Proposed Registration Decision PRD2011-02

2-Methyl-4-isothiazolin-3-one

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Table of Contents

Overview 1
Proposed Registration Decision for 2-Methyl-4-isothiazolin-3-one 1
What Does Health Canada Consider When Making a Registration Decision? 1
What Is 2-Methyl-4-isothiazolin-3-one? 2
Health Considerations 2
Environmental Considerations 4
Value Considerations 5
Measures to Minimize Risk 5
Next Steps 6
Other Information 6
Science Evaluation 7
1.0 The Active Ingredient, Its Properties and Uses 7
1.1 Identity of the Active Ingredient 7
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Products 7
1.3 Directions for Use 11
1.4 Mode of Action 11
2.0 Methods of Analysis 11
2.1 Methods for Analysis of the Active Ingredient 11
2.2 Method for Formulation Analysis 11
3.0 Impact on Human and Animal Health 12
3.1 Toxicology Summary 12
3.1.1 PCPA Hazard Characterization 18
3.2 Determination of Acute Reference Dose 19
3.3 Determination of Acceptable Daily Intake 19
3.4 Occupational and Residential Risk Assessment 19
3.4.1 Toxicological Endpoints 19
3.4.2 Occupational Exposure and Risk 21
3.4.3 Dermal Absorption 22
3.4.4 Occupational Exposure and Risk 22
3.4.5 Secondary Exposure and Risk to Workers & Homeowners 23
3.4.6 Dermal Sensitization Exposure and Risk 29
3.4.7 Post-Application Exposure and Risk to Bystanders 30
3.5 Food Residues Exposure Assessment 32
4.0 Impact on the Environment 32
4.1 Fate and Behaviour in the Environment 32
4.2 Environmental Risk Characterization 32
4.2.1 Risks to Terrestrial Organisms 33
4.2.2 Risks to Aquatic Organisms 33
4.2.3 Incident Reports 34
5.0 Value 34
5.1 Effectiveness Against Pests 34
5.1.1 Acceptable Efficacy Claims 34
5.2 Economics 35

5.3 Sustainability 35
5.3.1 Survey of Alternatives 35
5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management 35
5.3.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance 35
6.0 Pest Control Product Policy Considerations 36
6.1 Toxic Substances Management Policy Considerations 36
6.2.1 Formulants and Contaminants of Health or Environmental Concern 36
7.0 Summary 37
7.1 Human Health and Safety 37
7.2 Environmental Risk 38
7.3 Value 38
7.4 Unsupported Uses 38
8.0 Proposed Regulatory Decision 38
List of Abbreviations 39
Appendix I Tables and Figures 41
Appendix II Dermal Exposure Input Calculations for Dermal Exposure to Metalworkers: 53
References 55

Overview

Proposed Registration Decision for 2-Methyl-4-isothiazolin-3-one

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Kordek 573T Technical Microbicide, Kordek 573F Industrial Microbicide, Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide and Neolone M-10 Industrial Microbicide, containing the technical grade active ingredient 2-methyl-4-isothiazolin-3-one, to be used as a material preservative in paint, coatings, metal-working fluids, household products and polymer latices.

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

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 Kordek 573T Technical Microbicide, Kordek 573F Industrial Microbicide, Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide and Neolone M-10 Industrial Microbicide.

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.

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 (for example, 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 risk-reduction programs, please visit the Pesticide and Pest Management portion of Health Canada's Web site at healthcanada.gc.ca/pmra.

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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."

Before making a final registration decision on 2-methyl-4-isothiazolin-3-one, 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[4] on 2-methyl-4-isothiazolin-3-one, 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 2-Methyl-4-isothiazolin-3-one?

The compound 2-methyl-4-isothiazolin-3-one is a new active ingredient proposed for use as an in-container preservative to prevent bacterial spoilage in polymer latices, metal-working fluids, mineral slurries, paints, detergents, cleaners, and polishes. This active ingredient is a broad-spectrum biocide that acts by disrupting microbial metabolism. While the combination of 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one has been registered as an integrated system product (ISP) for in-can preservation of a number of materials, the use of 2-methyl-4-isothiazolin-3-one alone constitutes a new active ingredient.

Health Considerations

Can Approved Uses of 2-methyl-4-isothiazolin-3-one Affect Human Health?

2-Methyl-4-isothiazolin-3-one is unlikely to affect your health when used according to label directions.

Potential exposure to 2-methyl-4-isothiazolin-3-one may occur when handling and applying the product or through contact with materials containing the product as a preservative. 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 (for example, 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.

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. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when 2-methyl-4-isothiazolin-3-one products are used according to label directions.

In laboratory animals, 2-methyl-4-isothiazolin-3-one was of high acute toxicity by the oral and dermal route, and of moderate acute toxicity via the inhalation route. 2-Methyl-4-isothiazolin-3-

[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*.

one was corrosive to the eyes and to the skin, and caused an allergic skin reaction. Consequently, the hazard signal words "DANGER – POISON, CORROSIVE TO EYES AND SKIN, POTENTIAL SKIN SENSITIZER" are required on the label. End-use products containing 2-methyl-4-isothiazolin-3-one have similar acute toxicity and require the same hazard signal words on their label.

2-Methyl-4-isothiazolin-3-one did not cause cancer in animals and is unlikely to damage genetic material. There was no indication that 2-methyl-4-isothiazolin-3-one caused damage to the nervous system and concerns for adverse effects on the immune system were low. 2-Methyl-4-isothiazolin-3-one did not cause birth defects in animals. Health effects in animals given repeated doses of 2-methyl-4-isothiazolin-3-one included effects on body weight, body weight gain and food consumption and irritation at the site of contact (skin, stomach or nasal cavity/lungs) as well as slight changes in blood parameters.

When 2-methyl-4-isothiazolin-3-one was given to pregnant rabbits, effects of a serious nature (increased incidence of embryo/foetal loss in the developmental toxicity study) were observed at doses that were toxic to the mother. Changes in organ weights as well as delayed sexual maturation and slight decreases in the number of live births were also observed at doses that were toxic to the mother in the rat reproduction study. The risk assessment takes these effects into account in determining the allowable level of human exposure to 2-methyl-4-isothiazolin-3-one.

The risk assessment protects against the effects of 2-methyl-4-isothiazolin-3-one by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

No food uses were proposed with this application, therefore a food residue assessment was not required.

Risks in Residential and Other Non-Occupational Environments

Estimated risk for non-occupational exposure is not of concern.

A quantitative risk assessment conducted for individuals using paints and cleaning products, containing Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide, indicated that the risk is not of concern.

Risks in Secondary Occupational Environments

Estimated occupational risks to secondary workers are not of concern.

Secondary workers can come in direct contact with 2-methyl-4-isothiazolin-3-one on the skin or through inhalation while working with paints, cleaning products or metal-working fluids.

Quantitative risk assessments were conducted for individuals handling Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide, which indicated that the risk for workers is not of concern when handling paints, cleaning products or metal-working fluids.

Occupational Risks From Handling Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide

Occupational risks are not of concern when Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide are used according to the proposed label directions, which include protective measures.

A quantitative risk assessment conducted for individuals handling Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide indicated that the risk for workers is not of concern when these products are used according to label directions.

Workers mixing and loading Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide can come in direct contact with 2-methyl-4-isothiazolin-3-one on the skin or through inhalation. Therefore, the label will specify that workers must wear coveralls over a long-sleeved shirt and long pants, chemical-resistant gloves, socks, chemical-resistant footwear and a full face NIOSH-approved respirator when mixing and loading Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide.

Environmental Considerations

What Happens When 2-Methyl-4-isothiazolin-3-one Is Introduced Into the Environment?

2-Methyl-4-isothiazolin-3-one is the active ingredient in a number of end-use products, which will be used as a material preservative in paint, coatings, metal-working fluid, household products and polymer latices. Based on the proposed use pattern, terrestrial and aquatic environmental exposure is expected to be minimal. 2-Methyl-4-isothiazolin-3-one and its four major transformation products are categorized as non persistent to slightly persistent in aerobic soil. In laboratory studies 2-methyl-4-isothiazolin-3-one is stable to hydrolysis; however, based on its chemical structure and low concentration during use, it is expected to be susceptible to

microbial degradation in the aquatic environment (including water/sediment systems), resulting in negligible concentrations in waterbodies. Based on rapid dissipation in soil, concentrations in groundwater are expected to be low.

Under the use pattern proposed, 2-methyl-4-isothiazolin-3-one is not expected to present a risk to wild mammals, birds, freshwater or marine invertebrates and fish, amphibians, algae, and aquatic and terrestrial plants.

Value Considerations

What is the value of 2-methyl-4-isothiazolin-3-one and the end-use products Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Microbicide Industrial, and Neolone M-10 Industrial Microbicide?

As a broad-spectrum biocide, 2-methyl-4-isothiazolin-3-one acts to inhibit the growth of spoilage microorganisms within a number of aqueous-based materials.

When used according to label instructions, Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide, and Neolone M-10 Industrial Microbicide are able to provide effective in-can protection to a number of aqueous-based materials. These end-use products, when added to polymer latices, metal-working fluids, mineral slurries, paints, detergents, cleaners, and polishes at rates ranging from 25-150 ppm active ingredient, were able to provide effective protection against a broad range of bacteria, mould and yeast. Without a preservative, these materials supported abundant microbial growth, which may lead to foul odours, discoloration, pH changes and destabilization of the product formulation. For a number of materials, such as metal-working fluids and paints, where there is the potential to introduce spoilage bacteria multiple times over the life of the product from opening and closing the container, data was provided to show that the end-use products continued to provide protection against multiple inoculations. While there are a number of different active ingredients currently registered as in-container preservatives for susceptible materials, 2-methyl-4-isothiazolin-3-one provides an alternative option that may be useful to address future cost, availability or microbial resistance issues.

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 Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide, and Neolone M-10 Industrial Microbicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

- Anyone handling Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide, and Neolone M-10 Industrial Microbicide, in an occupational setting, must wear all the personal protective equipment as stated on the label.

Environment

- Label statements for toxicity will be required for aquatic organisms.

Next Steps

Before making a final registration decision on 2-methyl-4-isothiazolin-3-one, 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 of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, 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

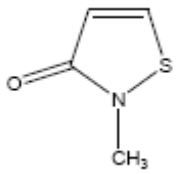
When the PMRA makes its registration decision, it will publish a Registration Decision on 2-methyl-4-isothiazolin-3-one (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

2-Methyl-4-isothiazolin-3-one

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	2-Methyl-4-isothiazolin-3-one
Function	Material preservative
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	2-Methylisothiazol-3(2H)-one
2. Chemical Abstracts Service (CAS)	2-Methyl-3(2H)-isothiazalone
CAS number	2682-20-4
Molecular formula	C_4H_5NOS
Molecular weight	115.16
Structural formula	
Purity of the active ingredient	99.0%

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Products

Technical Product—Kordek 573T Technical Microbicide

Property	Result
Colour and physical state	Light brown solid
Odour	Not available
Melting range	46.7-48.3°C
Boiling point or range	Not applicable
Density at 25°C	1.35 g/mL
Vapour pressure at 20°C	0.408 Pa

Property	Result
Henry's law constant at 20°C	8.077×10^{-10} atm m^3/mole, potential to volatilize from water or moist soil
Ultraviolet (UV)-visible spectrum	pH — λ_{max} (nm) neutral — 274 acidic — 266, 212 basic — 274, 215
Solubility in water at 20°C	pH — Solubility (g/L) 6 — > 574.6 9 — > 489
Solubility in organic solvents	Solvent — Solubility(g/L) Ethyl acetate — 562.15 (10°C) > 1000 (30°C) Hexane — 0.9307 (10°C) 2.4204 (30°C)
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = -0.486
Dissociation constant (pK_a)	Not applicable
Stability (temperature, metal)	Stable for two weeks at 54°C; decomposes at 162-174°C.

