PRD2007-13

Proposed Registration Decision

Ferric Sodium EDTA

(publié aussi en français)

21 December 2007

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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ISBN: 978-0-662-47515-6 (978-0-662-47516-3)
Catalogue number: H113-9/2007-13E (H113-9/2007-13E-PDF)

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OVERVIEW

Proposed Registration Decision for Ferric Sodium EDTA

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and in accordance with the Pest Control Products Regulations, is proposing full registration for the sale and use of Safer's Ferric Sodium EDTA Technical, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer, containing the technical grade active ingredient ferric sodium EDTA to control slugs and snails in greenhouses and outdoors.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of Safer's Ferric Sodium EDTA Technical, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer.

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 label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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 (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). 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 PMRA regulates pesticides, the assessment process and the risk-reduction programs, please visit the PMRA's website at www.pmra-arla.gc.ca.

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

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

Before making a final registration decision on ferric sodium EDTA, the PMRA will consider all comments received from the public in response to this consultation document.[3] The PMRA will then publish a Registration Decision document[4] on ferric sodium EDTA, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

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

What Is Ferric Sodium EDTA?

Ferric sodium EDTA is a molluscicide used to control slugs and snails in a variety of fruit trees, turf, grasses, vegetables, berries and ornamentals in greenhouses and outdoors. The proposed registration is for one commercial product and one domestic product. While the mode of action is not completely understood, it is known that iron salts are toxic to slugs and snails as a contact and stomach poison.

Health Considerations

Can Approved Uses of Ferric Sodium EDTA Affect Human Health?

Ferric Sodium EDTA is unlikely to affect human health when used according to label directions.

Exposure to ferric sodium EDTA may occur when handling and 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 dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Although the technical grade active ingredient ferric sodium EDTA may cause eye corrosion in animals, given that the end-use products, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer, are in pellet form and contain only 6% ferric sodium EDTA, a precautionary label statement indicating that contact with eyes must be avoided is sufficient. Ferric sodium EDTA did not cause cancer in animals and was not genotoxic. There was also no indication that ferric sodium EDTA causes damage to the nervous system.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html)

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act* (http://laws.justice.gc.ca/en/P-9.01/92455.html)

When a similar chemical compound, disodium EDTA, was given to pregnant animals at a very high dose, effects on the developing fetus were observed at doses that were not toxic to the mother. This indicates that the fetus was more sensitive to disodium EDTA than the adult animal. These effects are believed to be the result of binding of the essential mineral zinc to EDTA in the pregnant animals and not directly due to the EDTA. To reduce the potential for exposure of sensitive populations to ferric sodium EDTA, the statement "Avoid hand-to-mouth contact" is required on the product labels.

Residues in Water and Food

Dietary risks from food and water are not of concern.

The acute toxicity of ferric sodium EDTA is low and there is no indication of genotoxicity, short-term or chronic toxicity, carcinogenicity, neurotoxicity, or reproductive toxicity in animal studies.

The overall low toxicity and proposed use of ferric sodium EDTA is such that risks due to exposure of fruits and vegetables in the diet of the general population, including infants and children, are not of concern.

Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are proposed to be applied to soil surface and not directly to water. Therefore, no risk from exposure to ferric sodium EDTA through drinking water is anticipated. As such, a quantitative assessment of residues in drinking water is not necessary.

The proposed use of ferric sodium EDTA is not expected to result in residues that are of toxicological concern. Therefore, the establishment of a Maximum Residue Limit (MRL) is not required for ferric sodium EDTA under section 4(*d*) of the *Food and Drugs Act* (adulteration of food) as defined under Division B.15.002 of the Food and Drugs Regulations. The Agency is not aware of any country requiring a tolerance for ferric sodium EDTA, nor have any CODEX MRLs been established for any crop. In the U.S., the Environmental Protection Agency has proposed EDTA chemicals be exempt from the requirement of a tolerance in or on raw agricultural commodities.

Occupational Risks From Handling Safer's Slug & Snail Bait and Safer's Slug & Snail Killer

Occupational risks are not of concern when Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are used according to label directions, which include protective measures.

Farmers and pesticide applicators loading or applying Safer's Slug & Snail Bait as well as field workers re-entering freshly treated fields may have direct skin contact with ferric sodium EDTA. Applying Safer's Slug & Snail Killer for domestic purposes can also result in direct skin contact with ferric sodium EDTA. Therefore, the label specifies that hands should be washed with soap and water after handling Safer's Slug & Snail Bait and

Safer's Slug & Snail Killer. Based on this label statement and the expectation that occupational exposure will be brief, these products are not likely to be a concern to farmers, applicators, workers or domestic users.

For bystanders, exposure is expected to be negligible. Therefore, health risks to bystanders are not of concern.

The wheat in Safer's Slug & Snail Killer and Safer's Slug & Snail Bait may be of concern to individuals with wheat sensitivities. Therefore, the pre-cautionary label statement "Warning, contains the allergen wheat" is required.

Environmental Considerations

What Happens When Ferric Sodium EDTA is Introduced Into the Environment?

Ferric sodium EDTA is nonpersistent in aerobic soils, although it is relatively stable in anaerobic soils. Ferric sodium EDTA is soluble in water, where it is rapidly degraded by natural light. No major breakdown products are formed in soil and water. Ferric sodium EDTA or EDTA associated with another metal may leach to groundwater under acidic and sandy soil conditions (pH < 5). Based on its low volatility, ferric sodium EDTA is not expected to enter the atmosphere.

Ferric sodium EDTA is ubiquitous in the environment as a result of its widespread use in detergents, pharmaceuticals, food additives, analytical chemistry, textile, metal treatment and agricultural industries. For the proposed use pattern, negligible ferric sodium EDTA will enter the environment as compared to other industrial, agricultural and domestic uses.

Ferric sodium EDTA is expected to pose negligible risk to terrestrial and aquatic organisms under conditions of use.

Value Considerations

What is the Value of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer?

Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are lower risk alternatives to conventional molluscicides used to control slugs and snails in a variety of vegetable, fruit, grass and ornamental crops in greenhouses and outdoors.

Safer's Ferric Sodium EDTA Technical is to be used in two end-use products: a new commercial class molluscicide, Safer's Slug & Snail Bait and a domestic class molluscicide, Safer's Slug & Snail Killer. Both products are to be applied around various vegetable, fruit, grass and ornamental crops, both in greenhouses and outdoors, to control slugs and snails. The efficacy data demonstrates that slugs and snails can be adequately controlled using Safer's Slug & Snail Bait and Safer's Slug & Snail Killer at the application rate of 11 to 22 kg product/ha.

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 labels of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

- **Human Health**

  Because there is a concern that users coming into direct contact with ferric sodium EDTA on the hands and then transferring it to the eyes, anyone loading, applying or cleaning up after applying Safer's Slug & Snail Bait and Safer's Slug & Snail Killer must wash hands with soap and water after handling.

