Evaluation Report for Category A, Subcategory 1.1 Applications

Application Numbers: 2011-3808, 2011-3810, 2011-3811, 2011-3812, 2011-3813
Application: New Active Ingredient-Domestic Registration
Products: Acticide M50, Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid, Acticide MBS Microbiocide Liquid, Acticide M20S MC
Registration Number: 31768
Active ingredients (a.i.): 2-Methyl-4-Isothiazolin-3-one, 5- chloro-2-methyl-4-isothiazolin-3-one, 1,2-benzisothiazolin-3-one
PMRA Document Number: 2360325

Purpose of Applications

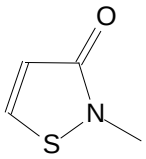
The purpose of these applications was to register a new technical grade active ingredient (Acticide M50) with three associated end-use products, and a new manufacturing concentrate.

The end-use products are to be used as material preservatives and industrial microbiocide for water-based materials; Acticide MBS 2550 Microbiocide Liquid (contains 2-methyl-4-isothiazolin-3-one and 1,2-benzisothiazolin-3-one), Acticide MBS Microbiocide Liquid Acticide (contains 2-methyl-4-isothiazolin-3-one and 1,2-benzisothiazolin-3-one) and CBM 2 Microbiocide Liquid (contains 5-chloro-2-methyl-4-isothiazolin-3-one, 2-methyl-4-isothiazolin-3-one and 1,2-benzisothiazolin-3-one). Two of the end-use products, Acticide MBS 2550 Microbiocide Liquid (2-methyl-4-isothiazolin-3-one and 1,2-benzisothiazolin-3-one) and Acticide MBS Microbiocide Liquid, are proposing a new combination of active ingredients.

Chemistry Assessment

Identity of the Active Ingredient

Active substance	2-methyl-4-isothiazolin-3-one
Function	Material preservative/slimicide
Chemical name	
1. **International Union of Pure and Applied Chemistry (IUPAC)**	2-methyl-4-isothiazolin-3-one
2. **Chemical Abstracts Service (CAS)**	3(2*H*)-isothiazoline, 2-methyl-

CAS number	2682-20-4
Molecular formula	C_4H_5NOS
Molecular weight	115.16
Structural formula	
Purity of the active ingredient	49.7%

Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—2-methyl-4-isothiazolin-3-one Technical

Property	**Result**
Colour and physical state	Yellow to amber liquid
Odour	Mild
Melting range	N/A
Boiling point or range	The compound starts to decompose at 236°C.
Density	1.17 g/cm^3 at 20°C
Vapour pressure at 20°C	0.60 mPa
Ultraviolet (UV)-visible spectrum	λmax = 275 nm, ε = 7760 L.mol^{-1}.cm^{-1} no absorbance observed above 310 nm
Solubility in water at 20°C	pH — Solubility (g/L) 5.0 — 751.3 7.0 — 737.3 9.0 — 706.1
Solubility in organic solvents at 20°C	Solvent — Solubility (g/L) n-hexane — 1.46 xylene — 143.6
n-Octanol-water partition coefficient (K_{ow})	pH — log Kow 5 — -0.26 7 — -0.32 9 — -0.28
Dissociation constant (pK_a)	N/A
Stability (temperature, metal)	Stable at 54°C for 14 days

End-Use Product—Acticide MBS 2550 Microbiocide Liquid

Property	Result
Colour	Yellow to amber
Odour	Mild
Physical state	Liquid
Formulation type	Solution
Guarantee	2-methyl-4-isothiazolin-3-one ... 2.50% 1,2-benzisothiazolin-3-one … 5.00%
Container material and description	HDPE jugs having a net contents of 1-1000 L
Density	1.044 g/cm^3
pH of 1% dispersion in water	8.1
Oxidizing or reducing action	The product does not contain an oxidizing or reducing agent.
Storage stability	During one year storage at ambient temperature, 2-methyl-4-isothiazolin-3-one was observed to be stable, while levels of 1,2-benzisothiazolin-3-one showed a downward trend and declined by 5.5% at the end of the storage period.
Corrosion characteristics	Not corrosive to HDPE containers was observed after one year stored at room temperature.
Explodability	The product is not expected to be explosive.

End-Use Product—Acticide CBM 2 Microbiocide Liquid

Property	Result
Colour	beige
Odour	Mild
Physical state	Liquid
Formulation type	Solution
Guarantee	5-chloro-2-methyl-4-isothiazolin-3-one ... 1.00% 2-methyl-4-isothiazolin-3-one ... 5.00% 1,2-benzisothiazolin-3-one … 10.0%
Container material and description	HDPE jugs having a net contents of 1-1000 L
Density	1.09 g/cm^3
pH of 1% dispersion in water	4.6
Oxidizing or reducing action	The product does not contain an oxidizing or reducing agent.
Storage stability	The product is stable for one year stored at room temperature.
Corrosion characteristics	The product is not corrosive to the packaging material during 1 year of storage.
Explodability	The product is not expected to be explosive.