Manufacturing Concentrate—Kordek 573F Industrial Microbicide

Property	Result
Colour	Gold
Odour	Not available
Physical state	Liquid
Formulation type	Solution
Guarantee	50.0% 2-methyl-4-isothiazolin-3-one
Container material and description	High-density polyethylene bottles ranging from 4-200 L
Density at 25°C	1.11 g/mL
pH of 1% solution in water	3.53
Oxidizing or reducing action	Not applicable
Storage stability	Stable for 24 months when stored at 25°C.
Corrosion characteristics	The product is not corrosive to the container material.
Explodability	Not applicable

End-Use Product—Kordek LX 5000 Industrial Microbicide

Property	Result
Colour	Gold
Odour	Not available
Physical state	Liquid
Formulation type	Solution
Guarantee	50.0% 2-methyl-4-isothiazolin-3-one
Container material and description	High-density polyethylene bottles ranging from 4-200 L
Density at 25°C	1.11 g/mL
pH of 1% solution in water	3.53
Oxidizing or reducing action	Not applicable
Storage stability	Stable for 24 months when stored at 25°C.
Corrosion characteristics	The product is not corrosive to the container material.
Explodability	Not applicable

End-Use Product—Kordek MLX Industrial Microbicide

Property	Result
Colour	Clear colourless to light yellow
Odour	Not available
Physical state	Liquid
Formulation type	Solution
Guarantee	9.7% 2-methyl-4-isothiazolin-3-one
Container material and description	High-density polyethylene bottles ranging from 4-200 L
Density at 25°C	1.02 g/mL
pH of 1% solution in water	3.87
Oxidizing or reducing action	Not applicable
Storage stability	Stable for 24 months when stored at 25°C.
Corrosion characteristics	The product is not corrosive to the container material.
Explodability	Not applicable

End-Use Product—Rocima 550 Microbicide

Property	Result
Colour	Clear colourless to light yellow
Odour	Not available
Physical state	Liquid
Formulation type	Solution
Guarantee	9.7% 2-methyl-4-isothiazolin-3-one
Container material and description	High-density polyethylene bottles ranging from 4-200 L
Density at 25°C	1.02 g/mL
pH of 1% solution in water	3.87
Oxidizing or reducing action	Not applicable
Storage stability	Stable for 24 months when stored at 25°C.
Corrosion characteristics	The product is not corrosive to the container material.
Explodability	Not applicable

End-Use Product—Neolone M-10 Industrial Microbicide

Property	Result
Colour	Clear colourless to light yellow
Odour	Not available
Physical state	Liquid
Formulation type	Solution
Guarantee	9.7% 2-methyl-4-isothiazolin-3-one
Container material and description	High-density polyethylene bottles ranging from 4-200 L
Density at 25°C	1.02 g/mL
pH of 1% solution in water	3.87
Oxidizing or reducing action	Not applicable
Storage stability	Stable for 24 months when stored at 25°C.
Corrosion characteristics	The product is not corrosive to the container material.
Explodability	Not applicable

1.3 Directions for Use

The compound 2-methyl-4-isothiazolin-3-one is a broad spectrum microbicide for use as an in-container preservative for a number of aqueous-based materials. The four associated end-use products can be incorporated into the materials at a range of rates (Table 1.3.1). Other than the metal-working fluids, which include tank-side addition of the preservative, the other materials have 2-methyl-4-isothiazolin-3-one incorporated into them upon their formulation, with no further additions of preservative.

Table 1.3.1 In-container preservative uses and rates for 2-methyl-4-isothiazolin-3-one

Material	Rate range (ppm a.i.)	End-Product	Frequency
Metal-working fluids	75 – 150	Kordek LX 5000	Every 1 – 6 weeks
Polymer latices	100	Kordek LX 5000, Kordek MLX	once
Mineral Slurries	25 – 50	Kordek MLX	once
Paints/Coatings	50 – 65	Rocima 550	once
Detergents	25 – 150	Neolone M-10	once
Cleaners	25 – 150	Neolone M-10	once
Polishes	25 – 150	Neolone M-10	once

1.4 Mode of Action

The compound 2-methyl-4-isothiazolin-3-one inhibits the growth of bacteria, yeasts and fungi by disrupting metabolic activity. It inhibits key enzymes within the Kreb's cycle, impairing the ability of the microbes to generate the energy necessary for life functions.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Kordek 573T Technical Microbicide, containing 2-methyl-4-isothiazolin-3-one, have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation 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.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry and UV detection (HPLC-MS/MS, HPLC-UV) were developed and proposed for data generation and

enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1; methods for residual analysis in plant and animal matrices were not required for this use pattern (material preservative).

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Kordek 573T Technical Microbicide contains 99.0% of the active ingredient 2-methyl-4-isothiazolin-3-one. 2-Methyl-4-isothiazolin-3-one is contained in Kathon 886 Technical Microbicide (Registration number 21799), which is currently registered in Canada. Kathon 886 Technical Microbicide is comprised of a 1:3 ratio of 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one. Together, the active ingredients 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one constitute 14% of Kathon 886 Technical Microbicide. 2-Methyl-4-isothiazolin-3-one is structurally similar to 5-chloro-2-methyl-4-isothiazolin-3-one, the only difference being the lack of a chlorine atom. For this document, Kathon 886 Technical Microbicide will be referred to as Kathon.

The isothiazolinones are a family of related chemicals with a broad spectrum of antimicrobial properties. They are electrophiles that bind to thiol groups on proteins, and inhibit key respiration and energy generation enzymes. Irritation and dermal sensitization are common toxicological findings associated with the isothiazolinones.

A detailed review of the toxicological database for 2-methyl-4-isothiazolin-3-one was conducted. Although most of the toxicology studies were conducted with 2-methyl-4-isothiazolin-3-one, a request was made to bridge to the Kathon toxicology database to satisfy the data requirements for the 90-day rat dermal study, the 90-day rat inhalation study, the rat chronic/oncogenicity study and the mouse oncogenicity study. In order to assess this request, an examination of the Kathon database was undertaken and a comparison of the toxicology profiles for 2-methyl-4-isothiazolin-3-one and Kathon was made. Although some deficiencies were identified in the bridging studies, overall, the submitted data for 2-methyl-4-isothiazolin-3-one, when combined with the Kathon database, were considered sufficient to conduct a hazard assessment. Most studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Although some studies were conducted before implementation of Good Laboratory Practices, they were considered to contain scientifically valid information.

Oral toxicokinetic studies with radiolabelled 2-methyl-4-isothiazolin-3-one in rats showed rapid and extensive absorption and excretion following administration of a single low- or single high-dose. The majority of the administered dose (AD) was recovered within the first 24 hours. Urine was the primary route of excretion. A separate biliary cannulation study in rats demonstrated that most of the AD found in feces was excreted via the bile, supporting the conclusion of extensive absorption. Radioactivity in expired air was not measured, but recovery of radioactivity was

high, suggesting that only a low amount would have been excreted via expiration. A repeat dose study was not available.

Metabolism of 2-methyl-4-isothiazolin-3-one was extensive, with no parent compound found in the excreta. The proposed metabolic pathway for 2-methyl-4-isothiazolin-3-one involved Phase I metabolism with oxidative or reductive cleaving of the molecule (thus opening the ring), followed by Phase II metabolism involving conjugation of Phase I metabolites with mercapturic acid moieties. Fourteen metabolites were identified and structurally elucidated with 13 of these found in urine. The primary metabolites in urine were N-methyl malonamic acid (M1) and a 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propanamide (M12). M2 (the primary fecal metabolite), M3 (urine and feces) and M9 (urine) were also characterised. Thirteen fecal metabolites were identified but not characterized, comprising a small proportion of the administered dose. In a separate bile duct cannulation study, most biliary metabolites identified were various glutathione, cysteinylglycine and glucuronic acid conjugates.

After oral dosing, radiolabelled 2-methyl-4-isothiazolin-3-one was distributed mostly to highly vascularised tissue with peak blood and plasma concentrations reached after 1-3 hours. A biphasic kinetic profile was suggested with an initial plasma half-life of 3-6 hours (low/high-dose) followed by a terminal half-life of 27-29 hours (both groups). Higher levels of radioactivity were found in the adrenals, whole blood, heart, kidneys, liver, lungs, spleen and thyroid; of these tissues, the thyroid contained the highest levels. Levels of radioactivity in plasma were markedly lower at 96 hours than in many other tissues, indicating possible tissue binding or incorporation in the general carbon pool. No marked differences between sexes were noted, apart from a tendency for females to have higher levels of radioactivity in the thyroid and gonads when compared with males. Low levels of radioactivity remained in the carcass after 96 hours. A separate tissue distribution study in mice showed similar results, although males had higher tissue concentrations than females.

Toxicokinetic studies performed with Kathon revealed a similar profile to 2-methyl-4-isothiazolin-3-one with rapid absorption and excretion following oral dosing. Like 2-methyl-4-isothiazolin-3-one, the primary metabolite was M1. Radioactivity was distributed to the liver, kidney, brain and testes. A repeat dose study with Kathon resulted in 20% of the AD remaining in the carcass after the last dose. However, the interval between the last dose and the measurement of radioactivity was not reported. This resulted in difficulties in comparing the single and repeat dose studies findings. From the perspective of bridging the two toxicology databases, it was concluded that the available information demonstrates that 2-methyl-4-isothiazolin-3-one and Kathon have similar toxicokinetic profiles.

2-Methyl-4-isothiazolin-3-one was of high acute toxicity to rats and mice via the oral route and of high acute toxicity to rats via the dermal route. 2-Methyl-4-isothiazolin-3-one was moderately toxic to rats via the inhalation route and corrosive to eyes and skin of rabbits. Several dermal sensitization studies in guinea pigs using various test methodologies indicated that 2-methyl-4-isothiazolin-3-one had sensitization potential. A local lymph node assay (LLNA) in mice was also provided. The results of this study were similar to those reported in the published literature. The published literature also contains information on human repeat insult patch tests (HRIPT) conducted with volunteers which confirmed the sensitization potential (Basketter *et al.*, 2005).

Kathon had a similar acute toxicity profile to 2-methyl-4-isothiazolin-3-one; however, Kathon was somewhat more toxic via the oral route and slightly less toxic via the inhalation route than 2-methyl-4-isothiazolin-3-one. The biggest difference noted was that Kathon is a more potent sensitizer (in both the LLNA and HRIPT studies) which has been attributed to the presence of 5-chloro-2-methyl-4-isothiazolin-3-one.

The end-use products Kordek 573F Industrial Microbicide and Kordek LX 5000 Industrial Microbicide (guarantee 50% 2-methyl-4-isothiazolin-3-one) as well as the end-use products Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide, and Neolone M10 Industrial Microbicide (guarantee 9.7% 2-methyl-4-isothiazolin-3-one) had similar acute toxicity profiles as Kordek.

The metabolite M1 was of low acute oral toxicity to rats and was not a dermal sensitizer in mice.

2-Methyl-4-isothiazolin-3-one was not considered to be genotoxic. Bacterial gene mutation assays, *in vitro* mammalian gene mutation assays, *in vitro* and *in vivo* unscheduled DNA synthesis assays and an *in vivo* micronucleus assay were all negative. An *in vitro* chromosomal aberration study in Chinese hamster ovary cells did indicate clastogenicity, but only at cytotoxic concentrations. A bacterial gene mutation assay performed with the metabolite M1 was also negative. Although a positive result with the TA100 strain in the bacterial gene mutation assay was noted in testing with Kathon (only in the absence of metabolic activation), all other tests were negative and it was concluded overall that Kathon, like 2-methyl-4-isothiazolin-3-one, was not genotoxic.

Repeat-dose studies with 2-methyl-4-isothiazolin-3-one were conducted in rats and dogs. In addition to oral studies in both of these species, 90-day inhalation and dermal studies with Kathon were submitted to satisfy data requirements for 2-methyl-4-isothiazolin-3-one. The majority of oral studies for 2-methyl-4-isothiazolin-3-one and Kathon incorporated the test material in drinking water, with the exception of the dog studies for which the test material was incorporated in the diet. As a result, lowered water consumption was frequently observed throughout the database, presumably on account of 2-methyl-4-isothiazolin-3-one's irritating properties. The primary toxic effects observed following repeated dosing with 2-methyl-4-isothiazolin-3-one were reduced body weight and body weight gain, as well as findings indicative of gastric irritation. Marginal effects on the spleen and heart were noted in some studies with 2-methyl-4-isothiazolin-3-one at higher dose levels. It was noted that studies employing gavage dosing resulted in increased systemic toxicity and mortality when compared to drinking water studies, wherein 2-methyl-4-isothiazolin-3-one appeared to be better tolerated. In the Kathon studies, the same general toxicity was observed following repeated oral dosing, although signs of stomach irritation were more commonly observed. Irritation of the skin and respiratory tissue in the repeat dose dermal and inhalation studies, respectively, demonstrated Kathon's irritation potential. There was evidence of increased toxicity with increased duration of testing for both 2-methyl-4-isothiazolin-3-one and Kathon in the rat; it was not possible to conduct a similar comparison for other species tested on the basis of the information provided. There was no indication of sex-sensitivity to either chemical.

In a 90-day drinking water study with 2-methyl-4-isothiazolin-3-one in rats, decreases in body weight, body weight gain and food consumption at the high-dose level were noted in both sexes, as well as decreased blood glucose in females. Slight, treatment-related, but non-adverse, effects on red blood cell counts, haemoglobin and hematocrit were also noted. In this study, 2-methyl-4-isothiazolin-3-one's potential for neurotoxicity was evaluated via detailed weekly clinical observations, a functional observational battery and motor activity tests performed at week 13. No adverse effects were noted. A 90-day drinking water study in rats with Kathon also revealed effects on body weights at the high-dose level. Effects on blood protein levels, AST, relative liver and kidney weight and stomach irritation were noted as well at the high-dose level. It is noteworthy that the high-dose level in the Kathon study, at which body weight effects were noted, was three-fold lower than the dose level that produced body weight effects in the 2-methyl-4-isothiazolin-3-one study, thus demonstrating a higher degree of toxicity with Kathon.

In a 90-day dietary study with 2-methyl-4-isothiazolin-3-one in dogs, decreases in body weight, body weight gain and food consumption were observed at the high-dose level. Toxicologically significant decreases in red blood cell counts, hemoblogin and hematocrit, as well as a decrease in blood calcium were also noted at this dose level. A 90-day dietary study in dogs with Kathon did not reveal any signs of toxicity, but the study had numerous deficiencies which precluded a comparison with the 2-methyl-4-isothiazolin-3-one dog study. Significant difficulties with dose verification in the 2-methyl-4-isothiazolin-3-one study, probably due to 2-methyl-4-isothiazolin-3-one binding to proteins in food, rendered the study unacceptable for regulatory purposes.