  To reduce the potential for exposure of sensitive populations from ingestion of ferric sodium EDTA during hand-to-mouth contact, the product label advises against this type of contact.

Next Steps

Before making a final registration decision on ferric sodium EDTA, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision document, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision, and the Agency's response to these comments.

Other Information

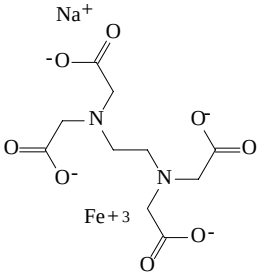
When the PMRA makes its registration decision, it will publish a Registration Decision document on ferric sodium EDTA (based on the Science Evaluation section of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Ferric Sodium EDTA

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance		Ferric Sodium EDTA
Function		Molluscicide
Chemical name		
1.	**International Union of Pure and Applied Chemistry (IUPAC)**	Iron(III) sodium ethylenediamine tetraacetic acid
2.	**Chemical Abstracts Service (CAS)**	[[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']-ferrate(1-), sodium
CAS number		15708-41-5
Molecular formula		$C_{10}H_{12}FeN_2NaO_8$
Molecular weight		367.05
Structural formula		
Purity of the active ingredient		100% nominal (limits: 99–100%)

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Safer's Ferric Sodium EDTA Technical

Property	Result
Colour and physical state	Dark yellow-green powdery solid
Odour	No detectable odour

Property	Result	
Melting range	No melting point observed up to 400°C	
Boiling point or range	TGAI is not a liquid at room temperature	
Density	1.05 g/cm^3 at 20°C	
Vapour pressure at 20°C	No vapour pressure could be measured at or above ranges listed in OPPTS 830.7950 as the product has a melting point of less than 400°C.	
Henry's law constant at 20°C		
Ultraviolet (UV)—visible spectrum	λ_{max} < 300 nm at pH 4, 6, 8 and 10	
Solubility in water at 20°C	90 g/L	
Solubility in organic solvents at 20°C (% w/w))	**Solvent** n-heptane xylene 2,2-dichloroethane methanol isopropanol acetone ethyl acetate	**Solubility** < 0.1 < 0.1 < 0.1 < 0.1 < 0.1 < 0.1 < 0.1
n-Octanol–water partition coefficient (K_{ow})	The product has a solubility in n-octane of less than 0.1% w/w. Therefore, the partition coefficient for octanol/water over a pH range of 4 to 9 is less than 0.005	
Dissociation constant (pK_a)	pK_1 = 1.99 pK_2 = 2.67 pK_3 = 6.16 pK_4 = 10.29	
Stability (temperature, metal)	No significant changes greater than 5% from the mean control samples were observed when the test material was placed in direct contact with copper sulphate, zinc sulphate, copper shot and zinc at ambient and elevated temperatures for 0 to 14 days.	

End-use Product — Safer's Slug & Snail Bait and Safer's Slug & Snail Killer

Property	Safer's Slug & Snail Bait	Safer's Slug & Snail Killer
Colour	Rust	Rust
Odour	Flour-like odour of mild intensity	Flour-like odour of mild intensity
Physical state	Solid	Solid
Formulation type	Pellets	Pellets
Guarantee	6.0% nominal (limits: 5.70%–6.30%)	6.0% nominal (limits: 5.70%–6.30%)

Property	Safer's Slug & Snail Bait	Safer's Slug & Snail Killer
Container material and description	Nylon-lined paper bags, 1kg	Nylon-lined paper bags, 1kg
Density	0.76 g/mL	0.76 g/mL
pH of 1% dispersion in water	6.63 at 20°C	6.63 at 20°C
Oxidizing or reducing action	The product does not contain any oxidizing or reducing agents.	The product does not contain any oxidizing or reducing agents.
Storage stability	Not provided	Not provided
Explodability	The product is not potentially explosive.	The product is not potentially explosive.

1.3 Directions for Use

The commercial class end-use product, Safer's Slug & Snail Bait, controls slugs and snails in various vegetable, fruit, grass and ornamental crops in greenhouses and outdoors. For most uses, Safer's Slug & Snail Bait is to be applied at an application rate of 11 to 22 kg product/ha, with application of the higher rate when pest pressure is elevated. For greenhouse vegetables and ornamentals, the product is to be applied at a rate of 2 g product/m^2 or 1g product/10 pots measuring 23 cm in diameter. For outdoor container-grown nursery plants, the application rate is 2 g product/m^2 or 3 g product/10 pots measuring 46 cm in diameter. For outdoor ornamentals and turf, the application rate is 2 g product/m^2. The product may be reapplied as the bait is consumed or at 14-day intervals if slugs and snails continue to be a problem.

The domestic class product, Safer's Slug & Snail Killer, controls slugs and snails in vegetables, orchard fruits, berries, ornamentals (shrubs, flowers, trees) and lawns. The end-use product can be used both outdoors and in greenhouses at an application rate of 2 g product/m^2. The product may be reapplied as the bait is consumed or at 14-day intervals if slugs and snails continue to be a problem.

1.4 Mode of Action

While the mode of action is not completely understood, it is known that iron salts are toxic to slugs and snails as a contact and stomach poison.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Technical Grade of Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Safer's Ferric Sodium EDTA Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulations Analysis

The method provided for the analysis of the active ingredient in the formulations has been validated and assessed to be acceptable for use as an enforcement analytical method.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The PMRA has conducted a detailed review of the submitted data and publicly available toxicological information for ferric sodium EDTA. The database is considered adequate, consisting of the full array of laboratory animal (in vivo) and cell culture (in vitro) toxicity studies and waivers for specific elements of information currently required for health hazard assessment purposes. The submitted toxicology studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is such that the database is considered adequate to qualitatively assess the toxicological hazards of this pest control product.

Ferric sodium EDTA is of low acute toxicity by the oral, dermal and inhalation routes in Sprague Dawley rats. It was slightly irritating to the skin and corrosive to the eyes in one of three New Zealand albino rabbits. Results of skin sensitization testing in Dunkin-Hartley albino guinea pigs using the Buehler method were negative.

The available acute toxicity data and irritation information for the technical grade active ingredient (TGAI) were used to estimate the acute toxicity and irritation of both Safer's Slug & Snail Bait and Safer's Slug & Snail Killer end-use products. It is anticipated that the acute toxicity will be low for both end-use products, regardless of the route of exposure. The end-use products are anticipated to be minimally irritating to the skin and neither are likely to be skin sensitizers. It is not possible to determine the eye irritation or potential for corrosion of either end-use product, based on the absence of product testing, but results for the TGAI showed it to be corrosive to eyes. There is the potential for an allergic reaction in sensitive individuals exposed to Safer's Slug & Snail Bait and Safer's Slug & Snail Killer because the formulations contain the allergen wheat.