End-Use Product—Acticide MBS Microbiocide Liquid

Property	Result
Colour	Yellow
Odour	Mild
Physical state	Liquid
Formulation type	Solution
Guarantee	2-methyl-4-isothiazolin-3-one ... 2.50% 1,2-benzisothiazolin-3-one … 2.50%
Container material and description	HDPE, 10-200 kg
Density	1.0030 g/cm^3
pH of 1% dispersion in water	8.5
Oxidizing or reducing action	The product does not contain an oxidizing or reducing agent.
Storage stability	During one year storage at ambient temperature, levels of 2-methyl-4-isothiazolin-3-one declined by 7.8%, and levels of 1,2-benzisothiazolin-3-one declined by 5% at the end of the storage period.
Corrosion characteristics	Not corrosive to HDPE containers was observed after one year stored at room temperature.
Explodability	The product is not expected to be explosive.

Manufacturing Concentrate—Acticide M20S MC

Property	Result
Colour	Yellow to amber
Odour	Mild
Physical state	Liquid
Formulation type	Solution
Guarantee	20.0%
Container material and description	HDPE, bulk and refillable (10-1050 kg)
Density	1.12833 g/cm^3
pH of 1% dispersion in water	4.27
Oxidizing or reducing action	The product does not contain an oxidizing or reducing agent.
Storage stability	Stable for one year stored in HDPE bottles at ambient temperature.
Corrosion characteristics	Not corrosive to HDPE containers was observed after one year stored at room temperature.
Explodability	The product is not expected to be explosive.

Methods for Analysis of the Active Ingredient
The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

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

Health Assessments

Toxicology Summary
A detailed review of the toxicological database for Acticide M50 was conducted. Acticide M50 is a technical grade active ingredient (TGAI) containing 2-methyl-4-isothiazolin-3-one (ISL). The supporting toxicology database was comprised of studies conducted with Acticide M50 (acute toxicity, 28-day and 90-day oral gavage toxicity, rat oral gavage developmental toxicity, in vitro and in vivo genotoxicity). The toxicology evaluation of Acticide M50 relied also on the toxicology database for Kordek 573T Technical Microbiocide (Reg. No. 29996, hereafter referred to as Kordek), a registered TGAI that also contains ISL and was considered appropriate for the purposes of bridging the toxicology studies. For some of the studies conducted with Acticide M50, corresponding study types were also available in the Kordek database. A 90-day dermal toxicity study with a surrogate test compound, Acticide 14, comprised of a 3:1 mixture of 5-chloro-2-methyl-4-isothiazolin-3-one (IST) and ISL was provided to supplement the Acticide M50 database. A rat toxicokinetic study with ISL was available.

The toxicology studies were of acceptable scientific quality, carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices, and adequate to define the majority of toxic effects that may result from exposure to Acticide M50. Although there were some differences noted in the findings of the corresponding studies for the Acticide M50 and Kordek databases, it was concluded that the toxicity profiles for both chemicals were largely comparable and that toxicology endpoints for risk assessment for Kordek were also relevant to Acticide M50. The detailed evaluation of the Kordek toxicology database and endpoints for health risk assessment are outlined in PRD2011-02. Summaries of the remaining studies that support Acticide M50 are provided below and supplement the overall toxicology databases for both Acticide M50 and Kordek.

A toxicokinetic study in which rats received a single oral dose of radiolabelled ISL supplemented toxicokinetic data contained in the Kordek database. The combined data indicated rapid and extensive absorption, with excretion occurring primarily via urine. Elimination was biphasic. By 168 hours post-dosing, radioactivity was primarily found in highly vascularized tissues and blood; levels were very low in plasma. This distribution suggested binding to red blood cells and tissues. Metabolism was extensive, and no unchanged parent compound was found in feces or urine. The metabolic pathway involved glutathione conjugation and opening of the ISL ring structure.

In acute toxicity testing in rats, Acticide M50 was highly acutely toxic via the oral route and moderately toxic via the inhalation route. It was corrosive to the eye and skin of rabbits and was positive in dermal sensitization studies in mice using the local lymph node assay (LLNA) and in guinea pigs using the Maximization test. Acticide M50 was of low acute dermal toxicity in rats; however, there were methodological issues in this study which confounded interpretation. On the strength of information for other isothiazolinones, including Kordek, Acticide M50 was considered to be of high acute toxicity via the dermal route.