As noted earlier, a 90-day dermal study performed on rabbits with Kathon was provided in lieu of a study with 2-methyl-4-isothiazolin-3-one. Dose-related increases in the incidence and severity of skin irritation were noted. This study was deemed unacceptable for regulatory purposes due to issues with study methodology and conduct, as well as animal health.

A 90-day rat inhalation study was performed with Kathon to satisfy the data requirement for 2-methyl-4-isothiazolin-3-one. Rhinitis, which defined the study NOAEL, was noted in the nasal cavity at the mid- and high-dose levels. Animals in the high-dose group also displayed clinical signs of toxicity, body weight and body weight gain decreases, decreased spleen and heart weights and lymphoid hyperplasia in the mesenteric lymph nodes.

A 24-month chronic/oncogenicity drinking water study in rats performed with Kathon was provided in lieu of a similar study with 2-methyl-4-isothiazolin-3-one. Reduced body weight, body weight gain and food consumption as well as various signs of irritation in the stomach were observed in both sexes. Increased urinary specific gravity was also noted at the same dose level but was deemed secondary to reduced water consumption. These effects occurred at a lower dose than in the 90-day drinking water study, indicating a durational effect for these findings. No evidence of carcinogenicity was noted.

A 30-month chronic dermal study in mice performed with Kathon was submitted in lieu of a mouse oncogenicity study with 2-methyl-4-isothiazolin-3-one. Irritation was noted at the application site. This study did not show an increase in tumours; however, the study was deemed unacceptable for regulatory purposes due to several deficiencies in study design. In spite of this limitation, the cancer hazard potential for 2-methyl-4-isothiazolin-3-one overall was considered

to be low on the basis of the negative results of the rat study, the overall negative genotoxicity profile, and the collective information for the isothiazolinones, as a class, which suggest that these chemicals are not carcinogenic.

In a 2-methyl-4-isothiazolin-3-one two-generation reproductive toxicity drinking water study in the rat, reduced water consumption, body weight, body weight gain and food consumption were noted in high-dose parents of both generations. Effects were also noted on parental pituitary and kidney organ weights at the high-dose level. There appeared to be some effects on reproductive organ weights at the high-dose level (ovary, seminal vesicle plus coagulating gland and fluids, cauda epididymis, prostate and uterus [accompanied by increased uterine luminal distension]). These changes may reflect a treatment-related response; however, the decreases in body weights confounded the interpretation of these findings. Decreases in implantation sites and a slight decrease in the mean number of pups/litter were noted at the high-dose level in the F_2 generation. Offspring were also affected at the high-dose level with reduced body weight in both generations, delayed sexual maturation in F_1 male and female pups, reduced spleen weights in F_2 pups, reduced thymus weights in both generations, and an increased incidence of dilated renal pelvis in the F_2 generation. There was no evidence of increased sensitivity of the young animal in this study.

Examination of the reproductive toxicity studies with Kathon was undertaken for the purpose of comparing the findings with those of the 2-methyl-4-isothiazolin-3-one studies. A supplemental 1-generation rat reproduction study performed with Kathon was available. Reduced body weights and reduced number of pups (due to a single litter loss) were noted at the high-dose level only. Summary results from a 2-generation reproductive toxicity study performed with Kathon indicated that stomach irritation was present at all dose levels, as well as body weight effects at the high-dose level. No reproductive effects were reported and there did not appear to be sensitivity of the young animal. When comparing the two chemicals, it appears that treatment with 2-methyl-4-isothiazolin-3-one resulted in reproductive toxicity whereas treatment with Kathon did not; however, the reproductive findings with 2-methyl-4-isothiazolin-3-one were observed at higher doses than those tested in the Kathon studies.

The developmental toxicity potential of 2-methyl-4-isothiazolin-3-one was investigated in rats and rabbits. In rats, excessive toxicity (including mortality) at the highest dose level resulted in reduction of the dose level shortly after treatment began. Decedents showed unsteady gait, hypoactivity, rales, gasping, laboured respiration and other clinical signs. Necropsy findings in the decedents included red discolouration of the glandular portion of the stomach and lungs, and lungs that were characterised as not fully collapsed. High-dose survivors displayed rales, gasping and laboured respiration, decreased body weight, body weight gain and food consumption. No developmental toxicity was noted.

In rabbits, evidence of developmental and maternal toxicity was noted at the highest dose level only. Decreased defecation, body weight loss, reduced food consumption and dark red areas in the stomach were noted in the dams. These effects were accompanied by an increased incidence of a serious effect, late resorptions, accompanied by a reduction in the number of live foetuses per dam.

As was done for the reproductive toxicity studies, an examination of the developmental toxicity studies with Kathon was undertaken for the purpose of comparing the findings of the two chemicals. A developmental toxicity study in rats with Kathon demonstrated no adverse effects on development. In this study, reduced body weight gain was observed at the highest dose level. Two rabbit developmental toxicity studies with Kathon were available. In the first study, all animals at the high-dose level were sacrificed moribund before gestation day 15. At the mid-dose level, decreased body weight and body weight gains were noted. Foetuses at this dose level displayed extra ribs, partially ossified sternebra and heart malformations. In the second study, performed on a different strain of rabbits, mortality, body weight effects and stomach irritation were observed at all doses in dams. No litters from the high-dose group and only one litter from the mid-dose animals were produced. A dose-related increase in the mean number of resorptions was observed, but no malformations or variations in foetuses were noted. When comparing the two chemicals, 2-methyl-4-isothiazolin-3-one appears to be slightly more toxic to rat dams but not significantly different from Kathon in terms of developmental toxicity. For rabbits, these results indicate that 2-methyl-4-isothiazolin-3-one was less toxic than Kathon with respect to maternal and developmental toxicity.

Overall, in determining the adequacy of the data from Kathon submitted to bridge to the 2-methyl-4-isothiazolin-3-one database, the following was noted: The toxicokinetic properties of Kathon and 2-methyl-4-isothiazolin-3-one were similar, and their chemical structures are closely related. The systemic toxicity profiles of 2-methyl-4-isothiazolin-3-one and Kathon were largely comparable. Although some differences in toxicity were noted, Kathon generally elicited effects at lower dose levels than 2-methyl-4-isothiazolin-3-one. A similar observation was made with respect to the reproductive and developmental toxicity of 2-methyl-4-isothiazolin-3-one; although 2-methyl-4-isothiazolin-3-one appeared to produce greater reproductive toxicity than Kathon, it did so only at higher dose levels. Both chemicals were non-genotoxic. Despite the fact that two of the studies with Kathon that were submitted to bridge the 2-methyl-4-isothiazolin-3-one database were unacceptable (90-day dermal study, 30-month mouse carcinogenicity study), the overall information from the combined databases was adequate to characterize the hazard profile of 2-methyl-4-isothiazolin-3-one.

Results of the toxicology studies conducted on laboratory animals with 2-methyl-4-isothiazolin-3-one and its associated end-use products, are summarized in Appendix 1, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix 1, Table 4.

Incident reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website. Incidents from Canada and the United States were searched and reviewed for 2-methyl-4-isothiazolin-3-one and Kathon.

No incidents following exposure to 2-methyl-4-isothiazolin-3-one were reported within Canada or the United States.

As of January 6th, 2011, four incidents in workers following accidental exposure to products containing Kathon have been reported in Canada. The most common effects noted were skin irritation (4 incidents), burns (2 incidents), blisters (1 incident), pain (1 incident) and itchy/tingling skin (1 incident). Causality has not been established for the effects noted in the incident reports; however, the effects are consistent with overexposure to an isothiazolinone causing dermal irritation and possibly sensitization.

In California, 18 events were reported for Kathon in the 1992-2008 period. As a result of exposures to Kathon that were mostly accidental in nature, or in some cases due to poor industrial hygiene, burns, rashes, blisters and other forms of dermal irritation occurred and were reported. One instance of upset stomach and vomiting following dermal exposure was also reported. In one case, following eye exposure, blurry vision was reported.

Four incident reports with an unidentified isothiazoline were also reported by the US EPA. Following accidental exposure, workers exposed to izothiazoline disinfectants reported inflammation, irritation and in some cases blisters to the exposed area. One worker reported headaches as well.

The PMRA concluded that the information from the incident reports supported the current toxicity database; however, it did not impact the risk assessment. Detailed information for the incidents can be found on the PMRA Public Registry.

3.1.1 PCPA Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for 2-methyl-4-isothiazolin-3-one. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats.

With respect to potential prenatal and postnatal toxicity, no evidence of sensitivity of the young was observed in the 2-generation reproductive toxicity study. Parents and offspring demonstrated effects on body weight and organ weight at the highest dose level tested. An increased incidence of dilated renal pelvis and a delay in sexual maturation in offspring were also noted at this dose level. In a developmental toxicity study in rats, significant systemic toxicity occurred in dams at the highest dose level, but no developmental toxicity was observed. In the rabbit developmental toxicity study, an increased incidence of late resorptions, accompanied by a reduction in the number of live foetuses per dam, were observed in the presence of maternal toxicity (e.g. decreased defecation, body weight loss, reduced food consumption and dark red areas in the stomach) at the highest dose level tested.

Overall, the database is adequate for determining the sensitivity of the young. There is a low concern for sensitivity of the young and effects on the young are well-characterized. The late resorptions (accompanied by a reduction in the number of live foetuses per dam) were considered serious endpoints although the concern for these findings was tempered by the presence of maternal toxicity. Therefore, the PCPA factor was reduced to 3-fold when using the rabbit developmental toxicity study to establish the point of departure for assessing risk to women of child-bearing age. The PCPA factor was reduced to one-fold when the selected endpoint was considered protective of pre- and post-natal concerns.

3.2 Determination of Acute Reference Dose

An acute reference dose (ARfD) for 2-methyl-4-isothiazolin-3-one was not established as there are no food uses.

3.3 Determination of Acceptable Daily Intake

An acceptable daily intake (ADI) for 2-methyl-4-isothiazolin-3-one was not established as there are no food uses.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-term Dermal

For short-term dermal risk assessment for consumers, the developmental toxicity study in rabbits was selected. The short-term dermal toxicity study was not suitable for regulatory purposes, thus necessitating the use of an oral study for risk assessment. At doses of 30 mg/kg bw/day, decreased defecation, body weight loss, reduced food consumption and dark red areas in the stomach were noted in the dams. These effects were accompanied by an increased incidence of a serious effect, late resorptions (accompanied by a reduction in the number of live foetus per dam), occurring at the maternally toxic dose level. A NOAEL of 10 mg/kg bw/day was established.

The target Margin of Exposure (MOE) for these scenarios is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a PCPA factor of 3-fold for the reasons outlined in the PCPA Hazard Characterization section. The selection of the rabbit developmental toxicity study and the MOE is considered to be protective of all populations, including nursing infants and unborn children.

Long-term Dermal

In the absence of an acceptable long-term dermal toxicity study, the rat 2-year oral toxicity study with Kathon was selected for long-term occupational and residential dermal risk assessment. At doses of 6.6 mg/kg bw/day, reduced body weight, body weight gain and food consumption as well as various signs of irritation in the stomach were observed in both sexes. A NOAEL of 2.0 mg/kg bw/day was established.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. The selection of the rat 2-year oral toxicity study and MOE is considered to be protective of all populations, including nursing infants and unborn children. For residential scenarios, the PCPA factor was reduced to 1-fold for the reasons outlined in the PCPA Hazard Characterization section.

Short-term Inhalation

For short-term inhalation risk assessment for consumers, the 90-day inhalation study performed with Kathon in rats was selected. At concentrations of 1.15 µg/L, rhinitis in the nasal cavity was noted. A NOAEL of 0.34 µg/L was established. This dose is considered equivalent to 0.06 mg/kg bw/day.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of 1-fold for the reasons outlined in the PCPA Hazard Characterization. The selection of the rat 90-day inhalation study and MOE is considered to be protective of all populations, including nursing infants and unborn children.

Long-term Inhalation

For long-term inhalation occupational risk assessment, the 90-day inhalation study performed with Kathon in rats was selected. A long-term inhalation study was not available for either 2-methyl-4-isothiazolin-3-one or Kathon. In the 90-day study, at concentrations of 1.15 µg/L, rhinitis in the nasal cavity was noted. A NOAEL of 0.34 µg/L was established for this study. This dose is considered equivalent to 0.06 mg/kg bw/day.

The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation, 10-fold for intraspecies variability, and a 3-fold uncertainty factor. This latter factor was employed due to the need to extrapolate from a short-term to long-term scenario in view of evidence of increased toxicity with increased duration of dosing in the database. The selection of the rat 90-day inhalation study and MOE is considered to be protective of nursing infants and unborn children of exposed female workers.

Non-Dietary Oral Ingestion (Children, Short-term)

For assessment of non-dietary (incidental) oral risk to children, the developmental toxicity study in rabbits was selected. At doses of 30 mg/kg bw/day, decreased defecation, body weight loss, reduced food consumption and dark red areas in the stomach were noted in maternal animals. These findings are considered relevant endpoints in an assessment of risk to children. A NOAEL of 10 mg/kg bw/day was established.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability, as well as a PCPA factor of 1-fold (for the reasons outlined in the PCPA Hazard Characterization Section).