Swine exposed to radiolabelled ferric sodium EDTA (5 mg introduced into the esophagus) resulted in 95% recovery in the feces and 0.3% in the urine. Absorption of a single, nonlethal, oral dose of ferric sodium EDTA introduced into the esophagus was anticipated to be poor, with nearly complete excretion in the feces. Metabolism of ferric sodium EDTA is anticipated to be negligible, based on a review of published scientific information.

The requirement for a short-term study was waived on the strength of the chronic toxicity information for similar compounds below.

Published literature demonstrating the chronic toxicity potential of ferric sodium EDTA was not available for evaluation. However, information on the chronic effects of similar compounds was considered in lieu of actual data. Fischer 344 rats and B6C3F1 mice fed trisodium EDTA in their diets for 103 weeks did not show any treatment-related signs of toxicity at any of the dose levels tested or any treatment-related tumours.

Likewise, in a chronic toxicity study performed on mongrel dogs, calcium sodium EDTA fed to the animals for one year did not result in any treatment-related effects at any of the dose levels tested.

Publicly available information suggests that normal individuals are capable of controlling iron absorption and that chronic toxicity (i.e. hemochromotosis) is generally limited to individuals with inherited metabolic disorders affecting maintenance of iron balance in the body.

Administration of a large quantity of disodium EDTA (954 mg/kg bw/day) in the diet of pregnant CD rats (day 7 through 14 of gestation) resulted in maternal effects marked by weight loss, decreased food consumption and diarrhea in all test animals. Gross fetal malformations included cleft palate, micrognathia, microphthalmia, menigocoele, phocomelia, clubfoot and electrodactyly, umbilical hernia, and short curly tail. Internal malformations were identified as great vessel anomalies, interventricular septal defects, small or missing lung lobes, missing thymus, small kidneys with associated hydronephrosis and hydroureter, and small undifferentiated gonads lateral to the kidneys. Skeletal malformations included extreme dysplasia, including shortened, missing or wavy ribs, misaligned and fused centra, as well as anomalies associated with external defects. Gross external brain malformations were also noted. There was also a significant increase in the mean percentage of fetal resorptions per litter and mean percentage of malformed fetuses per litter. The average fetal weight was also significantly reduced. Since only one dose of disodium EDTA was assessed, it was not possible to identify an appropriate no observed adverse effect level (NOAEL).

When disodium EDTA (3% by weight) was added to the diet of pregnant Sprague Dawley rats from days 6 to 14 of gestation or from day 6 to term, the majority of fetuses were grossly malformed. When the diet of exposed rats was supplemented with zinc (1000 ppm), no fetal malformations were noted, suggesting that the malformations were not directly caused by EDTA but were the result of secondary effects due to sequestering of zinc required for normal fetal development.

In short, the published sources of information suggest that oral administration of EDTA to rodents will result in significant teratogenic effects. With the available information, it cannot be definitively ascertained whether this is a direct result of the presence of EDTA or of EDTA binding with an essential component such as zinc, required for normal fetal development. There was evidence of genotoxic potential of ferric sodium EDTA in mouse lymphoma cells in the presence and absence of metabolic activation. It should be noted, however, that it is anticipated that the Fe and EDTA will dissociate in solution and that Fe uptake by a transferrin-independent transport system requires reduction of Fe^{3+} to Fe^{2+} at the cell surface. The ferrous ion is then subject to a Fenton reaction.

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH + OH^-$$

The hydroxyl free radical is expected to attack the DNA, resulting in the observed genotoxicity. The genotoxic reaction is therefore likely to be an indirect result of iron and not of the ferric sodium EDTA.

There was no evidence of genotoxicity/mutagenicity when trisodium EDTA was tested in mouse lymphoma cells, *Salmonella typhimurium* strains (TA98, TA100, TA1535, TA1537, and TA1538) with and without metabolic activation, or *Escherichia coli* WP uvrA. This suggests that the EDTA moiety is not mutagenic/genotoxic and that ferric sodium EDTA is not likely to be mutagenic/genotoxic.

An evaluation of available literature suggests that ferric sodium EDTA is not expected to be neurotoxic.

3.2 Determination of Acceptable Daily Intake

As indicated in Section 3.4.5, the promulgation of an MRL for ferric sodium EDTA is not required. Thus, a value for an acceptable daily intake was not necessary.

3.3 Determination of Acute Reference Dose

A NOAEL could not be determined from the administration of a single dose of ferric sodium EDTA, regardless of the route of exposure. Therefore, an acute reference dose could not be set.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to either Safer's Slug & Snail Bait or Safer's Slug & Snail Killer is expected to be short-term and predominantly by the dermal route when pellets are handled during application. Inhalation of loose particles is also possible but is likely to only be a minor route of exposure. A developmental study demonstrated that administration of disodium EDTA in the diet (954 mg of EDTA/kg bw/day) to pregnant CD rats (day 7 through 14 of gestation) resulted in gross, internal and skeletal malformations in the fetuses. There was also a significant increase in the mean percentage of resorption per litter and mean percentage of malformed fetuses per litter. A NOAEL could not be identified as only one concentration of disodium EDTA was tested. Although a margin of exposure could not be estimated with available information, it is not expected that exposure to the end-use products in pellet form, as per label instructions, will result in any significant potential for adverse effects. An accidental ingestion of the end-use products by a pregnant animal (human or companion pet) may result in the adverse effects noted above. The publicly available information supports the position that ferric sodium EDTA is unlikely to have any chronic or nervous system toxicity or to be classified as a carcinogen or genotoxicant.

In lieu of insufficient information regarding the potential for developmental toxicity necessary to calculate an MOE, mitigation will be proposed such that the statements **"Avoid contact with skin, eyes, and clothing"** and **"Avoid hand-to-mouth contact"** be included in the **PRECAUTIONS** section of the draft label.

Note that the developmental toxicity noted in the test animal study was not a primary effect of ferric sodium EDTA but the result of zinc sequestering by EDTA in the animal, that is, the developmental toxicity appears to be a secondary effect.

3.4.2 Dermal Absorption

Since the available published literature suggests a negligible dermal absorption of the administered dose and since adequate hygiene statements have been placed on the product label, a dermal absorption study was not considered necessary to complete the health hazard assessment of ferric sodium EDTA.

3.4.3 Mixer, Loader and Applicator Exposure and Risk Assessment

Significant exposure to the loader and applicator is not anticipated based on the physical properties of the pellets and the mitigating statements on the product label. As such, an operator exposure assessment was not performed.