Acticide CBM 2 Microbiocide Liquid was considered of low acute toxicity via the oral and dermal routes, and slightly toxic via the inhalation route when tested in rats. It was considered corrosive to the eye on the basis of skin corrosion observed in testing in rabbits. Acticide CBM 2 Microbiocide Liquid was a dermal sensitizer when tested in mice using the LLNA.

Acticide MBS Microbiocide Liquid was of low acute toxicity in rats via the oral, dermal and inhalation routes. Although the product was slightly irritating to the skin of rabbits, it was considered corrosive to the eye on the basis of corrosive properties of similar products. Acticide MBS Microbiocide Liquid was a dermal sensitizer on the basis of testing in guinea pigs (Maximization method) and mice (LLNA).

Acticide MBS 2550 Microbiocide Liquid was of low acute toxicity to rats via the oral, dermal and inhalation routes. It was non-irritating to the skin of rabbits, but was considered corrosive to the eye on the basis of the results of skin irritation testing in rabbits with Acticide MBS. Acticide MBS 2550 Microbiocide was considered a dermal sensitizer on the basis of the findings with Acticide MBS.

On the basis of results of acute toxicity testing with Acticide M50, the manufacturing concentrate Acticide M20S MC was considered highly acutely toxic via the oral and dermal routes and moderately toxic via the inhalation route. It was considered corrosive to eyes and skin and a dermal sensitizer.

In a rat 28-day oral gavage study with Acticide M50, treatment-related effects were noted at the highest dose level only. These included mortality, clinical signs, and reductions in body weight/body weight gain as well as food consumption/food efficiency. No adverse effects were noted in a rat 90-day oral gavage study with Acticide M50, where the highest dose was comparable to the mid-dose of the 28-day study. In both studies, pneumonia-like effects were observed in the lungs of all groups, including controls, which may have been the result of animal husbandry issues. Nevertheless, the studies were deemed to be acceptable for hazard characterization purposes. When compared to the Kordek rat 90-day drinking water study, the results of these studies were generally concordant in terms of effect levels. However, the somewhat more severe nature of findings in the Acticide M50 28-day study was likely attributable to the method of administration (gavage as opposed to drinking water).

In the 90-day dermal toxicity study with Acticide 14, there was no evidence of systemic toxicity up to and including the highest dose tested; this dose level was considered to be very low. However, the ability to test at higher doses in order to establish a LOAEL for systemic toxicity was limited due to the observation of severe dermal irritation at the highest dose tested.

Slight maternal toxicity was observed in the rat gavage developmental toxicity study with Acticide M50 as demonstrated by reduced body weight gain and food efficiency at the top two dose levels. At the highest dose level, an increased incidence of fetal skeletal variations (non-ossified metatarsals and cervical vertebral bodies, bipartite ossification of the thoracic vertebral bodies) in addition to an increased incidence of dilated cerebral lateral ventricles were observed. These findings were considered to be evidence of developmental toxicity occurring in the presence of maternal toxicity. There was no evidence of sensitivity of the young in this study.

When comparing the findings of the rat oral gavage studies in the Acticide M50 database with those in the Kordek database, there were some inconsistencies with regards to the occurrence of mortality. Maternal deaths were observed in the Kordek developmental toxicity study at doses that produced only effects on body weight and food consumption in the corresponding Acticide M50 developmental toxicity study. This may have been due, in part, to differences in administered dose volumes between the two studies. However, mortality and clinical signs were also observed in the Acticide M50 28-day study which used a comparable dose volume to that of the Acticide M50 developmental toxicity study. Respiratory health issues in the 28-day study noted previously may have exacerbated the effects of treatment. Although these discrepancies cannot be fully explained, the endpoints selected for risk assessment are considered protective of any residual uncertainty in this regard.

The battery of genotoxicity studies for Acticide M50 was negative and included a bacterial gene mutation assay, a mammalian cell gene mutation assay with Chinese hamster ovary cells, a chromosome aberration assay in human cultured lymphocytes, and an in vivo mouse bone marrow micronucleus assay.

Results of the toxicology studies conducted on laboratory animals with Acticide M50 and its associated end-use products, as well as the manufacturing concentrate, are summarized in Tables 1-5 of Appendix I. The toxicology endpoints for use in human health risk assessment are summarized in Table 6 of Appendix I.

Incident Reports

Since April 26, 2007, registrants have been required by law to report incidents to the PMRA, including adverse effects to Canadian health or the environment. Information on the reporting of incidents can be found on the PMRA website. As of March 5, 2015, 5 human incidents (3 moderate, 2 minor) were reported in Canada with IST:ISL products. No incidents with ISL alone were reported. All cases occurred in occupational settings and involved dermal effects (burns, red/painful/tingly/itchy skin). There is a high degree of plausibility that the symptoms were caused by exposure to the products. As the exposures resulted from preventable accidents, these incident reports do not warrant further action at this time.