Dermal Sensitization

Because of the positive skin sensitization study findings, the well-known sensitization potential of the isothiazolinones, and the use patterns proposed for 2-methyl-4-isothiazolin-3-one, a sensitization risk assessment was deemed appropriate. A quantitative approach to the sensitization risk assessment was undertaken in light of the fact that an LLNA study with 2-methyl-4-isothiazolin-3-one was available. An EC3 of 0.86%, equivalent to 215 $\mu g/cm^2$ was established in the study and was considered appropriate for use in risk assessment.

The target MOE is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability. As a confirmatory measure, published human data (HRIPT) were also considered. Sensitization thresholds of 15 $\mu g/cm^2$ have been reported in humans. For the human data, the target MOE is 10 comprising an uncertainty factor of 10-fold for intraspecies variability.

Cancer Risk Assessment

There was no evidence of carcinogenicity and therefore, no cancer risk assessment is necessary.

3.4.2 Occupational Exposure and Risk

Occupational and secondary worker exposure to the end-use products will occur predominantly via the dermal and inhalation routes, and is characterized as being of long-term duration.

Residential exposure to the end-use products will occur via the dermal, inhalation and incidental oral routes, and is characterized as being of short-term duration, except in the case of laundered clothing which may be considered a long-term exposure scenario.

3.4.3 Dermal Absorption

An *in vitro* dermal absorption study on human skin was provided. As noted in the draft NAFTA Harmonization Position Paper on Methodology Issues (January 18, 1999), *in vitro* dermal absorption studies, alone, are not sufficiently validated for use in deriving estimates of systemic exposure for risk assessments. Further to this, there were several limitations to the study that rendered it unacceptable. Therefore, a dermal absorption value of 100% is recommended.

3.4.4 Occupational Exposure and Risk

Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide would be added to formulating systems via automated metered systems or manual addition. There is potential for occupational exposure to Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide during the loading, transfer or during maintenance of the system. The end-use products could potentially be used throughout the year, thus the workers have a potential for long-term exposure to Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide.

Exposure estimates for workers loading and transferring Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide into processing systems used to manufacture polymer latices, mineral slurries, metal-working fluids, paints and cleaning products were generated from the CMA Antimicrobial Exposure Assessment Study.

The following exposure estimates and margins of exposure (MOE) were derived for mixer/loader/applicators:

Table 3.4.1 Estimated Mixer/Loader Exposure for Open Pour Scenarios

Scenario[a]	Daily Dermal Exposure[b] (mg/kg bw/day)	Daily Inhalation Exposure[b] (mg/kg bw/day)	Dermal MOE[c]	Inhalation MOE[d]
Single Layer	0.1034	0.001	14	58
Chemical Resistant Coveralls and Respirator	0.01034	0.0001	193	580

a. A 90% protection factor was added to CMA exposure data for the addition of chemical resistant coveralls and respirator
b. Daily exposure values taken from CMA exposure data for open pour scenarios
c. Long-term Dermal NOAEL of 2.0 mg/kg bw/day from a 2 year rat study using IST/ISL; Target MOE = 100
d. Long-term Inhalation NOAEL of 0.058 mg/kg bw/day from a 90-day rat study using ISL; Target MOE = 300

With the addition of chemical resistant coveralls and a respirator the margins of exposure for open transfer equipment are acceptable (> 100 for dermal; > 300 for inhalation).

3.4.5 Secondary Exposure and Risk to Workers & Homeowners

3.4.5.1 Metalworkers

There is a potential for secondary exposure to metalworkers handling fluids treated with Kordek LX 5000 Industrial Microbicide. Exposure potential would occur primarily via the dermal and inhalation routes and is expected to be of long-term duration.

The approach to estimate dermal exposure was based on the US EPA Superfund Risk Assessment. The approach assumes the immersion of parts of the body in fluid preserved with 2-methyl-4-isothiazolin-3-one. For the purpose of this exposure assessment, it is assumed that the surface area exposure for metalworkers includes hands and forearms (2077 cm^2). Though it is not expected that metalworkers' hands and forearms will be submerged continuously for 10 hours, it is assumed that contact with treated metalworking fluids occurs throughout a work day. A 10-hour work day was considered appropriate as the National Institute for Occupational Safety and Health (NIOSH) suggests that a 40 hour work week could be made up of 10-hour work days.

The equation used to estimate metalworker dermal exposure was derived as follows:

$$\mathbf{E = [FA \times K_p \times SA \times PF \times C_w \times CF \times (t/(1+B) + 2\tau(1 + 3B + 3B^2/(1 + B)^2)] / BW}$$

where,

E = total dermal exposure (mg/kg bw/day)
FA = fraction of absorbed water (dimensionless, default = 1)
K_p = permeability coefficient (cm/hr); see Appendix II for calculation
SA = surface area exposed; assumed hands and forearms (2077 cm^2)
PF = protection factor from clothing; assume 1 as hands and forearms may not be protected by clothing
C_w = concentration of ai in water (maximum approved application rate; 150 ppm (mg/L))
CF = conversion factor to convert cm^3 to L; 0.001L = 1 cm^3
t = duration of work day (hours/event); 10 hours/day
B = dimensionless ratio of two permeability coefficients (one for stratum corneum and one for the epidermis); see Appendix II for calculation
τ = lag time per event (hours/event); see Appendix II for calculation
BW = body weight; 70 kg

The following dermal exposure estimate was derived for metalworkers:

Table 3.4.2 Estimated Dermal Exposure to Metalworkers

Total Dermal Exposure (mg/kg bw/day)[a]	Margin of Exposure[b]
8.2×10^{-3}	242

a. see Appendix I for calculation of dermal exposure
b. Based on a long-term dermal NOAEL of 2.0 mg/kg bw/day from a 2-year rat study using IST/ISL; Target MOE = 100

Inhalation exposure to metalworkers was derived in the following manner (TNsG, 2007):

$$\mathbf{E = C_{air} \times \%a.i. \times IR \times ET/BW}$$

where,

C_{air} = reported air concentrations for aerosolized metalworking fluids to American autoworkers (Greaves *et al*., 1997)
% a.i. = percent of active ingredient added to metalworking fluid
IR = hourly inhalation rate; light activity rate
ET = exposure time; assumed 10 hours per day
BW = body weight; 70 kg

The inhalation exposure model estimates inhalation exposure based on the air concentration, percent of active ingredient available, inhalation rates and exposure time. Air concentration, specific to metalworkers, was taken from literature (Greaves *et al.*, 1997). Air concentrations of aerosolized metal-working fluids to American autoworkers were measured and reported for approximately 1000 metalworking machinists. The purpose of the study was to measure metalworking particles capable of penetrating the larynx (thoracic particles) and alveolar region of the lungs (respirable particles). Based on the outcome of the study, examining vapours available for inhalation from straight, soluble and synthetic oils, an air concentration value, 0.55 mg/m^3, taken from soluble oil exposure values, is appropriate in calculating inhalation exposure to metalworkers. This value represented the highest time-weighted average concentration of metalworking fluids potentially treated with antimicrobial pesticides.

The following inhalation exposure estimate was derived for metalworkers:

Table 3.4.3 Estimated Inhalation Exposure to Metalworkers

Air Concentrations (mg/m^3)	% Active Ingredient	Inhalation Rate (m^3/hour)	Exposure Time (hours/day)	Daily Inhalation Exposure (mg/kg bw/day)	Margin of Exposure[a]
0.55	0.015	1.0	10	1.2×10^{-5}	4921

a. Long-term Inhalation NOAEL of 0.058 mg/kg bw/day from a 90-day inhalation study using ISL; Target MOE = 300

The estimated dermal and inhalation exposures for metalworkers exceed the target margins of exposure (>100 for dermal; >300 for inhalation).

3.4.5.2 Painters (Professional and Residential)

There is potential for exposure to professional and residential painters using paints containing Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide or Rocima 550 Industrial Microbicide. Kordek LX 5000 Industrial Microbicide and Kordek MLX Industrial Microbicide are proposed for use in polymer latices, which the applicant has indicated could constitute a maximum of 50% of the final paint product. Kordek MLX Industrial Microbicide is also proposed for use in mineral slurries, to be used in paint, paper production and building materials. The applicant has indicated that mineral slurries can be added to paints and can make up to 30% of the final paint formulation. Thus, 80% of the final paint product could contain polymer latices and mineral slurries containing 2-methyl-4-isothiazolin-3-one. At maximum application rates a final paint product could contain a maximum of 120 ppm of 2-methyl-4-isothiazolin-3-one.

Rocima 550 Industrial Microbicide is proposed as an in-can paint and coating preservative containing 2-methyl-4-isothiazolin-3-one at rates of 50 – 75 ppm. The risk assessment focused on paint as a high-end exposure scenario, as compared to mineral slurries for use in building materials and paper.

Dermal and inhalation exposure estimates for professional and residential painters were generated using the Pesticide Handlers Exposure Database (PHED; Version 1.1, 2002).

Exposure to professionals using paints containing Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide or Rocima 550 Industrial Microbicide is expected to be long-term in duration and to occur primarily by the dermal and inhalation routes. The exposure estimates for professional painters are based on the applicator wearing a single layer of clothing without gloves.

Exposure to homeowners using paints containing Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide or Rocima 550 Industrial Microbicide is expected to be short-term in duration and to occur primarily by the dermal and inhalation routes. The exposure estimates for residential users of paint products are based on individuals wearing short pants, short-sleeve shirt and without gloves.

Dermal and inhalation exposures were estimated by coupling the unit exposure values with the amount of product handled per day and 100% absorption. Exposure was normalized for body weight (70 kg).

Table 3.4.4 Dermal and Inhalation Estimates for Painters

Scenario	Concentration a.i. (mg/L or ppm)	Amount Used Per Day[a] (L)	Daily Dermal Exposure[b] mg/kg bw/day)	Daily Inhalation Exposure[c] (mg/kg bw/day)	Dermal Margin of Exposure[d]	Inhalation Margin of Exposure[e]
Professional Painters					**Target = 100**	**Target = 300**
Airless Sprayer	120	187.5	2.7×10^{-2}	3.4×10^{-4}	73	172
	75		1.7×10^{-2}	2.2×10^{-4}	117	268
	65		1.5×10^{-2}	1.9×10^{-4}	135	310
Paint Brush	120	18.7	1.2×10^{-2}	3.4×10^{-5}	159	1688
Residential Painters					**Target = 300**	**Target = 100**
Airless Sprayer	120	56.8	1.8×10^{-2}	1.0×10^{-5}	10372	20555
Paint Brush		7.57	6.7×10^{-3}	9.6×10^{-6}	1498	6015
Aerosol		1.01	9.6×10^{-4}	2.87×10^{-6}	565	556

a. Values for professional painters taken from a survey conducted by the PMRA to estimate professional paint uses[6]; default values for residential users taken from the US EPA Residential SOP (1997).
b. Dermal Exposure = [Application Rate (mg/L) × Volume Handled (L) × PHED Exposure (µg/kg a.i. handled) × 1×10^{-6} kg/mg] / bw (70 kg)
c. Inhalation Exposure = [Application Rate (mg/L) × Volume Handled (L) × PHED Exposure (µg/kg a.i. handled) × 1×10^{-6} kg/mg] / bw (70 kg)
d. MOE_{Dermal} = Dermal NOAEL (mg/kg bw/day) / Dermal Exposure (mg/kg bw/day); NOAEL (long-term) = 2.0 mg/kg bw/day; NOAEL (short term) = 10 mg/kg bw/day
e. $MOE_{Inhalation}$ = Inhalation NOAEL (mg/kg bw/day) / Inhalation Exposure (mg/kg bw/day); NOAEL (all durations) = 0.058 mg/kg bw/day

The estimated dermal and inhalation exposures for all scenarios, except professional painters using airless sprayers, met the target margins of exposure. Therefore, the maximum concentration in the final paint product cannot exceed 65 mg/L (or ppm) of 2-methyl-4-isothiazolin-3-one. Based on the proportions of polymer latices and mineral slurries in the final paint product this correlates to a maximum concentration of 100 ppm 2-methyl-4-isothiazolin-3-one for polymer latices and a maximum concentration of 50 ppm 2-methyl-4-isothiazolin-3-one for mineral slurries.

3.4.5.3 Detergents (Professional and Residential)

Exposure to professional cleaners is expected to be of long-term duration via the dermal and inhalation routes, while exposure to homeowners is expected to be of short-term duration via the dermal and inhalation routes.