3.4.4 Bystander Exposure and Risk Assessment

Significant exposure to bystanders is not anticipated due to the physical properties of the pellets and due to the mitigating statements on the product label. As such, a bystander exposure assessment was not performed.

3.4.5 Food Residue Exposure Assessment

Section 3.1 details the overall toxicity of ferric sodium EDTA and demonstrates that the active ingredient is of low acute toxicity. Aside from being categorized as mildly irritating to the skin and corrosive to eyes, ferric sodium EDTA is not genotoxic, carcinogenic or considered to have any significant effect with respect to short-term chronic toxicity and reproductive toxicity. Based on short- and long-term clinical observations and on the structure and associated functional groups of ferric sodium EDTA, it is not expected that the active ingredient will be neurotoxic. It should also be noted that although developmental toxicity was associated with ingestion of an EDTA complex in rodents, the amount necessary to elicit this effect was excessive and above exposure levels expected from the proposed use of the end-use products.

The proposed application of both Safer's Slug & Snail Bait and Safer's Slug & Snail Killer is to the soil surface and not directly to water. It is therefore anticipated that there will be no risk from exposure to ferric sodium EDTA in drinking water. As such, a quantitative assessment of residues in drinking water is not necessary.

The pelleted end-use product is applied on top of the soil and is not likely to come in contact with foods such as fruits and vegetables. The risk due to exposure from the diet is therefore considered negligible.

Ferric sodium EDTA falls under the category of a mineral nutrient as per the definition in Part D, Division 2 of the Food and Drug Regulations and may also be exempt from the status of agricultural chemical as per the definitions provided in Part B, Division 1 of the Food and Drug Regulations. Ferric sodium EDTA has also been listed as a micronutrient component of fertilizers and may also be exempt from the adulteration provisions of food, as per Division 15, Part B.15.002(2)(a) of the Food and Drug Regulations.

When used as proposed, ferric sodium EDTA would not result in residues that are of toxicological concern. As such, promulgation of maximum residue limits for ferric sodium EDTA is not necessary. The Agency is not aware of any country requiring a tolerance for ferric sodium EDTA, nor have any CODEX MRLs been established for any crop. In the U.S., the Environmental Protection Agency has proposed exempting EDTA chemicals from the requirement of a tolerance in or on agricultural commodities.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Ferric sodium EDTA is soluble in water and will not bioaccumulate. Based on the vapour pressure (2×10^{-12} mm Hg) and Henry's law constant (7.7×10^{-16} atm $\times$ m^3/mol) of EDTA, its organic component, ferric sodium EDTA is expected to be relatively nonvolatile from water and moist surfaces under field conditions. Ferric sodium EDTA is mobile under some environmental conditions. However, it is expected to be readily biotransformed under environmental conditions in aerobic soil, reducing its potential to leach to groundwater. In acidic soil, ferric sodium EDTA is resistant to biotransformation and is relatively stable to transformation in anaerobic soil. Ferric sodium EDTA is rapidly phototransformed by natural light in water and is degraded by a mixed population of aerobic aquatic microorganisms.

Data on the fate and behaviour of ferric sodium EDTA are summarized in Table 2 of Appendix I.

4.2 Effects on Nontarget Species

Risk characterization integrates environmental exposure and ecotoxicology data to estimate the potential for adverse effects on nontarget species. A deterministic quotient method is used where appropriate. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity endpoint. A screening-level risk assessment is initially performed using the expected environmental concentrations (EECs) for a conservative scenario and the most sensitive toxicity endpoint. Negligible risk is predicted if the RQ is less than the level of concern (LOC) of one. In these cases, no further assessment is done. For those groups of organisms for which the RQ is greater than one, a refined assessment is undertaken. A refined assessment takes into consideration more realistic exposure scenarios and may consider additional toxicity endpoints.

4.2.1 Effects on Terrestrial Organisms

An original avian acute oral toxicity study was submitted based on the potential for birds to consume ferric sodium EDTA through feeding on end-use products Safer's Slug & Snail Bait and Safer's Slug & Snail Killer, which are applied in pellet form. Waiver requests for most of the data requirements were submitted and were based on the claim that ferric sodium EDTA would only target the copper-based blood system (with hemocyanin as an oxygen carrier), found in crustaceans and molluscs. Data on invertebrates were submitted in support of this claim. Waiver requests and data were deemed acceptable. Data for terrestrial organisms is summarized in Table 3 of Appendix I.

4.2.1.1 Birds

The risk to birds was assessed using the acute oral toxicity of ferric sodium EDTA to the Northern bobwhite (*Colinus Virginianus*) assuming exposure through direct consumption of pellet bait. The screening level risk assessment indicated that there was a potential risk (RQ > LOC) to birds that directly consume Safer's Slug & Snail Bait and Safer's Slug & Snail Killer (Table 4 and Table 5 of Appendix I). However, wild birds might have limited access to the pellets since the pellets will be scattered only in areas of infestation in damp, shady places around plants where birds are expected to spend limited time. According to the label, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are applied to soil while the ground is moist, in early morning, late evening or after rainfall. Additionally, the large diameter of the pellets (1.6 mm to 6.4 mm, averaging 4.8 mm) indicates that they are unlikely to be consumed by small birds. Larger birds, such as gulls, crows, and pheasants, could consume the pellets but must consume a significant number of pellets (over 200) to reach a potentially toxic dose; consumption of this number of pellets is unlikely. Therefore, considering the proposed use pattern in damp shady areas, the size of the pellets, and the large number of pellets that would need to be consumed to reach a potentially toxic dose, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are expected to pose a minimal risk to wild birds.

4.2.1.2 Invertebrates

The proposed use of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer is expected to target pill bugs, crustaceans and molluscs, but will not pose a risk to beneficial insects such as *N. gravis* and *D. bellulus* (Table 3 of Appendix I). Other invertebrates using haemocyanin as an oxygen carrier—including stoneflies, the Entognatha, and most hemimetabolan taxa, some of which are beneficial arthropods (Hagner-Holler et al. 2004)—are expected to be targeted by ferric sodium EDTA. However, the limited use pattern of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer is not expected to impact populations of those beneficial insects.

4.2.2 Effects on Aquatic Organisms

No data were submitted by the registrant addressing potential toxic effects of ferric sodium EDTA on aquatic organisms (invertebrates, fish, plants). While ferric sodium EDTA is expected to be toxic to aquatic organisms with haemocyanin blood systems, such as daphnia, crabs, crayfish, lobsters and shrimp, it is expected to pose negligible risk under conditions of field use, as there is negligible potential for exposure.