PCPA Hazard Characterization
Please refer to PRD2011-02.

Acute Reference Dose
An acute reference dose was not established as there are no food uses.

Acceptable Daily Intake
An acceptable daily intake was not established as there are no food uses.

Occupational and Residential Risk Assessment
Dermal and inhalation exposures from BZZ to mixer/loader/applicator and post-application workers is expected from handling the three products (Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid/ Acticide MBS Microbiocide Liquid). Since BZZ rates and application methods are within the currently registered rates and those assessed during the re-evaluation (PRVD2008-13: *Benzisothiazolin-3-one*), qualitative risk assessments for BZZ demonstrated that the potential mixer/loader/applicator and post-application exposures are not expected to result in increased risks compared to those from the currently registered uses.

As ISL and IST are considered to be toxicologically equivalent, the combined concentrations of ISL and IST were used in the risk assessments. The combined concentrations of ISL and IST were higher than those of the currently registered products; therefore, quantitative risk assessments were required.

Dermal and inhalation exposures from ISL/IST to mixer/loader/applicator are expected from handling the Acticide CBM 2 Microbiocide Liquid product. Dermal and inhalation exposures from only ISL to mixer/loader/applicator are expected from handling Acticide MBS 2550 Microbiocide Liquid and Acticide MBS Microbiocide Liquid. Although the total ISL rates in Acticide CBM 2 Microbiocide Liquid and Acticide MBS Microbiocide Liquid for treatment of paint did not fit within the currently registered rates for ISL or ISL/IST, these were within the currently registered rates for preserving cleaning products. Occupational risk is not expected to be different among the use scenarios, since the rate and application methods are the same. Therefore, the exposure to ISL from Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid and Acticide MBS Microbiocide Liquid fits within the exposure from the registered uses. Hence, risks to mixer/loader/applicator handling the products will not increase beyond the exposure from the currently registered uses.

For paint, exposure to post-application professional painters using paint brush (or roller) resulted in MOEs exceeding the target MOE's (100 for dermal; 300 for inhalation) at the maximum approved application rates; 150 ppm for total combined ISL. However, when using airless sprayers, MOEs met the target MOE's when the maximum application rate was reduced to 75 ppm of total ISL. An application rate of 75 ppm is equivalent to a concentration of 0. 3% Acticide MBS 2550 and Acticide CBM 2 Microbiocide Liquids, and 0. 125% Acticide MBS Microbiocide liquid. Post-application exposure to professional painters and residential painters from handling treated paint was expected to be of long-term and short-term durations, respectively. Dermal and inhalation exposures to residential painters resulted in acceptable MOEs.

While the dermal and inhalation routes of exposure could not be aggregated due to the different systemic effects resulting from each route, the incidental oral and dermal routes of exposure could be aggregated. The aggregate dermal exposure to adults from painting and contacting painted surfaces did not result in any risks of concern. Accordingly, for the aggregate inhalation exposure to adults from painting and being in the vicinity of a room recently painted, no risks of concern were identified. For children, the target MOE was met when aggregating exposures from dermal contact with painted surfaces and incidental oral exposure from hand-to-mouth activities.

For detergents, exposure to professional cleaners and residential cleaners are expected to be of long-term and short-term durations, respectively, via the dermal and inhalation routes. The MOE for professional cleaners from dermal exposure met the target MOE. However, for inhalation exposure, the target MOE was only met when the concentration was lowered to 30 ppm. For post-application exposure, there were no risks of concern from dermal exposure when wearing laundered clothing or from incidental oral exposure to children mouthing laundered clothing. There were no risks of concern from aggregate exposure to adults and youth from cleaning and wearing laundered clothing as well as to children from contacting cleaned surfaces and incidental oral exposure from mouthing laundered clothing.

As ISL and IST are skin sensitizers and dermal irritants, sensitization risk assessments were conducted. Toxicological sensitization endpoints were determined for each end use product based on a Local Lymph Node Assay (LLNA). The estimated dermal contact exposure was found to be acceptable.

In light of the above, no human health concern is expected for adults, youth, and children (including incidental oral ingestion) from exposure to the products, provided that the recommended label amendments are applied.

Toxicological Endpoints

Short- and long-term dermal and inhalation; non-dietary oral ingestion (Children, Short-term)

Please refer to PRD2011-02.

Dermal sensitization

Because of the positive skin sensitization study findings, the well-known sensitization potential of the isothiazolinone class of compounds, and the use patterns for Acticide M50, a quantitative dermal sensitization risk assessment was deemed appropriate. All three end-use products contain more than one active ingredient that is a dermal sensitizer. Two of the end-use products contain both ISL and BZZ, while the remaining one contains ISL, IST and BZZ. In order to account for potential interactions between or among these active ingredients when conducting a quantitative dermal sensitization risk assessment, the results of LLNA conducted with the end-use products (or suitable surrogates) were used. Adjustments were made[1] to the obtained EC3 values from LLNA in which the concentration(s) of respective isothiazolinone(s) in the surrogate test material differed from that in the product. The adjustment is based on the principle that an increased concentration of isothiazolinones will result in a greater sensitizing potential, thus a lower EC3.

