg/mL)
L5178Y TK +/- mouse lymphoma assay PMRA# 3156540	Na2 EDTA is Negative No evidence of mutagenicity neither with metabolic activation (0, 250, 500, 1000, 1500, 2000 µg/mL)

Table 3 Acute toxicity profile of VNT Selective Herbicide Ready-to-Use and VNT MFG

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity Sprague-Dawley rat (♀) PMRA# 2822433	LD_{50} > 5000 mg/kg bw Low toxicity

Study Type/Animal/PMRA #	Study Results
Acute Dermal Toxicity Sprague-Dawley rat PMRA# 2822435	LD_{50} > 5050 mg/kg bw Low toxicity
Acute Inhalation Toxicity Sprague-Dawley rat PMRA# 2822437	LC_{50} > 2.13 mg/L Low toxicity
Eye Irritation New Zealand albino rabbit PMRA# 2822437	MAS = 0/110 MIS (1 h) = 2.67/110 Minimally irritating
Dermal Sensitization (Beuhler) Hartley guinea pig PMRA# 2822442	Negative Not a dermal sensitizer

Physical and chemical properties relevant to the environment

Table 4 Physical and chemical properties of Indole-3-Butyric Acid relevant to the environment

Property	Value	Comments
Water solubility at 20–25°C	0.346 g/L (pH 4), 14.7 g/L (pH 7)	Very high solubility
Vapour pressure at 25°C	<0.01 mPa	Volatilization from dry soil is not expected. Exist in both the vapour and particulate phases in the ambient atmosphere.
Henry's law Constant	1.3×10^{-11} atm cu m/mol	The undissociated form of indole-3-butyric acid is not expected to volatilize from moist surfaces.
Dissociation constant in water (20°C)	$pK_a = 4.8$	This compound will primarily exist in the dissociated form in the environment; anions

Property	Value	Comments
		generally do not adsorb to organic carbon and clay as strongly as their neutral counterparts. Volatilization from water surfaces is not expected to be an important fate process.
Octanol/water partition coefficient (K_{ow})	pH: 10, 7, 4 log K_{ow}: -0.83, 0.36, 2.3	Bioconcentration/bioaccumulation is unlikely.
UV/visible absorption spectrum	Media: Neutral; Basic; Acidic λ_{max} (nm): 220; 281; 222 absorbance: 1.29; 0.54; 1.30	Low potential for phototransformation. Stable in neutral, acidic or alkaline media. Susceptible to direct photolysis by sunlight.
Adsorption/desorption in soil	K_{oc} (Adsorption): 550	Moderate to low mobility in soil; not expected to adsorb to suspended solids and sediment.

Table 5 Physical and chemical properties of Calcium Disodium EDTA Hydrate relevant to the environment

Property	Value	Comments
Water solubility at 20°C	14.47 g/100 mL	
Vapour pressure	$<8.62 \times 10^{-5}$ Pa at 50°C	Volatilization from dry soil is not expected.
Henry's Law Constant	1.3×10^{-11} atm cu m/mol	The undissociated form of indole-3-butyric acid is not expected to volatilize from moist surfaces.
Dissociation constant in water (20°C)	pK_{a1} 2.35, pK_{a2} 7.73	This compound will primarily exist in the dissociated form in the environment; anions generally do not adsorb to organic carbon and clay as strongly as their neutral counterparts.

Property	Value	Comments
Ultraviolet (UV)-visible spectrum	N/A	
Octanol/water partition coefficient (K_{ow})	log K_{ow} = -5.01 (calculated for EDTA)	Bioconcentration/bioaccumulation is unlikely.

Table 6 Toxicity to non-target species (Indole-3-Butyric Acid)

Organism		Endpoint value	Degree of toxicity	Reference (PMRA#)
Terrestrial Non-Target Organisms				
Honey bees (*Apis mellifera*)	Acute (48-h Oral)	48-hour LD_{50} > 100 µg/bee	Practically non-toxic	2822393
	Acute (48-h Contact)	48-hour LD_{50} > 100 µg/bee		2822392
Bobwhite quail (*Colinus virginianus*)	Acute (Oral)	LD_{50} > 2250 mg a.i./kg bw	Practically non-toxic	
		LC_{50} > 2150 ppm		
	Dietary	LC_{50} > 5620 ppm NOEC = 3160 ppm (slight reduction in weight gain, reduction in food consumption)	Practically non-toxic	
		LC_{50} > 5000 ppm NOEC = 5000 ppm		
Mallard duck (*Anas platyrhynchos*) Dietary		LC_{50} > 5620 ppm NOEC = 5620 ppm	Practically non-toxic	
Rat	Acute (Oral)	LD_{50} > 200 mg/kg body weight	Practically non-toxic	
	Acute (Dermal)	LD_{50} > 3800 mg/kg body weight (male) LD_{50} > 3800 mg/kg body weight (male)	Practically non-toxic	
		LD_{50} > 5800 mg/kg body weight (female)		