5.0 Value

5.1 Effectiveness Against Pests

Four small-scale outdoor field trials were submitted that examined the efficacy of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer to control slugs and snails in the presence of alternative food sources (strawberries, petunias, lettuce). The efficacy trials tested application rates between 6 and 45 kg product per hectare on garden snails (*Helix aspersa*) and two slug species (*Arion fasciatus* and *Agriolimax reticulates*). The efficacy data demonstrated that adequate control of slugs and snails is obtained using Safer's Slug & Snail Bait and Safer's Slug & Snail Killer at the application rate of 11 to 22 kg product/ha. Higher application rates should be used at higher pest pressures. In trials where plant damage was assessed, there were lower levels of plant damage in petunias and higher yields of lettuce compared to the untreated control.

5.1.1 Acceptable Efficacy Claims

Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are to be used to control slugs and snails in various vegetable, fruit, grass and ornamental crops in greenhouses and outdoors. Both end-use products are to be scattered at an application rate of 11 to 22 kg/ha or equivalent to protect plants from slugs and snails. The product may be reapplied as the bait is consumed or at 14-day intervals if slugs and snails continue to be a problem. For further details, refer to Table 5.1.1.1, Acceptable uses and application rates for Safer's Slug & Snail Bait and Safer's Slug & Snail Killer.

Table 5.1.1.1 Acceptable uses and application rates for Safer's Slug & Snail Bait and Safer's Slug & Snail Killer

Product	Pest	Use Sites	Application Rate	Remarks
Safer's Slug & Snail Bait (Commercial)	Slugs and Snails	vegetables, orchard fruits, berries, field crops, vineyards, wheat, grass grown for seed production	11-22 kg/ha*	*Use the higher application rate at higher pest pressures. The product may be reapplied as the bait is consumed or at 14-day intervals if slugs and snails continue to be a problem.
		greenhouse vegetables and greenhouse ornamentals	2 g/m^2 or 1 g/10 pots measuring 23 cm in diameter	
		outdoor container-grown nursery stock	2 g/m^2 or 3 g/10 pots measuring 46 cm in diameter	
		turf, golf courses, sod farms	2 g/m^2	
Safer's Slug & Snail Killer (Domestic)	Slugs and Snails	vegetables, orchard fruits, berries, ornamentals (shrubs, flowers, trees) and lawns, in greenhouses and outdoors	2 g/m^2	The product may be reapplied as the bait is consumed or at 14-day intervals if slugs and snails continue to be a problem.

5.2 Phytotoxicity to Host Plants

It is unlikely that the application of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer will result in phytotoxicity to host plants. No phytotoxic effects were observed in the efficacy trials and ferric sodium EDTA is used as a micronutrient in some fertilizers. A phytotoxicity warning statement was added to the labels of the end-use products because of the extensive diversity of crops being treated.

5.3 Impact on Succeeding Crops

It is unlikely that the application of Safer's Slug & Snail Bait and Safer's Slug & Snail Killer will impact succeeding crops.

5.4 Economics

No information was provided.

5.5 Sustainability

5.5.1 Survey of Alternatives

Several active ingredients are registered to control slugs and snails, including silicon dioxide present as diatomaceous earth, metaldehyde and ferric phosphate. Non-chemical practices used to control slugs and snails include hand removal of the pest, traps, habitat modification (e.g. removal of vegetable refuse, leaves, weeds, bricks, boards and other places slugs and snails may live) and barriers (e.g. copper wires, eggshells). Refer to Table 6 for further information on alternatives.

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

The two end-use products, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer, are considered to be lower risk alternatives to conventional molluscicides. These products could be used in conjunction with current slug and snail control practices, such as removal of habitat, barriers, traps and hand removal of the pest.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Resistance to ferric sodium EDTA is unlikely.

5.5.4 Contribution to Risk Reduction and Sustainability

Safer's Slug & Snail Bait and Safer's Slug & Snail Killer provides an alternative to conventional molluscicides used to protect a variety of vegetable, fruit, grass and ornamental crops from slugs and snails in greenhouses or outdoors.

6.0 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy, which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

During the review process, ferric sodium EDTA was assessed in accordance with the PMRA Regulatory Directive DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*. Substances associated with the use of

ferric sodium EDTA were also considered, including major transformation products formed in the environment, microcontaminants in the technical product and formulants in end-use products Safer's Slug & Snail Bait and Safer's Slug & Snail Killer. The PMRA has reached the following conclusions:

1. Ferric sodium EDTA is not expected to be persistent and is not bioaccumulative. The octanol-water partition coefficient (log K_{ow}) is less than 0.005, which is below the TSMP Track 1 cut-off criterion of greater than or equal to 5.0.

2. Ferric sodium EDTA does not form any major transformation products that meet the TSMP Track 1 criteria.

3. Ferric sodium EDTA (technical grade) does not contain any by-products or microcontaminants that meet the TSMP Track 1 criteria. Impurities of toxicological concern are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process.

4. Ferric sodium EDTA does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

5. Safer's Slug & Snail Bait and Safer's Slug & Snail Killer do not contain any formulants of health or environmental concern identified in the *Canada Gazette*, Part II, Volume 139, Number 24, pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

Therefore, the use of ferric sodium EDTA is not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Human Health and Safety

The available information for ferric sodium EDTA is adequate to qualitatively define the majority of toxic effects that may result from human exposure to ferric sodium EDTA. Eye corrosion was observed in a single laboratory animal exposed to ferric sodium EDTA. As well, fetal malformations occurred in cases where an excessive amount of disodium EDTA, a compound chemically similar to ferric sodium EDTA, was ingested by pregnant animals. No other toxicologically significant effects were observed in any other available studies for ferric sodium EDTA.

Loaders, applicators, workers and bystanders entering treated areas are not expected to be exposed to levels of ferric sodium EDTA that will result in an unacceptable risk when Safer's Slug & Snail Bait and Safer's Slug & Snail Killer are used according to label directions.

The precautionary statements on the product labels are adequate to protect workers and bystanders, and no additional personal protective equipment is required.

Because ferric sodium EDTA is of low toxicity, does not represent a risk due to exposure from the diet or drinking water, may be considered a mineral nutrient, may be exempt from the status of agricultural chemical, has been listed as a micronutrient component of fertilizers, and may be exempt from the adulteration provisions of food in the Food and Drug Regulations, promulgation of an MRL is unnecessary.

The Agency is not aware of any country requiring a tolerance for ferric sodium EDTA nor have any CODEX MRLs been established for any crop. In the U.S., the Environmental Protection Agency has proposed that EDTA chemicals be exempt from the requirement of a tolerance in or on raw agricultural commodities.

Supervision of children around areas containing Safer's Slug & Snail Bait and Safer's Slug & Snail Killer is suggested, especially in cases where an individual is allergic to wheat. Accidental ingestion may result in an allergic reaction.

7.2 Environmental Risk

Based on the use pattern for ferric sodium EDTA as pelleted bait around ornamentals, vegetables, fruit crops, shrubs and crops in greenhouses, or on lawns and gardens, ferric sodium EDTA presents a negligible risk to nontarget terrestrial and aquatic organisms.