[1] [1]$EC3_P = EC3_S * (C_S / C_P)$, where: $EC3_P$ is the expected EC3 of the proposed product, $EC3_S$ is the measured EC3 of the surrogate, C_P is concentration of isothiazolinones in the proposed product and C_S is the concentration of the isothiazolinones in the surrogate

For products containing both ISL and BZZ, the concentrations of both actives were added together as they are of similar sensitizing potencies. For products containing ISL, IST and BZZ, only the IST concentration was considered as it is a far more potent sensitizer than either ISL or BZZ, i. e. the contribution of the latter two compounds to the sensitizing potential of the product is considered to be minor. The adjusted EC3 values for risk assessment are included below. The target margin of exposure (MOE) is 100, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability.

EC3 values used for dermal sensitization risk assessment

Product	**EC3 value**
Acticide MBS 2550 Microbiocide	EC3: 12% (3000 µg/cm^2)
Acticide CBM 2 Microbiocide Liquid	EC3: 1. 7% (425 µg/cm^2)
Acticide MBS Microbiocide Liquid	EC3: 16. 8% (4200 µg/cm^2)
Acticide M20S MC	Default to Acticide M50 EC3: 1. 5% (388 µg/cm^2)

Cancer Risk Assessment
There was no evidence of carcinogenicity and therefore a cancer risk assessment was not necessary.

Environmental Assessment

The active ingredient 2-methyl-4-isothiazolin-3-one is present in a number of end-use products used as a material preservative and slimicide in paint, coatings, metalworking fluid, household products and polymer lattices. In a laboratory study 2-methyl-4-isothiazolin-3-one was stable to hydrolysis, however, based on its the use pattern, terrestrial and aquatic environmental exposure was expected to be minimal. Low concentrations in formulated products are expected to result in negligible concentrations in the terrestrial environment and waterbodies.

Under this use pattern, 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.

Measures to Minimize Risk
Key Risk-Reduction Measures
Environment

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

Value Assessment

Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid and Acticide MBS Microbiocide Liquid are new in-can preservatives for a variety of products: paints and coatings, polymer emulsions, dispersions and solutions, adhesives and building materials, inks and ink components, household, consumer, institutional and janitorial products and dispersed pigments. These combinations of active ingredients have value as an alternative to other registered in-can preservatives to effectively control bacteria and fungi commonly associated with the degradation of materials during manufacture and storage.

Several laboratory trials were provided to support the use of Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid and Acticide MBS Microbiocide Liquid as in-can preservatives to control bacteria and fungi. Each trial was found to have an appropriate experimental design and used relevant bacterial, fungal and yeast species as challenge organisms in conditions representing worst-case scenarios.

For Acticide MBS 2550 Microbiocide Liquid, data have shown that 0. 03-0.3% of Acticide MBS 2550 Microbiocide Liquid could control the microbial growth in a variety of aqueous-based materials for several weeks.

For Acticide CBM 2 Microbiocide Liquid, data have shown that 0. 03-0.125% of Acticide CBM 2 Microbiocide Liquid could control the microbial growth in a variety of aqueous-based materials for several weeks.

For Acticide MBS Microbiocide Liquid, data have shown that 0. 03-0.3% of Acticide MBS Microbiocide Liquid could control the microbial growth in a variety of aqueous-based materials for several weeks.

Scientific literature suggests that resistance to isothiazolones is possible, but not frequent, in industrial settings, and that the rotation of active ingredient is an accessible way of avoiding the development of resistance. These three end-use products have been registered in the US for several years. According to the applicant, no adverse effects have been reported from their use from a value standpoint. A statement has been added to the label indicating that the user should test the product on a small batch prior to large-scale application. This will be useful in mitigating potential incompatibilities.

The information submitted in support of Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid and Acticide MBS Microbiocide Liquid was adequate to demonstrate their value for use against bacteria and fungi in a variety of materials. These preservatives for in-can use will help in reducing the proliferation of microorganisms during manufacture and storage of various aqueous materials and provides a new combination of active ingredients.

Conclusion

The Pest Management Regulatory Agency has completed an assessment of the information provided, and has found the information sufficient to support the registration of Acticide M50, Acticide MBS 2550 Microbiocide Liquid, Acticide CBM 2 Microbiocide Liquid, Acticide MBS Microbiocide Liquid, and Acticide M20S MC.