Dermal exposure to professional cleaners was derived based on guidance from the European Human and Environmental Risk Assessment Project. Parameters representative of Canadian exposure were used as inputs to the current risk assessment. Dermal exposure was derived in the following manner:

$$\mathbf{E = SA \times FT \times DA \times C_{ai} \times ET / BW}$$

where,

E	=	potential dermal exposure (mg/kg bw/day)
SA	=	surface area exposure; assumed hands and forearms (2077cm^2; NAFTA, 1999)
FT	=	film thickness; 2.1×10^{-3} cm taken from US EPA DERMAL Model for general purpose cleaners (1995)
DA	=	dermal absorption; assume 100% dermal penetration
C_{ai}	=	concentration of active ingredient; 0.15 mg/cm^3 = 150 ppm
ET	=	exposure time per day; 8 hours/24 hours = 0.33 days

The following dermal exposure estimate was derived for professional cleaners:

Table 3.4.5 Dermal exposure estimate for professional cleaners

Dermal Exposure (mg/kg bw/day)	Margin of Exposure[a] (target = 100)
0.003	648

a. MOE_{Dermal} = NOAEL Dermal (mg/kg bw/day) / Dermal Exposure (mg/kg bw/day); NOAEL of 2.0 mg/kg bw/day from a 2-year rat study using IST/ISL; Target MOE = 100

Dermal exposure estimates for professional cleaners exceed the target margin of exposure of 100. The estimate derived is highly conservative as it assumes that professional cleaners will handle the concentrated product for a continuous 8-hour period.

Homeowner dermal exposure, to household cleaning products, was derived using the US EPA DERMAL model software (1995). Two scenarios were considered in estimating exposure; general purpose cleaners and hand washing with laundry detergents. Though the equations to estimate dermal exposure are the same, the inputs used to estimate exposure were scenario specific. The equation assumes that the general purpose cleaner will be used in undiluted form, while a default dilution value is used for laundry detergents. Surface area for general purpose cleaners was assumed to be that of two hands, while a larger surface area is considered for laundry detergents to take into account that forearms may also be immersed in water while hand washing. All of the cleaning scenarios assume that cleaning activities will only be conducted by adults. The equation was derived in the following manner:

$$\mathbf{E = WF \times SA \times FT \times FD \times DF \times CF / BW}$$

where,

E	=	dermal exposure (mg/kg bw/day)
WF	=	weight fraction of active ingredient (0.015% = 150 ppm)

SA = surface area; assumed surface area of hands for general purpose cleaner (904 cm^2) and surface area of hands and forearms for detergents (2077 cm^2);
FT = film thickness; 2.1×10^{-3} cm and 4.99×10^{-3} cm for general purpose cleaners and laundry detergent, respectively; default values provided by DERMAL Model
FD = formula density; 1.02 g/mL
DF = dilution fraction; assumed 1 for general cleaner and 1.85×10^{-3} for liquid laundry detergents based on default values provided by DERMAL Model
CF = conversion factor to convert g to mg; 1000 mg = 1g
BW = body weight; 70 kg

The following dermal exposure estimates were derived for homeowners using cleaning products:

Table 3.4.6 Dermal Exposure Estimates for Homeowners Using Cleaning Products

Scenario	Dermal Exposure (mg/kg bw/day)	Margin of Exposure (target = 300)
General Purpose Cleaner	4.1×10^{-3}	2410
Liquid Laundry Detergent	4.2×10^{-5}	238615

a. MOE_{Dermal} = Dermal NOAEL (mg/kg bw/day) / Dermal Exposure (mg/kg bw/day); NOAEL of 10.0 mg/kg bw/day from a rabbit development study using ISL; target MOE = 300

The margins of exposure for homeowners using cleaning products containing 2-methyl-4-isothiazolin-3-one are acceptable as the estimated MOE's are greater than 300.

Inhalation exposure estimates for both professional cleaners and homeowners to cleaning products containing 2-methyl-4-isothiazolin-3-one were derived in the same manner. The major difference between the two scenarios considered was the duration of cleaning events. Professional cleaners were assumed an 8-hour exposure duration per day, while homeowners were assumed a 0.75-hour duration (Exposure Factors Handbook; Table 16-16, 1997; Total Exposure Time for Ten Product Groups Most Frequently Used for Household Cleaning). The exposure time chosen was based on the liquid dish detergent, as it was the most conservative value. The 90^{th} percentile time value reported (hours per year) was chosen and normalized for daily use.

The approach taken to estimate inhalation exposure was derived from the US EPA Residential SOP approach to estimate vapour inhalation to pool water (1997). As these products are formulated as aqueous products, likely water based, and will be used in scenarios such as general purpose cleaning, mopping and washing dishes, assessing inhalation exposure to vapours was the most suitable approach.

Inhalation to water vapours is derived in the following manner:

$$\mathbf{E = C_{VP} \times IR \times ET / BW}$$

where,

E = inhalation exposure (mg/kg bw/day)
C_{VP} = concentration of vapour pressure (mg/m^3; derived below)
IR = inhalation rate; 1.0 m^3/hr
ET = exposure time; assume 8 hours professional, 0.75 hour homeowner per day
BW = body weight; 70 kg
where,

$C_{VP} = (C_W \times VP \times 273K \times MW \times 1000L/m^3 \times L/1000g) / (760\ mm\ Hg \times T \times 22.4L/mole)$

where,

C_W = concentration of ISL in water (150 mg/L)
VP = vapour pressure (7.3×10^{-4} kPa = 5.5×10^{-3} mm Hg)
T = temperature (vapour pressure based on 25°C; 273K + 25 = 298K)
MW = molecular weight of water (18 g/mole)

The following inhalation exposure estimates were derived for use of cleaning products:

Table 3.4.7 Inhalation Exposure Estimates for Cleaning Scenarios

Scenario	Vapour Concentration (C_{VP}; mg/m^3)	Inhalation Exposure (mg/kg bw/day)	Margins of Exposure[a]
Professional	8.0×10^{-4}	9.1×10^{-5}	635
Homeowner		8.6×10^{-6}	6774

a. $MOE_{Inhalation}$ = Inhalation NOAEL (mg/kg bw/day) / Inhalation Exposure (mg/kg bw/day); NOAEL of 0.058 mg/kg bw/day from a 90-day inhalation study using ISL; Target MOE (long-term) = 300; Target MOE (short-term) = 100

The margins of exposure for professional cleaners and homeowners using cleaning products containing 2-methyl-4-isothiazolin-3-one, specific to inhalation exposure, are acceptable as the estimated MOE's are greater than target MOE's (300 for professional; 100 for homeowners).

3.4.6 Dermal Sensitization Exposure and Risk

Due to the positive skin sensitization study findings, the well-known sensitization potential of the isothiazolinones and the use patterns proposed for these products, a sensitization risk assessment was deemed appropriate. A risk assessment for dermal sensitization was conducted. In order to determine whether the exposure via the dermal contact route is acceptable, dermal exposure must fall below the threshold for dermal sensitization, established by a Local Lymph Node Assay (LLNA) or Human Repeat Insult Patch Test (HRIPT).

Dermal sensitization is expected to occur through short-term contact exposure scenarios. A single contact event has the potential to cause dermal irritation, dependent on the active ingredient. Short-term exposure estimates are based on surface area and derived in the following manner:

$$\mathbf{E = \%a.i. \times FT \times CF}$$

where:

E = potential dermal contact exposure ($\mu g/cm^2$)
% a.i. = fraction of active ingredient in preserved liquids (150 ppm = 0.015%)
FT = film thickness of residue on hands (mg/cm^2)
CF = conversion factor to convert mg to μg; 1000 μg = 1 g

The application rate used in the estimate (150 ppm or 0.015%) was selected based on the highest application rate among all products.

The film thickness was assumed to be 10.3 mg/cm^2. This value was derived from a study commissioned by the US EPA to examine the retention of various liquids on hands. The value was chosen based on the retention of mineral oil on hands. In the absence of more specific data, this value represents a conservative estimate of dermal contact exposure. Furthermore, since the proposed products are aqueous liquids, estimation of dermal contact via residue loading represents an overestimate of dermal exposure as compared to dermal contact via mineral oil residue loading.

The dermal sensitization exposure estimate was derived as follows:

Table 3.4.8 Dermal Sensitization Exposure Estimate

Maximum Application Rate (% a.i.)	Film Thickness (mg/cm^2)	Dermal Contact Exposure ($\mu g/cm^2$)
0.015	10.3	1.5

The short-term dermal contact, to products containing the active ingredient 2-methyl-4-isothiazolin-3-one, is acceptable as the estimated exposure is below the target threshold value of 215 $\mu g/cm^2$.

3.4.7 Post-Application Exposure and Risk to Bystanders

3.4.7.1 Post-Application Paint Exposure

There is the potential for post-application exposure to Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide or Rocima 550 Industrial Microbicide following contact with surfaces treated with paints containing Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide or Rocima 550 Industrial Microbicide. The exposure scenarios

would include: dermal (adult and children); incidental oral from hand-to-mouth contact (children); and incidental oral from ingestion of paint chips (children). There is no available data to quantify potential dermal exposure to adults or children, or oral exposure to children from hand-to-mouth contact. Therefore, the post-application exposure for children eating paint chips was assessed.

The following assumptions were used in the assessment: ingestion rate of paint chips is 0.04 g/day; children 3 years of age weigh 15 kg; 20% of active ingredient is in the paint chip and is available for ingestion. The maximum concentration of 2-methyl-4-isothiazolin-3-one, 120 mg/L, is from the combination of polymer latices and mineral slurries in the final paint product.

Table 3.4.9 Exposure from the Ingestion of Paint Chips

Scenario	Exposure (mg/kg bw/day)	Margin of Exposure[a]
Ingestion of Paint Chips	6.4×10^{-5}	156250

a. Based on a NOAEL of 10 mg/kg bw/day from a rabbit developmental study using ISL; Target MOE = 100

The margin of exposure for ingestion of paint chips is considered acceptable. Dermal exposure, and oral exposure from hand-to-mouth contact are not expected to exceed exposure from ingestion of paint chips.

3.4.7.2 Post-Application Detergent Exposure

There is potential for post-application exposure to Neolone M-10 Industrial Microbicide following contact with surfaces and materials that have been cleaned with Neolone M-10 Industrial Microbicide. The exposure scenarios would include: dermal (adult and children); oral from use of dishware (adult and children); and oral for hand-to-mouth contact (children). There are no available data to quantify the exposure potential for oral exposure from dishware and hand-to-mouth contact. However, it is not expected that these exposures will exceed paint chip ingestion exposure, as most of the surfaces will be rinsed or wiped, thus decreasing the amount of 2-methyl-4-isothiazolin-3-one residues remaining on surfaces of dishware. Furthermore, in many instances, such as dishwashing and mopping, the detergent may be diluted with water, further decreasing the exposure to 2-methyl-4-isothiazolin-3-one.

The post-application exposure to laundry residues for adults and children was assessed. Unlike other residential exposures, dermal exposure to laundry residues is expected to be of long-term duration. The following assumptions were used in the assessment: the entire body could contact laundered clothing, therefore, the surface area for adults is 18440 cm^2 and 2-3 year old children is 5910 cm^2; 10% of active ingredient is available for dermal contact; 4×10^{-5} mg/cm^2 of active ingredient is deposited onto laundered clothing; and adults weigh 70 kg while children 3 years of age weigh 15 kg. Based on the maximum application rate of 150 mg/L 2-methyl-4-isothiazolin-3-one, as an in-can preservative, and the assumptions listed above, the following dermal exposures have been derived for laundry washed with cleaning products containing Neolone M-10 Industrial Microbicide:

Table 3.4.10 Dermal Exposure to Laundry Residues

Scenario	Dermal Exposure (mg/kg bw/day)	Margin of Exposure[a]
Adult	1.6×10^{-7}	1.3×10^{7}
Toddler	2.4×10^{-7}	8.5×10^{6}

a. Based on a NOAEL of 2.0 mg/kg bw/day from a 2 year rat study using IST/ISL; Target MOE =100.

The margin of exposure for dermal exposure to laundry residues is considered acceptable for both adults and toddlers.

3.5 Food Residues Exposure Assessment

A food residue exposure assessment was not required for this application.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

2-Methyl-4-isothiazolin-3-one is the active ingredient in a number of end-use products which will be used as a material preservative in paint, coatings, metal-working fluid, household products and polymer latices. Based on the proposed use pattern, terrestrial and aquatic environmental exposure is expected to be minimal. In the aquatic and terrestrial environment, 2-methyl-4-isothiazolin-3-one is stable to hydrolysis (~100% of the parent remains after 30 days) and undergoes rapid biotransformation in soil (DT_{50}: 4.5 hours) to four major transformation products, M1, M2, M3 and M4. The four transformation products undergo further biotransformation with half lives ranging from four to nineteen days. The ultimate product of aerobic soil biotransformation is carbon dioxide which reached 46.6% by study termination, and non-extractable residues which totalled 40% at study termination. Based on the short half lives of 2-methyl-4-isothiazolin-3-one and its transformation products on soil, it is expected that concentrations in groundwater will be low.