7.3 Value

The data submitted to register Safer's Slug & Snail Bait and Safer's Slug & Snail Killer demonstrates that the end-use products will control slugs and snails in the presence of an alternative food source. The product may be reapplied as the bait is consumed or at 14-day intervals if slugs and snails continue to be a problem. These products are lower risk alternatives to conventional molluscicides.

7.4 Unsupported Uses

All uses proposed by the applicant were supported from an efficacy perspective.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing full registration for the sale and use of the technical grade active ingredient ferric sodium EDTA and the end-use products, Safer's Slug & Snail Bait and Safer's Slug & Snail Killer, to control slugs and snails in greenhouses and outdoors. An evaluation of current scientific data from the applicant and scientific reports has resulted in the determination that, under the proposed conditions of use, the end-use product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
1/n	exponent for the Freundlich isotherm
a.i.	active ingredient
ADI	acceptable daily intake
ALS	acetolactate synthase
ARD	acute reference dose
atm	atmosphere
bw	body weight
CAS	chemical abstracts service
cm	centimetre(s)
d	day
DF	dry flowable
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in the test population)
DT_{75}	dissipation time 75% (the dose required to observe a 75% decline in the test population)
dw	dry weight
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EDE	estimated daily exposure
EEC	Expected environmental concentration
ER_{25}	effective rate for 25% of the population
Fe	iron
FeNaEDTA	ferric sodium EDTA
g	gram
ha	hectare(s)
HDT	highest dose tested
Hg	mercury
HPLC	high performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_d	soil-water partition coefficient
$K_{d\text{-}ads}$	soil-water adsorption coefficient
K_F	Freundlich adsorption coefficient
km	kilometre(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*-octanol–water partition coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LOAEL	lowest observed adverse effect level
LOC	level of concern
LOEC	low observed effect concentration
LOQ	limit of quantitation

LR_{50}	lethal rate 50%
m	metre(s)
mg	milligram(s)
mL	millilitre(s)
mm	millimetre(s)
MAS	maximum average score
MIS	maximum irritation score
MOE	margin of exposure
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
NOER	no observed effect rate
N/R	not required
NZW	New Zealand white
OC	organic carbon content
OM	organic matter content
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppm	parts per million
RSD	relative standard deviation
RQ	risk quotient
SC	soluble concentrate
$t_{1/2}$	half-life
T3	tri-iodothyronine
T4	thyroxine
TGAI	technical grade active ingredient
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UAN	urea ammonium nitrate
UF	uncertainty factor
µg	microgram(s)
µL	microlitre(s)
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution
w/w	weight per weight

Appendix I Tables and Figures

Table 1 Toxicity Profile of Technical Ferric Sodium EDTA

METABOLISM
Absorption of FeNa^{55}[2-^{14}C]EDTA in swine (5 mg introduced into the esophagus) demonstrated a rapid transfer of ^{55}Fe to the plasma pool (peak at 1 hour) and subsequent incorporation of 4.6% of the orally administered dose into the circulating hemoglobin. 0.3% of the administered ^{55}Fe was excreted in the urine and 95% remains unabsorbed and excreted via the feces (3% in a soluble form, e.g. FeEDTA, and 92% in an insoluble form). Very little ^{14}C[EDTA] could be detected in the plasma at any time. Approximately 5% of the administered dose of ^{14}C[EDTA] was absorbed by mucosal cells of the pylorus and upper jejunum portion of the digestive tract (5–20 hours) and quantitatively excreted in the urine. The literature points out that Fe dissociates from EDTA prior to being absorbed and that the Fe is absorbed by the normal pathway for Fe uptake. Intravenous injection of FeNaEDTA into rats resulted in 70–90% of the iron being excreted in the urine within 24 hours, with a small portion to be used in hemoglobin synthesis from the iron pool in the body. The available information suggests that neither Fe or EDTA undergo biotransformation to any significant degree, but are excreted unchanged after oral administration of FeNaEDTA. The data also suggests that EDTA metal complexes are rapidly excreted and not likely to accumulate.

STUDY	SPECIES, STRAIN AND DOSES	NOAEL AND LOAEL mg/kg bw/day	TARGET ORGAN, SIGNIFICANT EFFECTS, COMMENTS
ACUTE STUDIES - TECHNICAL			
Oral	Sprague Dawley Rats Dose: 3900, 5000 and 6300 mg/kg bw	LD_{50} (♂♀) > 5000 mg/kg bw	**Low toxicity** Significant effects greater than or equal to 5000 mg/kg include ano-genital staining, hypoactivity, hunched posture, soft feces and diarrhea as well as lung, liver, and intestinal discolouration for both male and female test animals in the mid- and high-dose groups.
Dermal	Sprague Dawley Rats Dose: 5000 mg/kg bw	LD_{50} (♂♀) > 5000 mg/kg bw	**Low toxicity**
Inhalation	Sprague Dawley Rats Dose: 2.05 mg/L	LC_{50} (♂♀) > 2.0 mg/L	**Low toxicity**
Skin Irritation	New Zealand Albino Rabbits (1♂ and 2♀) Dose: 0.56 g dry paste of ferric sodium EDTA (90% w/w with distilled water)	MAS = 0/8 (24, 48 and 72 hrs) MIS = 1.0/8 (24 hrs)	**Slightly irritating** Based on MIS of 1.0/8 at 24 hours.

Eye Irritation	New Zealand Albino Rabbits (1♂ and 2♀) Dose: 0.1 g	MAS = 9/110 (24, 48 and 72 hrs) MIS = 12/110 (24 hrs) Irreversible corneal opacity in the male rabbit at 21 days.	**Extremely corrosive or irritating** **Irreversible within 21 days** Based on corneal opacity in the male at 21 days.
Skin Sensitization (Buehler Method)	Albino Hartley Guinea Pigs (8♂ & 12♀) Induction dose: 0.4 g of Sodium Ferric EDTA (80 % w/w with distilled water) Challenge dose: 0.4 g of Sodium Ferric EDTA (75 % w/w with distilled water)	Negative results	**Negative skin sensitizer**
ACUTE STUDIES - FORMULATION [Safer's Slug & Snail Bait] N.B. The acute information for the TGAI was used as surrogate information for this EP.			
ACUTE STUDIES - FORMULATION [Safer's Slug & Snail Killer] N.B. The acute information for the TGAI was used as surrogate information for this EP.			
SHORT-TERM TOXICITY			
61-day dietary	0, 35, 70 and 140 mg/kg FeNaEDTA in the diet 0, 2.8, 5.7 and 11 mg Fe/kg BW/day Sprague Dawley Crl:CD BR rats (40 ♂ per dose group; 20 sacrificed at day 31 and 20 at termination)	Could not identify an NOAEL or LOAEL from the available information.	↑ non-haem iron in liver, spleen, and kidneys after 31 and 61 days (concentration not disclosed). Accumulation of iron in the spleen was confined to the red pulp (concentration not disclosed).
90-day dietary	0, 1, 5, and 10% Na_2H_2EDTA in the diet Holtzman rats (10 ♂ per dose group)	NOAEL 1% Na_2H_2EDTA LOAEL 5% Na_2H_2EDTA	1.0%: 47–118 mg/kg bw/day; 5.0%: 337–627 mg/kg bw/day; 10.0%: 596–1429 mg/kg bw/day. ↓ bw gain in the 5 and 10% groups. Diarrhea throughout study in the 5 and 10% groups. Priapism (10/10) in the 10% group and (2/10) in the 5% group. Mortality (2/10) in the 5% group and 6/10 in the 10% group.