List of Abbreviations

♂	male
♀	female
%	percent
AD	administered dose
ADI	acceptable daily intake
a. i.	active ingredient
bw	body weight
bwg	bodyweight gain
BZZ	1,2-benzisothiazolin-3-one
CHO	Chinese hamster ovary
°C	Celsius
cm	centimetre
EC_3	concentration required to induce a threshold positive sensitization response (SI=3)
fc	food consumption
fe	food efficiency
g	gram(s)
hr	hour
HDPE	high density polyethylene
HRPT	hypoxanthine-guanine phosphoribosyl transferase
ISL	2-methyl-4-isothiazolin-3-one
IST	5-chloro-2-methyl-4-isothiazolin-3-one
kg	kilogram(s)
K_{ow}	n–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LLNA	local lymph node assay
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
µg	microgram(s)
µm	micrometer
mg	milligram(s)
mL	millilitre(s)
MAS	maximum average score for 24, 48 and 72 hours
MC	manufacturing concentrate
MIS	maximum irritation score
MOE	margin of exposure
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
PCPA	*Pest Control Product Act*
pKa	dissociation constant
pH	measure of the acidity or basicity of an aqueous solution
TGAI	technical grade active ingredient
UV	ultraviolet

Appendix I Tables and Figures

Table 1 Toxicity Profile of Acticide MBS 2550 Microbiocide Liquid

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity (Acute toxic class) Rat, Wistar Acticide MBS 5050 4. 99% ISL, 5. 06% BZZ PMRA # 2094139	Low toxicity LD_{50} between 2000 and 5000 mg ISL/kg bw (♀ only tested)
Acute Dermal Toxicity Rat, Wistar Acticide MBS 5050 4. 99% ISL, 5. 06% BZZ PMRA # 2094137	Low toxicity LD_{50} ♂/♀ > 2000 mg ISL/kg bw
Inhalation Rat, Wistar Acticide MBS conc. 5. 15% ISL, 4. 8% BZZ PMRA # 2094134	Low toxicity LC_{50} ♂/♀ = 2. 9 mg ISL/L
Eye irritation PMRA # 2250410	Corrosive Classified as corrosive to eyes based on results of skin irritation study for Acticide MBS
Skin irritation Rabbit, NZW ACTICIDE® MBS 5050 4. 99% ISL, 5. 06% BZZ PMRA # 2094130	Non irritating MAS (24, 48, 72 hr) = 0 MIS (1hr) = 1. 33
Sensitization PMRA # 2268603	Skin Sensitizer Based on bridge to Acticide MBS. Due to the increased active concentration, EC3 estimated to be 12%

Table 2 Toxicity Profile of Acticide CBM 2 Microbiocide Liquid

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity (Acute toxic class) Rat, Wistar Acticide CBM 3. 99% ISL, 0. 48% IST, 3. 80% BZZ PMRA # 2094214	Low toxicity LD_{50} >2000 mg ISL/kg bw (♀ only tested)
Acute Dermal Toxicity Rat, Wistar Acticide CBM 3. 99% ISL, 0. 48% IST, 3. 80% BZZ PMRA # 2094215	Low toxicity LD_{50} ♂/♀ > 2000 mg ISL/kg bw
Acute Inhalation Toxicity Rat, Wistar Acticide CBM 3. 99% ISL, 0. 48% IST, 3. 80% BZZ PMRA # 2094216	Slight toxicity LC50 ♂ = 0. 73 mg/L LC50 ♀ = 0. 97 mg/L
Eye irritation PMRA # 2094217	Corrosive Classified as corrosive to eyes based on results of skin irritation study
Skin irritation Rabbit, NZW Acticide CBM 3. 99% ISL, 0. 48% IST, 3. 80% BZZ PMRA # 2094218	Corrosive due to persistence of effects (eschar and necrotic discoloration at day 14) MAS (24,48,72 hr) = 4. 8 MIS (1hr) = 8
Sensitization (LLNA) Mouse, CBA Acticide CBM 3. 99% ISL, 0. 48% IST, 3. 80% BZZ PMRA # 2094219	Skin Sensitizer EC3 of 1. 7%, equivalent to 425 µg/cm^2 Note: the results indicated an EC3 = 3. 6%, equivalent to 879 µg/cm^2; however, in view of the potency of IST and the increased amount of IST in the Acticide CBM 2 (vs. the amount present in the tested formulation, the EC3 of 1. 7% was extrapolated from the results of the tested formulation