Data on the fate and behaviour of 2-methyl-4-isothiazolin-3-one and its major transformation products are summarized in Appendix I, Figure 5-1 and Table 5-2.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates,

vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Based on the use pattern, terrestrial and aquatic environmental exposure is expected to be minimal. Neolone M-10 Industrial Microbicide is a material preservative used in a variety of household products including dishwashing detergent. A potential exposure scenario may include dish washing detergent being used and then entering a water body (based on lack of dissipation via hydrolysis). However, based on the rate of application for Neolone M-10 Industrial Microbicide at 25 to 150 mg/L, with dilution in water for dish washing and then additional dilution in water in sewers, treatment plants and bodies of water, the amount of active reaching aquatic environments is expected to be negligible. It should be noted that 2-methyl-4-isothiazolin-3-one is susceptable to microbial degradation (as observed in the aerobic soil and adsorption/desorption study), and thus would likely transform quickly once in the natural aquatic environment. Other end-use products, such as Kordex LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide and Rocima 550 Industrial Microbicide are proposed for use in metal-working fluids, polymer latices, mineral slurries and paint. These types of end-use products are not expected to result in significant environmental exposure to 2-methyl-4-isothiazolin-3-one during use. Post disposal of containment units or paint cans, or treatment plant production in metal-working facilities may potentially result in some point source exposure to 2-methyl-4-isothiazolin-3-one. However, based on its rapid dissipation in soil and susceptibility to aquatic transformation, concentrations of 2-methyl-4-isothiazolin-3-one are expected to be minimal.

4.2.1 Risks to Terrestrial Organisms

Data on toxic effects of 2-methyl-4-isothiazolin-3-one to terrestrial organisms is not currently required based on the current use pattern, as exposure to terrestrial organisms is not expected.

4.2.2 Risks to Aquatic Organisms

Based on submitted data the risks of 2-methyl-4-isothiazolin-3-one to freshwater aquatic organisms was characterized (see Appendix I, Table 6-1). The risk assessment was based upon evaluation of toxicity data for the following:

- 1 invertebrate species (acute exposure to daphnia)
- 1 fish species (acute exposure to rainbow trout)

For freshwater invertebrates, 2-methyl-4-isothiazolin-3-one caused acute mortality at concentrations of 2.2 mg a.i./L (LC_{50}: 2.4 mg a.i./L). For freshwater fish (rainbow trout), 2-methyl-4-isothiazolin-3-one caused sublethal effects (including rapid respiration) and acute mortality at 2.2 mg a.i./L and 6.0 mg a.i./L, respectively [LC_{50}: 7.1 mg a.i./L, NOEC (sublethal effects): 1.3 mg a.i./L].

4.2.3 Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the PMRA website http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/incident/index-eng.php. Incidents from Canada and the United States were searched and reviewed for products containing the active ingredient 2-methyl-4-isothiazolin-3-one. As of August, 2010, the PMRA concluded that there were no environmental incident reports found for 2-methyl-4-isothiazolin-3-one.

5.0 Value

5.1 Effectiveness Against Pests

Data from seven efficacy trials were submitted for the following aqueous-based materials: metal-working fluids, mineral slurries, polymer emulsions, paints, liquid detergent and polish. The studies were relevant to the pest problem, scientifically valid and conducted with a number of samples of each material, representing a variety of commercial products. The trials consisted of dosing the materials to be preserved with the active ingredient at a range of rates and inoculating them with relevant challenge bacteria and fungi.

Following an appropriate incubation period, the microorganisms within the material samples were enumerated. To determine the effectiveness of the treatment, the number of surviving bacteria and fungi were compared to those in the untreated material samples.

5.1.1 Acceptable Efficacy Claims

The submitted data established an effective range of rates for a number of materials requiring in-container preservation that are displayed in Table 5.1.1. As a result of the human exposure assessment, the rates were reduced but were still within an effective range.

Table 5.1.1 Rates supported by efficacy data and rates acceptable based on human exposure

Material	Effective rate range (ppm a.i.)	Accepted rate range (ppm a.i.)
Metal-working fluids	75 – 150	75 – 150
Polymer latices	100 – 150	100
Paints/Coatings	50 – 75	50 – 65
Mineral Slurries	25 – 150	25 – 50
Detergents	25 – 150	25 – 150
Cleaners	25 – 150	25 – 150
Polishes	25 – 150	25 – 150

5.2 Economics

No information was provided.

5.3 Sustainability

5.3.1 Survey of Alternatives

The availability of 2-methyl-4-isothiazolin-3-one would provide an additional preservative for the in-container treatment of a number of aqueous-based products. There are currently close to 20 different active ingredients or combinations of active ingredients that are registered for use as in-container preservatives for aqueous-based materials. Having a large variety of active ingredients available for formulators of aqueous-based products is advantageous, when considering differences in cost, availability and chemical compatibility of active ingredients with other formulants.

The key alternatives available for the in-container preservation of aqueous-based products are summarized in Appendix I, Table 8.

5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

The compound 2-methyl-4-isothiazolin-3-one is not known to be chemically incompatible with common formulants of paints, detergents or metal-working fluids. Aqueous-based products may vary in their susceptibility to microbial spoilage due to differences in the microbial load introduced when formulating the product and the microbial nutrition available in the formulation (e.g. cellulose fillers). It is also possible to have an unpreserved paint that contains biocides present as preservatives in paint formulants such as polymer latices and pigment slurries. For this reason, there is significant variation in the need for preservation. This has been addressed by registering a range of effective rates that allows formulators to use an appropriate amount of preservative, rather than a single rate for all materials.

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

It is unlikely that microbial resistance will be an issue in preserving the polymer latices, paints, detergents, cleaners and polishes. Antimicrobial resistance typically occurs when bacteria or fungi are repeatedly exposed to sub-lethal concentrations of a particular biocide. In the case of these materials, the biocide will be added once upon formulation. Metal-working fluids would be more susceptible to resistance development as the same material is recirculated and biocide is added tank side at intervals. However, there are a number of different preservatives available with a range of different modes of action that can be used to keep resistance from becoming an issue.

The compound 2-methyl-4-isothiazolin-3-one has been used as a preservative in combination with 5-chloro-2-methyl-4-isothiazolin-3-one for many years. During its use, there have not been reports of significant resistance issues.

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 (those that meet all four criteria outlined in the policy, i.e., CEPA-toxic or equivalent, predominantly anthropogenic, persistent and bio-accumulative).

During the review process, 2-methyl-4-isothiazolin-3-one and its transformation products (M1, M2, M3 and M4) were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- 2-Methyl-4-isothiazolin-3-one does not meet the Track 1 criteria and will not form any transformation products that will meet the Track 1 criteria.

6.2.1 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*[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: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade 2-methyl-4-isothiazolin-3-one and the end-use products do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

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

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

7 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, PMRA Formulants Policy.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for Kordek is adequate to define the majority of toxic effects that may result from exposure. In short and long term studies on laboratory animals, the primary effects noted were effects on body weight, body weight gain, food consumption and irritation at the site of application (skin, stomach or nasal cavity/lungs) as well as dermal sensitization. Kordex is not considered to have carcinogenic potential and is not considered to be genotoxic. Effects on the developing foetus were observed at dose levels that were toxic to the mother. There was an increased incidence of late foetal resorptions accompanied by a reduction in the number of live foetuses per dam in the developmental toxicity study in rabbits. Changes in parental and offspring organ weights as well as delayed sexual maturation and slight decreases in the number of live births were also observed at doses that were toxic to the mother in the rat reproduction study. Kordek is not considered to be a neurotoxicant.

Mixers, loaders and applicators handling Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide and workers entering treated areas where the manufacturing of the commercial products occurs are not expected to be exposed to levels of 2-methyl-4-isothiazolin-3-one that will result in an unacceptable risk when Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide area used according to label directions.

Residential exposure to individuals handling Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide or Neolone M-10 Industrial Microbicide containing 2-methyl-4-isothiazolin-3-one, is not expected to result in unacceptable risk.

Therefore, the health assessment has demonstrated that proposed uses for metalworking fluids and cleaning products are not expected to result in an unacceptable risk. Exposure to paints and coatings, polymer latices and mineral slurries was found to be acceptable, provided the final paint product contains a maximum concentration of 2-methyl-4-isothiazolin-3-one of 65 ppm. Therefore, the following application rates must be adhered to:

Rates Supported

Proposed Product	Proposed Use	Revised Applications Rates
Kordek LX 5000 Industrial Microbicide	Polymer Latices	100 ppm a.i.
Kordek MLX Industrial Microbicide	Polymer Latices	100 ppm a.i.
	Mineral Slurries	25 – 50 ppm a.i.
Rocima 550 Industrial Microbicide	Paints & Coatings	50 – 65 ppm a.i.

7.2 Environmental Risk

2-Methyl-4-isothiazolin-3-one is not expected to present a risk to wild mammals, birds, freshwater or marine invertebrates and fish, amphibians, algae, and aquatic and terrestrial plants. Due to the inherent aquatic toxicity of the active ingredient, mitigative label statements are required for some end-use products related to aquatic exposure and disposal.

7.3 Value

The data submitted to register 2-methyl-4-isothiazolin-3-one are adequate to describe its efficacy for use as an in-container preservative for metal-working fluids, polymer latices, paints, liquid detergents, cleaners and polishes. The compound 2-methyl-4-isothiazolin-3-one offers an additional active ingredient for aqueous-based material formulators that may aid in producing cost-effective products.

7.4 Unsupported Uses

All of the uses proposed by the applicant for 2-methyl-4-isothiazolin-3-one were supported by the PMRA.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Kordek 573T Technical Microbicide, Kordek 573F Industrial Microbicide, Kordek LX 5000 Industrial Microbicide, Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide and Neolone M-10 Industrial Microbicide, containing the technical grade active ingredient 2-methyl-4-isothiazolin-3-one, to be used as a material preservative in paint, coatings, metal-working fluids, household products and polymer latices.

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.

List of Abbreviations

µg	microgram(s)
a.i.	active ingredient
AD	administered dose
ADI	acceptable daily intake
ARfD	acute reference dose
AST	aspartate transaminase
atm	atmosphere(s)
BAF	bioaccumulation factor
BBG	1,2-dibromo-2,4-dicyanobutane
BCF	bioconcentration Factor
BND	bronopol
BRN	2,2-dibromo-3-nitrilopropionamide
bw	body weight
bwg	body weight gain
BZZ	1,2-benzisothiazolin-3-one
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
cm	centimetre(s)
CMA	chemical manufacturers association
CTA	1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride
DAZ	dazomet
DMY	1,3-bis(hydroxymethyl)-5,5-dimethylhydantoin
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DUW	dodecylguanidine hydrochloride
EC3	threefold elicitation concentration
EEC	estimated environmental exposure concentration
F_1, F_2	first generation, second generation
fc	food consumption
g	gram(s)
GD	gestation day
GLT	glutaraldehyde
HDO	oxirane derivatives (50% minimum) (mixture) 50; 5-hydroxymethoxymethyl-1-aza-3,7-dioxabicyclo-(3.3.0) octane; 5-hydroxymethyl-1-aza-3,7-dioxabicyclo-(3.3.0) octane.; 5-hydroxypoly [methyleneoxy 74%c2, 21%c3, 4%c4, 1%c5] methyl-1-aza-3, 7-dioxabicyclo(3.3.0) octane
Hg	mercury
HHT	hexahydro-1,3,5-tris(2-hydroxyethyl)-s-triazine
HPLC	high performance liquid chromatography
HPLC-UV	high performance liquid chromatography with ultraviolet detection
HPLC-MS/MS APCI+	high performance liquid chromatography with tandem mass spectrometry detection using atmospheric pressure chemical ionization, positive ion mode
hr	hour(s)
HRIPT	human repeat insult patch test
ISL	2-methyl-4-isothiazolin-3-one
ISP	integrated system product
IST	5-chloro-2-methyl-4-isothiazolin-3-one

IUPAC	International Union of Pure and Applied Chemistry
KDD	potassium dimethyldithiocarbamate
kg	kilogram(s)
K_{ow}	*n*–octanol-water partition coefficient
K_p	skin permeability coefficient
L	litre(s)
LC_{50}	lethal concentration 50%
LD	lactation day
LD_{50}	lethal dose at 50%
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
m	metre(s)
MAS	maximum average score
MBC	methylene bis(thiocyanate)
MCI	5-chloro-2-methyl-4-isothiazolin-3-one
mg	milligram(s)
MI	2-methyl-4-isothiazolin-3-one
MIS	maximum irritation score
MIT	2-methyl-4-isothiazolin-3-one
mL	millilitre(s)
MMY	hydroxymethyl-5,5-dimethylhydantoin
MOE	margin of exposure
MS	mass spectrometry
MWF	metal-working fluid
NAFTA	North American Free Trade Agreement
NIOSH	National Institute for Occupational Safety and Health
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NUO	[[[1-methyl-2-(5-methyl-3-oxazolidinyl)ethoxy]methoxy]methoxy]methanol
NZW	New Zealand white
OPP	2-phenylphenol
Pa	pascal(s)
PCPA	*Pest Control Products Act*
PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
POD	poly[oxyethylene(dimethyliminio)ethylene(dimethyliminio)ethylene dichloride]
ppm	part(s) per million
PVK	4-chloro-3-methylphenol
TBM	tri-n-butyltin maleate
TCM	2-(thiocyanomethylthio)benzothiazole
t_{max}	time of maximum concentration of the substance
TSMP	Toxic Substances Management Policy
US EPA	United States Environmental Protection Agency
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Soil	N/A	MI	HPLC-UV 275 nm	0.05 µg/g	1669184
		MCI			
Sediment		MI			
		MCI			
Water	N/A	MI	HPLC-MS/MS APCI+ 116 → 101 m/z	0.05 µg/L	1669185, 1669186