CHRONIC TOXICITY AND ONCOGENICITY			
1-year dietary	0, 58, 130 and 338 mg/kg bw/day Ca_2Na_2EDTA Mongrel dogs (4 per dose)	NOAEL 338 mg/kg bw/day Ca_2Na_2EDTA	No significant treatment-related effects.
103-week dietary	0, 3750 and 7500 ppm Na_3EDTA in diet B6C3F1 mice and Fischer 344 rats (50 ♂ and 50 ♀ for mid- and high-dose groups, 20 ♂ and 20 ♀ for the control group)	NOAEL (♂♀) 7500 ppm Na_3EDTA	No treatment-related effects.
REPRODUCTION AND DEVELOPMENTAL TOXICITY			
Single generation	F_0: 0, 0.5, 1 and 5% Na_2EDTA in diet for 12 weeks. Rats (number per dose not disclosed)	NOAEL 1% Na_2EDTA LOAEL 5% Na_2EDTA	Animals mated once they were 100 days old and 10 days after weaning. Diarrhea and ↓ food consumption at 5%. Test animals produced normal first and second litters, except at 5%, where dams failed to produce litters.

Developmental toxicity	0 and 954 mg of EDTA/kg bw/day in diet for days 7 to 14 of gestation. Administered Na_2EDTA. CD rats	NOAEL < 954 mg of EDTA/kg bw/day LOAEL 954 mg of EDTA/kg bw/day	<u>Maternal Toxicity</u> ↑ weight loss ($p < 0.001$) ↓ food consumption ($p < 0.001$) Severe diarrhea in all animals <u>Fetal Toxicity</u> ↓ fetal weight ($p < 0.001$) ↑ mean percentage of resorptions/litter ($p < 0.001$) ↑ mean percentage of malformed fetuses/litter ($p < 0.001$) Gross fetal malformations marked by cleft palate, micrognathia, microphthalmia, menigocoele, phocomelia, clubfoot and electrodactyly, umbilical hernia, and short curly tail. Internal malformations included great vessel anomalies, interventricular septal defects, small or missing lung lobes, missing thymus, small kidneys with associated hydronephrosis and hydroureter, and small undifferentiated gonads lateral to the kidneys. Skeletal malformations included extreme dysplasia, including shortened, missing or wavy ribs, misaligned and fused centra, as well as anomalies associated with external defects. Gross external brain malformations were also noted.
Developmental toxicity	3% (w/w) of Na_2EDTA in diet from day 6 to 14 of gestation or from day 6 to term. Sprague Dawley rats	Could not identify a NOAEL or LOAEL from the available information.	<u>Addition of 100 ppm zinc to the diet</u> Gross fetal malformations marked by cleft lip and palate, hydrocephalus, anencephalus, hydranencephalus, exencephalus, micro or anophthalimia, micro or agnathia, clubbed legs, fused or missing digits, curly, short or missing tail were noted in a significant portion of the fetuses. <u>Addition of 1000 ppm zinc to the diet</u> No fetal malformations observed.

GENOTOXICITY		
STUDY	**SPECIES and STRAIN or CELL TYPE AND CONCENTRATIONS or DOSES**	**RESULTS**
Gene mutations in bacteria	*Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538; *E. Coli* WP2uvrA Up to 1000 µg/plate without activation Up to 1000 µg/plate with activation	Negative for Na_3EDTA.
Gene mutations in mammalian cells in vitro	L5178Y TK +/- mouse lymphoma cells 0–5000 µg/ml without activation 0–5000 µg/ml with activation	Negative for Na_3EDTA.
Gene mutations in mammalian cells in vitro	L5178Y TK +/- mouse lymphoma cells 0–325 µg Fe/mL without activation 0–6.5 µg Fe/mL with activation	Positive for NaFeEDTA. Likely due to hydroxyl free radical produced from Fenton reaction of the available iron, not the direct result of NaFeEDTA.

Compound-Induced Mortality: Mortality was observed as a compound-induced effect in the 90-day short-term study at 5.0 (337–627 mg/kg bw/day) and 10.0% (596–1429 mg/kg bw/day) Na_2H_2EDTA in the diet.

Recommended ARD: As a result of a lack of an acute NOAEL, the ARD was not calculated.

Recommended ADI: Since an MRL will not be promulgated, the ADI was not calculated.
MOE for other critical endpoint(s): Although an MOE was not calculated, consideration must be provided for reproduction/developmental toxicity as a critical endpoint.

Tox Endpoints for Occupational Risk Assessment:

Reproduction and developmental toxicity
In lieu of insufficient information regarding the potential for developmental toxicity necessary to calculate an MOE, mitigation will be proposed such that the statements **"Avoid contact with skin, eyes, and clothing"** and **"Avoid hand-to-mouth contact"** be included in the **PRECAUTIONS** section of the draft label.

Note that the developmental toxicity noted in the test animal study was not a primary effect of the ferric sodium EDTA but the result of zinc sequestering by EDTA in the animal, i.e. developmental toxicity appears to be a secondary effect.