Table 3 Toxicity Profile of Acticide MBS Microbiocide Liquid

Study Type/Animal/PMRA #	Study Results
Acute Oral Toxicity (Acute toxic class) Rat, Wistar Acticide MBS 2. 57% ISL, 2. 57% BZZ PMRA # 1316242	Low toxicity LD_{50} >2500 mg ISL/kg bw (♀ only tested)
Acute Dermal Toxicity Rat, Wistar Acticide MBS 2. 57% ISL, 2. 57% BZZ PMRA # 1316243	Low toxicity LD_{50} ♂/♀ > 2000 mg ISL/kg bw
Acute Inhalation Toxicity Rat, Wistar Acticide MBS 2. 57% ISL, 2. 57% BZZ PMRA # 1316246	Low toxicity LC_{50} ♂/♀ ≥ 4. 2 mg ISL/L
Eye irritation PMRA # 1316248	Corrosive Classified as corrosive to eyes on corrosive properties of similar products
Skin irritation Rabbit, NZW Acticide MBS 2. 57% ISL, 2. 57% BZZ PMRA # 1316249	Slightly irritating MAS (24,48,72 hr) = 1. 1 MIS (1hr) = 2
Sensitization (Guinea Pig Maximization Test) Acticide MBS 2. 6% ISL, 2. 3% BZZ PMRA # 1316250	Sensitizer Positive reaction in 5/10 at 5% challenge and 7/10 at 50% challenge
Sensitization (LLNA) Mouse, CBA Acticide MBS 2. 65% ISL, 2. 5% BZZ PMRA # 2250382	Skin Sensitizer Positive at ≥ 25% EC3 = 16. 8%; equivalent to 4200 µg/cm^2

Table 4 Toxicity Profile Acticide M20S MC

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Bridged to Acticide M50	High toxicity LD_{50} ♂ = 328 mg ISL/kg bw LD_{50} ♀ ≥ 166 ≤ 248 mg ISL/kg bw
Acute dermal toxicity Bridged to Acticide M50	High toxicity LD_{50} > 2000 mg ISL/kg bw
Acute inhalation toxicity Bridged to Acticide M50	Moderate toxicity LC_{50} ♂ = 0. 15 mg ISL/L LC_{50} ♀ = 0. 12 mg ISL/L
Dermal irritation Bridged to Acticide M50	Corrosive
Eye irritation Bridged to Acticide M50	Corrosive
Dermal sensitization Bridged to Acticide M50	Positive at ≥2. 52% a. i. EC3 = 1. 55%; equivalent to 387. 5 µg/cm^2

Table 5: Toxicity Profile of Acticide M50

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweight otherwise noted. Effects seen above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity. Note: Acticide SR 3267= former name for Acticide M50

Study Type/Animal/PMRA #	Study Results
Metabolism, Acticide M50 (PMRA # 2095055, 2095057) Rat, Sprague Dawley	**Absorption**: Absorption was rapid and extensive with 75-92% of the administered dose (AD) recovered within the first 24 hours. Recovery was high (94-97% by 168 hours). **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. Radioactivity in cage wash was high (8-20%) and assumed to be due mostly to uncollected urine. When cage wash radioactivity was combined with urine results, levels were almost identical between sexes. Feces accounted for 24-29% of AD. As biliary excretion was not measured, it is unknown if this portion was absorbed. Assuming it was not, overall absorption was still high (66-70%). Radioactivity in expired air was very low (0. 04-0. 06%). **Metabolism:** The metabolism of (^{14}C)-ISL was extensive, with no parent compounds detected in urine or feces. Four urinary metabolites were identified with the primary metabolite (M1) being an open-ring version of the parent molecule, while the other three were open or closed-ring glutathione-conjugated metabolites. No fecal metabolites were successfully characterized. The full pathway of the metabolism of (^{14}C)-ISL was not elucidated, but involves phase II glutathione conjugation. **Distribution**: Radioactivity in the carcass was 1. 3-2% of the AD, and a further 2% was estimated to be present in blood 168 hours after dosing. Whole blood concentrations were markedly more elevated than plasma, indicating that the compound has a high affinity for blood cells. Radioactivity was distributed mostly in highly vascularized tissue 168 hours post dosing, with the highest concentrations found in the blood, adrenals (male only), heart, lungs and spleen. Females had high radioactivity levels in the gonads than males, and males had higher levels in the adrenal gland than females; no other sex differences were noted.
Acute Oral Toxicity Rat, Wistar Acticide SR 3267 49% ISL PMRA # 2095011	High toxicity LD_{50} ♂= 328 mg ISL/kg bw LD_{50} ♀ ≥ 166 ≤ 248 mg ISL/kg bw
Acute Dermal Toxicity Rat, Wistar Acticide SR 3267 49% ISL PMRA # 2095012	Low toxicity LD_{50} ♂ / ♀> 2000 mg ISL/kg bw
Acute Inhalation Toxicity Rat, Wistar Acticide SR 3267 49. 8% ISL PMRA # 2095013	Moderate toxicity LC_{50} ♂ = 0. 15 mg ISL/L LC_{50} ♀ = 0. 12 mg ISL/L