Organism	Endpoint value	Degree of toxicity	Reference (PMRA#)
Aquatic Organisms			
Water fleas (*Daphnia magna*)	48-hr LC_{50} = 55 mg/L NOEC = 28.7 mg/L (mortality)	Slightly toxic	
	24-hr LC_{50} = 199.8 mg/L NOEC = 131 mg/L		
	48-hr EC_{50} = 90.3 mg/L NOEC = 25 mg/L		
Rainbow trout (*Oncorhynchus mykiss*)	96-hr LC_{50} = 90.5 mg/L NOEC = 58.5 mg/L	Slightly toxic	
	96-hr LC_{50} = 147.9 mg/L NOEC = 125.1 mg/L		
	LC_{50} = 188 mg/L NOEC = 92 mg/L		

Table 7 List of supported uses

Items	Label claims that are supported
Application rate	Spray the target weeds from 30 cm above until foliage is thoroughly wetted, just to the point of runoff.
Efficacy claim	Control of annual sow-thistle, black medic, Canada thistle (season-long control), broadleaf plantain, dandelion, ground ivy, and common groundsel. Suppression of moss and white clover. Partial suppression of narrowleaf plantain and common ragweed.
Use-site	Turf grass (use-site category 30)
Application method	Directly spray the target weeds as a spot treatment, while minimizing contact with surrounding turf.
Application timing	The best time to apply is in the fall while the second best is in the spring or early summer when weeds are young and actively growing.
No. of application	One or two; a repeat application may be required after two or more weeks.

References

A. List of studies/information submitted by registrant

1.0 Chemistry

PMRA document number	Reference
2822503	2017, Manufacturing Summary, DACO: 2.11.1, 2.11, 2, 2.11, 3, 2.11.4 CBI
2822504	2015, Detailed production process description: Calcium disodium EDTA, DACO: 2.11, 3
2822505	2017, Detailed Production Process Description, DACO: 2.11, 3 CBI
2822506	2017, Establishing Certified Limits, DACO: 2.12.1 CBI
2822507	2017, Confirmation Of Identity, DACO: 2.13.1, 2.13, 2, 2.13, 3, 2.13.4 CBI
2822508	2017, Sample Of Analytical Stnds And Res Of Conc, DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.15, 2.14.16, 2.14, 2, 2.14, 3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 2.15,830.7000 CBI
2822509	2016, UV/Visible Absorption Spectra, DACO: 2.14.1, 2.14.12, 2.14.13, 2.14.15, 2.14, 2, 2.14, 3, 2.14.6, 2.14.7, 2.14.9,830.7000 CBI
2822510	2017, Storage Stability Data, DACO: 2.14.14 CBI
2882048	2013, Solvitar(TM) Product Data Leaflet, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11
2882049	2018, Technical Data Sheet: Trilon(R) CA, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11
2892591	2018, Batch Data, DACO: 2.13, 3 CBI
2895511	2017, Octanol/Water Partition Coefficient, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11 CBI
2895512	2017, Octanol/Water Partition Coefficient, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11 CBI
2895513	2017, Octanol/Water Partition Coefficient, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11 CBI
2895514	2017, Octanol/Water Partition Coefficient, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11 CBI
2895515	2017, Octanol/Water Partition Coefficient, DACO: 2.11, 2, 2.11, 3, 2.11.4, 2.13.1, 2.13, 2, 2.13, 3, 2.14.10, 2.14.11 CBI
2949569	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2949571	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2949573	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2949575	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2949577	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951280	2018, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951283	2017, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951284	2016, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951285	2015, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951286	2018, Confirmation Of Identity, DACO: 2.13, 2 CBI