Table 2 Fate and Behaviour in the Environment

Property	Test Substance	Value		Comments	Reference (PMRA #)
Biotransformation in terrestrial system (after 30 days)					
Biotransformation in aerobic soil Study carried out in aerated soil suspensions from 5 types of soils of different pHs.	FeEDTA Reaction between Fe and Na ^{14}C-labelled EDTA	pH 5.7 and 6.1 pH 6.75 pH 7.3 and 7.85	75–90% remaining 15–20% remaining <5% remaining	persistent slightly persistent nonpersistent	1122092 Norvell and Lindsay (1969)
Biotransformation in anaerobic soil Study carried out in anaerobic soils from 3 types of agricultural soils of different pHs.	FeEDTA Reaction between $FeCl_3$ salt and [^{14}C]EDTA	pH 6.0 pH 6.4 pH 7.4	not transformed	stable (no CO_2 was produced)	1122092 Tiedje (1975)
Mobility					
Adsorption/desorption in soil Study carried out on Rehovot sand (sand, 88%; silt, 5%; clay, 7%) [pH 7.1–7.2] in batches equilibrium studies and column studies. Only results from column studies were valid.	FeEDTA	$K_{d\text{-}ads}$ values of K_d were estimated from breakthrough curves of column experiments. No K_{oc} was calculated.	0.57	highly mobile	1122092 Lahav and Hochberg (1975)
Transformation in aquatic system					
Phototransformation in water Study was carried out in aqueous buffer solutions at different pHs. Photolysis was by artificial lamp (5500-W Xenon).	FeEDTA radiolabelled FeEDTA	pH 4.5 and pH 6.9 pH 8.5	No parent remaining after 24 hr No parent remaining after 32 hr	Photolysis is expected to be an important route of transformation.	1122094 Lockhart and Blakeley (1975)
Study was carried out in both distilled and lake water, each at pH 3.1 and 6.5. Photolysis was by UV radiation emitted by two black light lamps.	FeEDTA	pH 3.1 pH 6.5	$t_{½}$ = 14–31 min $t_{½}$ = 45–56.8 min		1434305 Metsärinne et al. (2001)
Biotransformation in aerobic water systems Study was carried out on serum media inoculated with biological extracts from water samples collected from an EDTA-contaminated lagoon.	FeNaEDTA	Transformation products were not quantified.	89% of parent compound disappeared after 5 days	Aerobic aquatic microbial degradation is expected to be an important route of transformation	1122092 Belly et al. (1975)

FeNaEDTA: ferric sodium EDTA
FeEDTA: ferric EDTA

Table 3 Toxicity to Nontarget Species - Terrestrial Organisms

Organism	Exposure	Test substance	Endpoint Value	Degree of toxicity	Reference (PMRA #)
Beneficial arthropods	Carabid beetle, *Notonomus gravis*; 48-h dietary	Multiguard® (total of 0.38 mg a.i. consumed/ larvae	no mortality	harmless (< 25% mortality)	1122100
	Ladybird larvae, *Harmonia conformis*; 48-h dietary	Multiguard® (total of 0.913 mg a.i. consumed/ larvae	no mortality	harmless (< 25% mortality)	
	Melyrid beetle, *Dicranolaius bellulus*; 48-h dietary	Multiguard® (total of 1.152 mg a.i. consumed/ larvae	no mortality	harmless (< 25% mortality)	
Other terrestrial arthropods	Woodlouse (*Porcello laevis*) 48-h dietary	Multiguard® (total of 0.271 mg a.i consumed /larvae)	mortality	harmful (70% mortality)	
Northern bobwhite	acute oral	FeNaEDTA	LD_{50} >2038 mg a.i/kg bw NOEL: 1253 mg a.i/kg bw *Sublethal and behavioural effects* Hyporeactivity, low body carriage, difficulty walking, lack of balance. Discoloured liver, kidney and heart, dehydrated organs, yellowish fluid in gastrointestinal tract.	practically nontoxic	1122103

Table 4 Screening Level Risk Assessment on Nontarget Species - Terrestrial Birds

Organism	Toxicity Endpoint value	EDE	RQ	Risk
Large bird (1000 g)	NOEL = 1253 mg a.i/kg bw (1.253 g a.i./kg bw)	3.5 g a.i./kg bw/day	3	RQ > LOC
Northern bobwhite (178 g)		6.37 g a.i./kg bw/day	5	RQ > LOC
Small bird (20 g)		15.3 g a.i./kg bw/day	12	RQ > LOC

Table 5 Screening Level Risk Assessment on Nontarget Species - Terrestrial Birds (values expressed in terms of number of pellets)

Organism	Toxicity Endpoint value in # pellets to reach toxicity endpoint (= Toxicity in mg a.i./kg bw × kg bw × pellet/6 mg a.i.)	Exposure in # pellets consumed/day (100% diet composed of pellets)	RQ (Exposure/ Toxicity)	% diet to reach RQ of 1	Risk
Large bird (1000 g)	NOEL = 209 pellets (1253 mg a.i./kg bw × 1 kg bw × pellet/6 mg a.i.)	581 pellets/day (58.1 g dw/d × pellet/0.10 g)	3	33%	RQ > LOC
	LD_{50} > 340 pellets (>2038 mg a.i./kg bw × 1 kg bw × pellet/6 mg a.i.)		>1.7	>58%	
Northern bobwhite (178 g)	NOEL = 37 pellets (1253 mg a.i./kg bw × 0.178 kg bw × pellet/6 mg a.i.)	189 pellets/day (18.9 g dw/d × pellet/0.10 g)	5	20%	RQ > LOC
	LD_{50} > 60 pellets (>2038 mg a.i/kg bw × 0.178 kg bw × pellet/6 mg a.i.)		>3	>32%	
Small bird (20 g)	NOEL = 4 pellets (1253 mg a.i/kg bw × 0.020 kg bw × pellet/6 mg a.i.)	51 pellets/day (5.1 g dw/d × pellet/0.10 g)	12	8%	
	LD_{50} > 7 pellets (>2038 mg a.i/kg bw × 0.020 kg bw × pellet/6 mg a.i.)		>7	>14%	RQ > LOC

Table 6 Alternative Molluscicides for the Control of Slugs and Snails

Active Ingredient	Class Designation	Pest	Locations of Use (Refer to product labels for specific use directions)
Carbaryl	Domestic/Commercial	slugs	
Ferric phosphate	Domestic/Commercial	slugs and snails	greenhouse or outdoor use; ornamentals (flowers, shrubs, trees), vegetables, fruit trees, berries, field crops, lawns, grass grown for seed production, nursery plants
Metaldehyde	Domestic	slugs and snails	greenhouse or outdoor use; ornamentals, pathways, rockeries, hedges, ivy and other ground covers, lawns, seedlings, fruit (melons, blackberries, apples, avocados, cherries, citron, grapes, peaches, plums, strawberries), vegetables (asparagus, beans, cabbage, carrots, celery, cucumbers, lettuce, onions, peas, peppers, potatoes, radishes, spinach, squash, tomatoes, turnips)
Methomyl	Commercial/Restricted	slugs	Brussels sprouts, strawberries
Methyl bromide	Restricted	slugs and snails	fumigant for raw agricultural commodities (post-harvest), processed foods, certain structures, pre-plant soil applications, mulch, wood and wood products
Silicon dioxide (in the form of diatomaceous earth)	Domestic	slugs	indoor or outdoor use; where pest is found, including along foundations, gardens, shrubs, flowerbeds

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A. LIST OF STUDIES/INFORMATION SUBMITTED BY REGISTRANT

1.0 Chemistry Assessment

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