Table 2 Toxicity Profile of End-use Products Containing 2-Methyl-4-isothiazolin-3-one (Kordek MLX Industrial Microbicide, Rocima 550 Industrial Microbicide, Neolone M-10 Industrial Microbicide)

Study Type/Animal/Reference	Study Results
Acute oral toxicity Waiver	Bridged to Technical Grade Active Ingredient Highly toxic
Acute dermal toxicity Waiver	Bridged to Technical Grade Active Ingredient Highly toxic
Acute inhalation toxicity Waiver	Bridged to Technical Grade Active Ingredient Moderately toxic
Dermal irritation Waiver	Bridged to dermal irritation study using Kordek 50C, supported by results of acute dermal toxicity study using 9.5% methylisothiazolininone (this study not submitted). Extremely irritating to the skin
Eye irritation Waiver	Based on dermal irritation data (see above) Corrosive to the eye
Dermal sensitization Waiver	Bridged to Technical Grade Active Ingredient Sensitizer

Effects are known or assumed to occur in both sexes unless otherwise noted)

Table 3 Toxicity Profile of Kordek 573T Technical Microbicide

Study Type/Animal/Reference	Study Results
Metabolism Rats, SD (main, cannulation) Mice CD-1 (supplemental tissue distribution) PMRA #1631280 (main) PMRA # 1792787 (cannulation) PMRA # 1792786 (mice distribution)	**Absorption**: Absorption was rapid and extensive, approximately 92% to 96% of the AD was recovered **Excretion**: Excretion was rapid and extensive. Urine accounted for 56-65% (low dose) and 47-50% (high dose) of AD, and feces accounted for 21-29% (low dose) and 34-37% (high dose) of AD. In a separate biliary excretion study, 29% of the AD was excreted via the bile supporting the conclusion of extensive absorption. **Kinetics:** Peak blood and plasma concentration were reached after 1-3 hours. A biphasic kinetic profile was suggested with an initial plasma half-life of 3-4 hours/5-6 hours (low/high dose) followed by a terminal half-life of 27-29 hours (both groups). Although radioactivity levels in whole blood were comparable to plasma at t_{max}, by 96 hours they exceeded plasma levels in a ratio of 110:1. **Distribution**: Radioactivity was distributed mostly in highly vascularized tissue. The highest levels at 96 hours were found in the adrenals, whole blood, heart, kidneys, liver, lungs, spleen and thyroid; of these tissues, the thyroid contained the highest levels. Plasma levels were markedly lower at 96 hours than many other tissues, indicating possible tissue binding or incorporation in the C1 pool. No marked differences between sexes were noted, apart from a tendency for females to have a higher tissue concentration in the thyroid, and higher levels in the gonads when compared with males. AD levels in the carcass were indirectly determined to be 2.5-3.65% (low-dose) and 1.9-2.2 % (high-dose) after 96 hours. In separate tissue distribution study, 15 CD-1 mice/sex were dosed at 100 mg/kg bw via oral gavage with radiolabeled Kordek to examine tissue distribution over time in serum, whole blood, bone, bone marrow and liver. Initial tissue levels were high with the liver being the highest (107 ppm in males, 56.5 ppm in females). After 24 hours, the AD tended to partition from plasma into tissue, but overall levels decreased rapidly reaching 0.510 to 7.50 ppm in males and 0.295 to 9.00 ppm in females. In general, males tended to have higher tissue residue than females.
Metabolism (cont)	**Metabolism:** Metabolism of Kordek was extensive, with no parent compound found in the excreta. The proposed metabolic pathway for Kordek involves Phase I metabolism with oxidative or reductive cleaving of the molecule (thus opening the ring), followed by Phase II metabolism involving conjugation of Phase I metabolites with mercapturic acid moieties. Fourteen metabolites were identified and structurally elucidated with13 of these found in urine. The primary metabolites were N-methyl malonamic acid (M1) and a 3-mercapturic acid conjugate of 3-thiomethyl-N-methyl-propanamide (M12). They were the major components of urine samples, accounting for 20.9-23.3% and 9.7-22.7% (low dose/high dose) of AD. M2 (the primary feces metabolite), M3 (urine and feces) and M9 (urine) also accounted for more than 5% of the dose recovered. Thirteen fecal metabolites were identified but not characterized, composing 0.66-1.73% of the administered dose. Kordek was extensively metabolized following administration of a single oral gavage dose of 50 mg/kg bw to four female bile duct cannulated rats. Bile, urine and feces were collected for 24 hours. Bile accounted for approximately 29% of the AD. Urinary and fecal excretion accounted for 53% and 6% of the AD, respectively. Total recovery (urine, bile, feces) was 88% of AD. M1 and M12 were the major urinary metabolites. Parent compound was not detected in either urine or feces. Most of the biliary metabolites were glutathione conjugates, its derived conjugates, or di-conjugates of glutathione (or cysteinylglycine) and glucuronic acid.

Study Type/Animal/Reference	Study Results
Acute Oral Toxicity Rat, CD PMRA #1631263	LD_{50} ♂ = 235 mg/kg bw LD_{50} ♀ = 183 mg/kg bw Highly toxic
Acute Oral Toxicity Rat, CD PMRA #1792768	LD_{50} ♂ = 232 mg/kg bw LD_{50} ♀ = 120 mg/kg bw Highly toxic
Acute Oral Toxicity Mouse,CD-1(ICR)BR PMRA # 1792769	LD_{50} = 167 mg/kg bw Highly toxic
Acute Dermal Toxicity Rat, CD PMRA #1631264	LD_{50} = 242 mg/kg bw Highly toxic
Acute Inhalation Toxicity Rat, CD PMRA # 1631265	LC_{50} ♂ = 0.13 mg/L LC_{50} ♀ = 0.10 mg/L Moderately toxic
Dermal Irritation Rabbit, NZW PMRA # 1631267	MAS = 8, MIS = 8 Corrosive
Eye Irritation	Waiver based on dermal irritation study. Considered corrosive to the eye
Skin Sensitization (Modified Buehler) Guinea Pig PMRA # 1631268	Skin Sensitizer Study is considered supplemental
Skin Sensitization (Maximization Test) Guinea Pig	Equivocal results Study is considered supplemental

Study Type/Animal/Reference	Study Results
PMRA # 1792771	
Skin Sensitization (Open Epicutaneous) Guinea Pig PMRA # 1792772	Positive Study is considered supplemental
Skin Sensitization (LLNA) Mouse, CBA/J PMRA # 1792774	Positive at ≥1.35% a.i. Interpolated EC3 = 0.86%, equivalent to 215 µg/cm^2
Acute Oral Toxicity (N-methyl-malonamic acid, M-1 metabolite) Rat PMRA # 1792770	LD_{50} ♂ = 3550 mg/kg bw LD_{50} ♀ = 4100 mg/kg bw Low toxicity
Skin Sensitization (LLNA) (N-methyl-malonamic acid, M-1 metabolite) Mouse, CBA/J PMRA # 1792773	Negative at up to 30% concentration
90-day Inhalation Kathon 886 Technical Microbicide Rat, SD PMRA # 1792779	NOAEL = 0.34 mg/m^3 LOAEL = 1.15 mg/ m^3 Based on very slight to slight rhinitis in nasal cavity
90 day Drinking Water Rat, CD PMRA # 1631269	NOAEL = 19.0/24.6 mg/kg bw/day (♂/♀) LOAEL = 65.7/93.5 mg/kg bw/day (♂/♀) Based on ↓ bw/bwg, ↓fc (slight in ♀), ↓ water consumption; ↓ bilirubin (♂); ↓ glucose (♀)

Study Type/Animal/Reference	Study Results
2-year Drinking Water Chronic/Carcinogenicity Kathon 886 Technical Microbicide Rat, SD PMRA # 1631270	NOAEL = 2.0/3.1 mg/kg bw/day (♂/♀) LOAEL = 6.6/9.8 mg/kg bw/day (♂/♀) Based on ↓bw/bwg, fc (♀); ↑urinary specific gravity (secondary to ↓water intake), ↑ incidence of dark foci/areas and depressed foci/areas in the gastric mucosa, prominent limiting ridge and/or thickened non-glandular mucosa of the forestomach, hyperplasia/hyperkeratosis of the squamous mucosa of the forestomach, focal necrosis of the glandular mucosa
2-Generation (drinking water) Reproductive Toxicity Rat, SD PMRA # 1631272	**Parental toxicity:** NOAEL = 15/22 mg/kg bw/day (♂/♀) LOAEL = 69/93 mg/kg bw/day (♂/♀) Based on ↓ water consumption (both generations), ↓ bw and fc (both generations), ↓bwg (♂ both generations, ♀ during pre-mating, gestation, beginning of lactation), organ weight effects (↑kidney, ↓pituitary) **Reproductive toxicity:** NOAEL = 15/22 mg/kg bw/day LOAEL = 69/93 mg/kg bw/day Based on organ weight effects (ovary, seminal vesicle + coagulating gland and fluids, left cauda epididymis, prostate, testes, uterus), ↑ uterine luminal distension; ↓ number of implantation sites and mean number of pups born **Offspring toxicity:** NOAEL = 15/22 mg/kg bw/day (♂/♀) LOAEL = 69/93 mg/kg bw/day (♂/♀) Based on ↓bw (LD7-21 in F_1, LD7-14 in F_2); ↑incidence of dilated renal pelvis (F_2); ↓ spleen weights (F_2) and thymus weights ($F_1 + F_2$); delayed sexual maturation (F_1)
Developmental (drinking water) Toxicity Rat, SD PMRA # 1631274	**Maternal Toxicity**: NOAEL = 20 mg/kg bw/day LOAEL = 40 mg/kg bw/day Based on mortality, agonal clinical signs and red areas in the glandular portion of the stomach, dark red discolouration of the lungs and/or lungs characterized as not fully collapsed in decedents; in survivors: rales, gasping and laboured breathing; ↓bw /bwg, fc, most significant on GD 6-9 with bw loss noted. **Developmental Toxicity:** NOAEL = 40 mg/kg bw/day LOAEL not established No developmental toxicity

Study Type/Animal/Reference	Study Results
Developmental (drinking water) Toxicity Rabbit, NZW PMRA # 1631275	**Maternal toxicity**: NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day Based on decreased defecation (4/24 females beginning on GD 7); body weight loss GD 6-9 (stat. sig. for GD 7-8); ↓ food consumption; dark red areas in stomach; increased incidence of late resorptions, ↓ live foetus per dam **Developmental toxicity:** NOAEL = 10 mg/kg bw/day LOAEL = 30 mg/kg bw/day Based on ↑ incidence of late resorptions and ↓ live foetus per dam
Gene mutations in bacteria *Salmonella typhimurium* PMRA # 1631276	Negative – tested up to cytotoxic concentrations
Gene mutations in bacteria *Salmonella typhimurium* PMRA # 1792782	Negative – study considered supplemental
Gene mutations in bacteria (N-methyl malonamic acid, metabolite) *Salmonella typhimurium* PMRA # 1792783	Negative – tested up to the limit concentration
Gene mutations in mammalian cells *in vitro* Chinese hamster ovary cells (HGPRT locus) PMRA # 1631277	Negative – tested up to cytotoxic concentrations

Study Type/Animal/Reference	Study Results
Unscheduled DNA synthesis (*in vivo*/*in vitro*) Primary rat hepatocytes PMRA # 1792784	Negative
Chromosome aberrations *in vitro* Chinese hamster ovary cells PMRA # 1631278	Increased chromosome aberrations at cytotoxic concentrations

(Effects are known or assumed to occur in both sexes unless otherwise noted; organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for 2-Methyl-4-isothiazolin-3-one

Exposure Scenario	Study	Point of Departure and Endpoint	Target MOE[1]
Short-term dermal[2]	Rabbit developmental toxicity study	NOAEL: 10 mg/kg bw/day Late resorptions accompanied by reduced number of live foetuses per dam, decreased defecation, body weight loss, reduced food consumption and dark red areas in the stomach	**300**
Long-term dermal[2]	2 year chronic/cancer rat study	NOAEL: 2 mg/kg bw/day (♂) Reduced body weight, body weight gain and food consumption, various signs of irritation in the stomach	**100**
Short-term inhalation	90 day inhalation rat study	NOAEL: 0.34 µg/L (≈ 0.06 mg/kg bw/day) Rhinitis in the nasal cavity	**100**
Long-term inhalation	90 day inhalation rat study	NOAEL: 0.34 µg/L (≈ 0.06 mg/kg bw/day) Rhinitis in the nasal cavity	**300**
Non-dietary oral ingestion (short-term)	Rabbit developmental toxicity study	NOAEL: 10 mg/kg bw/day Decreased defecation, body weight loss, reduced food consumption and dark red areas in the stomach	**100**
Dermal Sensitization	LLNA (mice) and HRIPT (humans, confirmatory)	EC3: 215 µg/cm^2 (LLNA) Threshold: 15 µg/cm^2 (HRIPT)	**100 (mice)** **10 (humans)**
Cancer	A quantitative cancer risk assessment was not required		

[1] MOE refers to a target MOE for occupational and residential assessments
[2] Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation

Table 5 Fate and Behaviour in the Environment

Figure 5.1 Proposed pathway of soil biotransformation

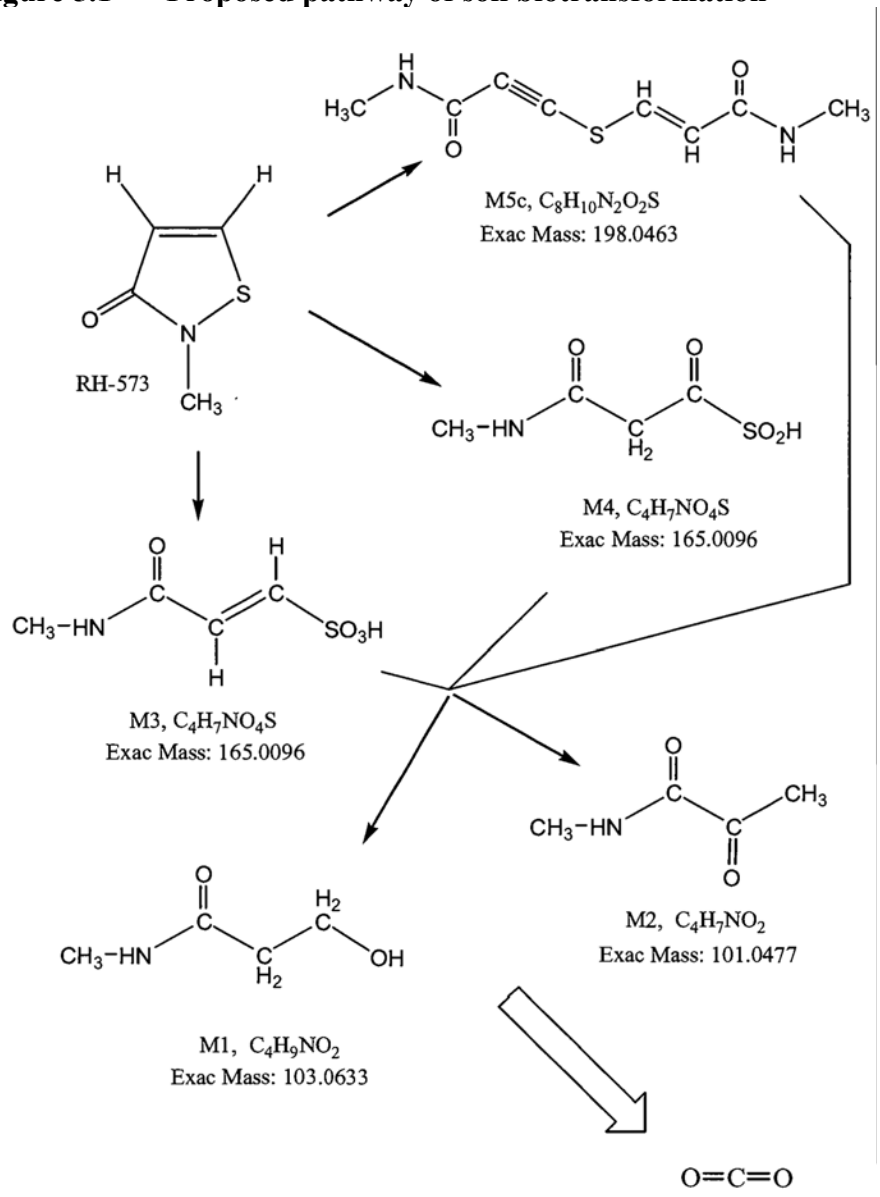

Table 5.2 Fate and Behaviour in the Environment

Property	Test substance	Value	Transformation products	Comments
Abiotic transformation				
Hydrolysis	2-methyl-4-isothiazolin-3-one	DT_{50}: >30 days	none	Hydrolysis is not an important route of transformation
Biotransformation				
Biotransformation in aerobic soil	2-methyl-4-isothiazolin-3-one	DT_{50}: 4.5 hours	M1 (DT_{50}: 463 hours) M2 (DT_{50}: 106 hours) M3 (DT_{50}: 160.7 hours) M4 (DT_{50}: 127 hours)	Aerobic soil biotransformation is an important route of transformation for the parent and major transformation products. Parent, M2, M3 and M4 are non-persistent and M1 is slightly persistent
Mobility				
Adsorption / desorption in soil	2-methyl-4-isothiazolin-3-one	2-methyl-4-isothiazolin-3-one is not stable under the test conditions because of microbial transformation. No isotherm determinations were conducted on the parent chemical.		

Table 6 Toxicity to Non-Target Species

Species	Test	LC50	NOEC	Comments
Daphnia magna	48 hour acute	2.4 mg a.i./L	2.2 mg a.i./L (mortality)	moderately toxic
Rainbow trout	96 hour acute	7.1 mg a.i./L	1.3 mg a.i./L (rapid respiration)	moderately toxic

Table 7 TSMP Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value	Active Ingredient Endpoints	Transformation Products Endpoints
Toxic or toxic equivalent as defined by the *Canadian Environmental Protection Act*[1]	Yes	.	
Predominantly anthropogenic[2]	Yes	Yes	

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints	Transformation Products Endpoints
Persistence[3]:	Soil	Half-life ≥ 182 days	4.5 hours	M1 (DT_{50}: 463 hours) M2 (DT_{50}: 106 hours) M3 (DT_{50}: 160.7 hours) M4 (DT_{50}: 127 hours)
	Water	Half-life ≥ 182 days	Stable to hydrolysis (> 30 days)	
	Sediment	Half-life ≥ 365 days	Not known	
	Air	Half-life ≥ 2 days or evidence of long range transport	Potential for long-range atmospheric transport based on the vapour pressure (0.73 Pa) and Henry's Law Constant (8.077×10^{-10} atm m^3/mole). May be negligible based on end-use product.	
Bioaccumulation[4]	Log $K_{OW} \geq 5$		0.486	
	BCF ≥ 5000		Value or not available	
	BAF ≥ 5000		Value or not available	
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet TSMP Track 1 criteria.	No, does not meet TSMP Track 1 criteria.

1 All pesticides will be considered toxic or toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the toxicity criterion may be refined if required (i.e., all other TSMP criteria are met).

2 The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

3 If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

4 Field data (e.g., BAFs) are preferred over laboratory data (e.g., BCFs) which, in turn, are preferred over chemical properties (e.g., log K_{OW}).

Table 8 Alternative material preservatives for the in-container protection of aqueous-based materials

Actives	Example of End-Use Product	Reg. No.	Registered Uses
CTA	DOWICIL 75 PRESERVATIVE	27569	paints, MWF, latices
NUO	NUOSEPT 145 PRESERVATIVE LIQUID	25554	paints, latices
BZZ	NIPACIDE BIT 20 LIQUID	27268	latices, paints, MWF
BBG	TEKTAMER 38 A.D.	17325	paints, MWF, latices, polishes, waxes, liquid detergents
TCM	BUSAN 30WB LIQUID	28093	MWF

Actives	Example of End-Use Product	Reg. No.	Registered Uses
	MICROBICIDE		
BRN	DOWICIL QK-20 ANTIMICROBIAL	27533	paints, mineral slurries, latices, polishes, waxes
OPP	DOWICIDE 1E ANTIMICROBIAL	27893	polish, MWF
PVK	PREVENTOL CMK-NA PRESERVATIVE	28308	latices, MWF, paints, mineral slurries, polishes, waxes
HHT	GROTAN BK METAL WORKING MICRO-BIOCIDE	11691	MWF, mineral slurries, latices, paints, polishes, liquid detergents
IST ISL	KATHON (TM) 886 MW BIOCIDE	15245	MWF, mineral slurries, latices, detergents, polishes
KDD	COOL SAVER	21125	MWF
POD	ALGEX LIQUID MICROBICIDE	22587	MWF
GLT	UCARCIDE 250 PRESERVATIVE	23784	paints, MWF
DAZ	AMA-35D-PC	23954	mineral slurries
BND	ULTRA-FRESH SAB	24221	mineral slurries, paints, latices, liquid detergents, polishes
TBM	ULTRAFRESH DM-50N	14498	latices
HDO	NUOSEPT 95 PRESERVATIVE	19201	latices, paint, mineral slurries
DMY MMY	GLYCOSERVE LAD	25755	liquid detergents
MBC DUW	SPECTRUM RX3100 MICROBIOCIDE AGENT	24506	mineral slurries

Appendix II Dermal Exposure Input Calculations for Dermal Exposure to Metalworkers:

To estimate dermal exposure, the approach taken relies on using theoretically derived values for skin permeability coefficients. The equations used to calculate skin permeability coefficients (K_p) are adapted from correlation of Potts and Guy (1992) which is based only on human *in vitro* data (RAGS-E, 2004). The equation addresses non-steady state exposure using the Cleek and Bunge Approach (1993). This approach was recommended by the US EPA (1992) for estimating exposure to organic compounds in water.

The following uncertainties exist with the application of these equations to estimate dermal exposure to active ingredients:

- The use of K_P for formulated antimicrobials may over- or underestimate exposure as the formulation may result in increased or decreased dermal absorption potential compared to the calculated K_p value, which is based on data from 2-methyl-4-isothiazolin-3-one in pure form.

- The equation used to derive K_p values is based on *in vitro* data rather than *in vivo* data. However, the relationship between *in vivo* and *in vitro* test results have not been reliably established. Different interlaboratory experimental conditions (e.g. skin sample characteristics, temperature, flow-through or static diffusion cells, concentration of chemicals in solution) in the data used to derive K_p introduce a considerable amount of uncertainty in this approach.

- This model assumes that the chemical concentration in the water contacting skin is constant.

- This immersion model is also applied to the areas of the body which are considered to be exposed by splashing rather than being immersed in solution.

- The Risk Assessment Guidance for Superfund, Part E model also relies on parameters B and τ. Calculations for these parameters depend upon many assumptions and limited, surrogate data.

The first step in the estimate of dermal dose, is to calculate the value of K_p, calculated using the US EPA's Empirical Predictive Correlation for Permeability Coefficients of Organics which is based on a dataset examining absorption of about 90 chemicals from water through human skin *in vitro*. The equation is derived as follows:

$$\mathbf{Log\ K_p = -2.80 + 0.66\ log\ \mathit{K}_{ow} - 0.0056\ MW}$$

where,

MW	=	molecular weight; 115.16
Log K_{ow}	=	octanol-water coefficient; -0.486

$$K_p = 1.7 \times 10^{-4} \text{ cm/hr}$$

The second step is the calculation of B, the dimensionless ratio of two permeability coefficients, one for the stratum corneum and one for the epidermis. The permeability coefficient for the epidermis is difficult to determine, therefore, B is estimated without knowing epidermal permeability and is, instead, based on empirical data and theory. B is estimated as follows:

$$B = P_{cw} [(MW)^{0.5}/(2.6 \text{ cm/hr})]$$

where P_{cw} is the estimated steady-state permeability of the stratum corneum from water containing 2-methyl-4-isothiazolin-3-one, calculated as follows:

$$\text{Log } P_{cw} = -2.8 - 0.006 (MW) + 0.74 \log K_{ow}$$
$$P_{cw} = 3.7 \times 10^{-3}$$

therefore,

$$B = 1.4 \times 10^{-2}$$

τ is the lag time per event (hours) or the time it takes for a chemical to cross the skin, including both the stratum corneum and the epidermis. τ is calculated as follows:

$$\tau = 0.105 \times 10^{(0.0056 \text{ MW})}$$
$$\tau = 0.46 \text{ hours}$$

The equation for dermal exposure per event DA_{event} in the US EPA Risk Assessment Guidelines for Superfund – Part E is as follows (modified from Equation 3.3 to account for surface area and body weight to achieve dermal exposure results in mg/kg bw/day rather than mg/cm^2):

$$E = [FA \times K_p \times SA \times PF \times C_w \times CF \times (t/(1+B) + 2\tau(1 + 3B + 3B^2/(1 + B)^2)] / BW$$ (Results reported in Table 3.4-2)

where,

E	=	total dermal exposure (mg/kg bw/day)
FA	=	fraction of absorbed water (dimensionless, default = 1)
K_p	=	permeability coefficient (1.7×10^{-4} cm/hr)
SA	=	surface area exposed; assumed hands and forearms (2077 cm^2)
PF	=	protection factor from clothing; assume 1 as hands and forearms may not be protected by clothing
C_w	=	concentration of a.i. in water (maximum application rate; 150 ppm (mg/L))
CF	=	conversion factor to convert cm^3 to L; 0.001 L = 1 cm^3
T	=	duration of work day (10 hours/event or day)
B	=	dimensionless ratio of two permeability coefficients (one for stratum corneum and one for the epidermis); 1.4×10^{-2}
τ	=	lag time (time for chemical to cross the skin) per event or day; 0.46 hr/event
BW	=	body weight; 70 kg

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number
Reference

1631254
2008, Applicants name and Manufacturer Info, DACO: 2.1,2.2,2.3,2.3.1,2.4,2.5,2.6,2.7,2.8,2.9 CBI

1631256
2001, Product Chemistry Series 830 Group A: Product Identity, Composition and Analysis of Zonen-MT 100% As An Alternate to Kordek 573T Industrial Microbicide, DACO: 2.12.1,2.13.1,2.13.2 CBI

1631257
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