PMRA document number	Reference
2951287	2018, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951288	2018, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951289	2016, Confirmation Of Identity, DACO: 2.13, 2 CBI
2951290	2016, Confirmation Of Identity, DACO: 2.13, 2 CBI
2961117	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2961118	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2961119	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2961120	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2961121	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2961122	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2949577	2019, Confirmation Of Identity, DACO: 2.13, 2 CBI
2822376	2017, Product Identification - VNT Selective Herbicide Ready-to-Use, DACO: 3.1.1, 3.1, 2, 3.1, 3, 3.1.4
2822377	2017, Description Of Starting Materials, DACO: 3, 2.1, 3, 2, 2, 3, 2, 3 CBI
2822378	2017, Establishing Certified Limits, DACO: 3, 3.1 CBI
2822379	2016, Enforcement Analytical Method, DACO: 3.4.1 CBI
2822380	2017, Impurities of Toxicological Concern - VNT Selective Herbicide Ready-to-Use, DACO: 3.4, 2
2822381	2017, Explodability, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14, 3.5.15, 3.5.16, 3.5, 2, 3.5, 3, 3.5.4, 3.5.5, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2822382	2017, Corrosion Characteristics, DACO: 3.5.10, 3.5.14 CBI
2822383	2016, PH, DACO: 3.5.10, 3.5.6, 3.5.7, 3.5.8, 3.5.9 CBI
2822425	2017, Product Identification - VNT RTU MFG, DACO: 3.1.1, 3.1, 2, 3.1, 3, 3.1.4
2822426	2017, Description Of Starting Materials, DACO: 3, 2.1, 3, 2, 2, 3, 2, 3 CBI
2822427	2017, Establishing Certified Limits, DACO: 3, 3.1 CBI
2822428	2016, Enforcement Analytical Method, DACO: 3.4.1 CBI
2822429	2017, Impurities Of Toxicological Concern, DACO: 3.4, 2 CBI
2822430	2017, Explodability, DACO: 3.5.1, 3.5.10, 3.5.11, 3.5.12, 3.5.13, 3.5.14,
2937475	2018, Batch Data, DACO: 2.13.3 CBI
2822461	2017, Chemistry: Registrant and molecular information for Intelligro IBA Technical, DACO: 2.1, 2.2, 2.3, 2.3.1, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9
2822462	2017, Manufacturing Summary, DACO: 2.11.1, 2.11.2, 2.11.3, 2.11.4 CBI
2822463	2017, Establishing Certified Limits, DACO: 2.12.1 CBI
2822464	2017, Confirmation Of Identity, DACO: 2.13.1, 2.13.2, 2.13.3, 2.13.4 CBI
2822465	2016, UV/Visible Absorption Spectra, DACO: 2.13.1, 2.13.2, 2.13.3, 2.14.12 CBI
2822466	2017, Sample Of Analytical Stnds And Res Of Conc. DACO: 2.14.1, 2.14.10, 2.14.11, 2.14.12, 2.14.13, 2.14.14, 2.14.15, 2.14.16, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.7, 2.14.8, 2.14.9, 2.15,830.7000 CBI
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2822470	2017, Melting Point/Melting Range, DACO: 2.14.4 CBI
2822471	CDS Tomlin, 2003, 464. 4-Indol-3-ylbutyric acid, in: The Pesticide Manual, Published by the British Crop Protection Council. DACO: 2.14.13, 2.14.7, 2.14.8, 2.14.9
2937474	2018, Detailed Production Process Description, DACO: 2.11.3 CBI
2937476	2018, Batch Data, DACO: 2.13.3 CBI
2937477	2018, UV/Visible Absorption Spectra, DACO: 2.14.10, 2.14.12,
2945421	2018, Description Of Starting Materials, DACO: 2.11.2 CBI

2.0 Human and animal health

PMRA document number	Reference
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2822473	2016, Indole-3-butyric acid (IBA) Acute oral toxicity (UDP) in rats, DACO: 4.2.1
2822474	2016, Indole-3-butyric acid (IBA) Acute Dermal Toxicity in Rats, DACO: 4.2.2
2822475	2017, Acute Inhalation Toxicity for Intelligro IBA Technical , DACO: 4.2.3
2822476	1992, Reregistration Eligibility Document (RED) Indole-3-butyric acid, DACO: 4.2.3,4.2.6
2822477	2016, Indole-3-butyric acid (IBA) Acute eye irrtation in rabbits, DACO: 4.2.4
2822478	2017, Primary Skin Irritation for Intelligro IBA Technical, DACO: 4.2.5
2822479	2016, Indole-3-butyric acid (IBA) 28-day dermal toxicity in rats, DACO: 4.2.5,4.3.4
2822480	2017, Dermal Sensitization for Intelligro IBA Technical, DACO: 4.2.6
2822481	2017, Short-Term Dermal Toxicity for Intelligro IBA Technical, DACO: 4.3.4
2822482	2017, Short-Term Inhalation Toxicity for Intelligro IBA Technical, DACO: 4.3.6
2822483	2016, Indole-3-butyric acid (IBA): a prenatal development toxicity study in rats, DACO: 4.5.2
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2822511	2017, Summary - Toxicology Profile Intelligro CaNa2 EDTA Technical, DACO: 4.1
2822512	2016, Calcium disodium ethylenediaminetetraacetic acid (CaNa2 EDTA) Acute Oral Toxicity (UDP) in Rats, DACO: 4.2.1

PMRA document number	Reference
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2822514	2016, Calcium disodium ethylenediaminetetraacetic acid (CaNa2 EDTA) Acute Inhalation Toxicity in Rats, DACO: 4.2.3
2822515	2017, Primary Eye Irritation - Intelligro CaNa2 EDTA Technical, DACO: 4.2.4
2822516	2016, Calcium disodium ethylenediaminetetraacetic acid (CaNa2 EDTA) Acute Dermal Irritation in Rabbits, DACO: 4.2.5
2822517	2017, Dermal Sensitization - Intelligro CaNa2 EDTA Technical, DACO: 4.2.6
2822518	2016, Calcium disodium ethylenediaminetetraacetic acid (CaNa2 EDTA) 28-day Dermal Toxicity in Rats, DACO: 4.3.4
2822519	2017, Short-Term Dermal Toxicity (90 Day) - Intelligro CaNa2 EDTA Technical, DACO: 4.3.4
2822521	2016, Calcium Disodium Ethylenediaminetetraacetic Acid (CaNa2 EDTA) Dihydrate: A Prenatal Developmental Toxicity Study In Rats, DACO: 4.5.2
2822522	2017, Genotoxicity: Bacterial Reverse Mutation Assay - Intelligro CaNa2 EDTA Technical, DACO: 4.5.4
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2822431	2017, Summary - Toxicology Profile - VNT RTU MFG, DACO: 4.1
2822433	2016, VNT Ready-to-Use Acute Oral Toxicity (UDP) in Rats, DACO: 4.6.1
2822435	2016, VNT Ready-to-Use Acute Dermal Toxicity in Rats, DACO: 4.6.2
2822437	2016, VNT Ready-to-Use Acute Inhalation Toxicity in Rats, DACO: 4.6.3
2822439	2016, VNT Ready-to-Use Acute Eye Irritation in Rabbits, DACO: 4.6.4
2822441	2016, VNT Ready-to-Use Acute Dermal Irritation in Rabbits, DACO: 4.6.5
2822442	2016, VNT Ready-to-Use Skin Sensitization in Guinea Pigs, DACO: 4.6.6
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3.0 Environment

PMRA document number	Reference
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2822385	2017, Environmental Toxicity Summary - VNT Selective Herbicide Ready-to-Use, DACO 9.1
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2822388	2017, Non-target plants: Toxicity to Freshwater algae - VNT Selective Herbicide Ready-to-Use, DACO 9.8.2

4.0 Value

PMRA document number	Reference
2822350	2015, Fall weed control trials with various herbicide formulations, DACO: 10.2.3.3(B).
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B. Additional information considered

i) Published information

1.0 Chemistry: None

2.0 Human and animal health

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3.0 Environment

PMRA document number	Reference
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#	U.S. Environmental Protection Agency. 2017. Final Health Risk Assessment: In Support of Registration of end use product, VNT Selective Herbicide Ready to Use, containing 1.25% w/w Indole-3-butyric acid (IBA) and 2.0% w/w $CaNa_2EDTA$ dihydrate as active ingredients from unregistered sources. DACO: 9.7.1
#	Assessments: In Support of Registration of end use product, VNT Selective Herbicide Ready to Use, containing 1.25% w/w Indole-3-butyric acid (IBA) and 2.0% w/w $CaNa_2EDTA$ dihydrate as active ingredients from unregistered sources. DACO 9.3.2, 9.5.2.1, 9.6.2.1, 9.6.2.4, 9.6.2.5

4.0 Value: None

ii) Unpublished information

None