Eye irritation PMRA # 2095085	Corrosive Classified as corrosive to eyes based on results of skin irritation study
Skin irritation Rabbit, NZW Acticide SR 3267 49% ISL PMRA # 2095015	Corrosive MAS (24, 48, 72h) = 2. 8 MAS (7, 10, 14 days) = 8 MIS (7 days) = 8
Sensitization (Guinea Pig Maximization Test) Acticide SR 3267 49% ISL PMRA # 2095015	Skin Sensitizer 10/10 test animals reacted at 24 and 48 hours 4/10 test animals displayed “intense erythema and swelling”
Skin Sensitization Mice, CBA (LLNA) Acticide M50 50. 5% ISL PMRA # 2250505	Skin Sensitizer Positive at ≥2. 52% ISL Interpolated EC3 = 1. 55% ISL; equivalent to 387. 5 µg/cm^2
90-day dermal Rat, Sprague Dawley Acticide 14 (13. 9% combined IST+ISL in a 3:1 ratio) PMRA #2250509	Systemic NOAEL (♂/♀) = 2. 6 mg ISL/kg bw/day (highest dose tested) Systemic LOAEL (♂ /♀) = Not established Dermal irritation NOAEL (♂/♀) = 0. 10 mg ISL/kg bw/day/not established Dermal irritation LOAEL (♂/♀) = 0. 52 / 0. 10 mg ISL/ kg bw/day Effects at dermal irritation LOAEL: erythema, desquamation; eschar (♀)
28-day oral (gavage) Rat, Wistar Acticide M50 50. 15% ISL PMRA # 2250506 and 2250507	NOAEL (♂/♀) = 28 mg ISL/kg bw/day LOAEL (♂/♀) = 71 mg ISL/kg bw/day Effects at LOAEL: mortality (1♂, 3♀), piloerection, lethargy/low arousal, abnormal breathing, kidney palor/pale foci in deceased animals, moderate myocardial fibrosis (1♂ (recovery), 1♀); ↓bw, bwg, fc and fe, adrenal focal hypertrophy, also in a single deceased animal enlarged heart with subendocardial infiltration of round cell (possibly lymphocytic) and hyperemia (♂); abnormal gait, reduced rearing, in one animal difficult reaction to handling, in another animal (deceased) nostril discharge(♀)
90-day oral (gavage) Rat, Wistar Acticide M50 50. 15% ISL PMRA # 2095018	NOAEL(♂/♀) = 30 mg ISL/kg bw/day (highest dose tested) LOAEL (♂/♀)= Not established as there were no treatment-related effects

Developmental toxicity (gavage) Rat, Wistar Acticide SR 3267 49. 8% ISL PMRA # 2452756	Maternal NOAEL = 33 mg ISL/kg bw/day Maternal LOAEL = 50 mg ISL/kg bw/day Effects at LOAEL: ↓ bwg, fc (GD6-15) Developmental NOAEL = 50 mg ISL/kg bw/day Developmental LOAEL = 75 mg ISL/kg bw/day Effects at LOAEL: ↑ fetal incidence non-ossified cervical vertebral bodies ↑ incidence (fetal/litter) dilated cerebral lateral ventricles , ↑ fetal incidence non-ossified metatarsals, ↑ incidence (fetal/litter) bipartite ossification of thoracic vertebral body No evidence of sensitivity of the young
Gene mutations in bacteria Acticide M50 49% ISL PMRA # 2095005	Negative in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535 and TA 1537; 3. 92-317. 82 µg ISL/plate, with and without metabolic activation; tested up to cytotoxic concentration
Gene mutations in mammalian cells (in vitro) Acticide M50 49. 8% PMRA # 2095004	Negative in CHO/HPRT forward mutation assay with and without metabolic activation; tested up to cytotoxic concentration
Chromosome aberrations (in vitro) Acticide M50 50. 7% PMRA # 2250514	Negative in cultured lymphocytes from healthy adult male donor, with and without metabolic activation. Pilot study showed cytotoxicity at doses of 10 µg ISL/mL and higher
Micronucleus assay (in vivo) Acticide M50 49. 8% PMRA # 2095007	Negative in male and female NMRI mice at 0, 50, 74 and 100 mg ISL/kg bw In pilot study, animals treated with 100 mg ISL/kg bw displayed incoordination, decreased activity and impaired breathing. At 149 mg ISL/kg bw, 5/6 animals died.

Table 6: Toxicology Endpoints for Use in Health Risk Assessment for Acticide M50

Exposure Scenario	**Study**	**Point of Departure and Endpoint**	**Target MOE[1]**
Short-term dermal[2]	Rabbit developmental toxicity	NOAEL: 10 mg ISL/kg bw/day; based on late resorptions accompanied by ↓live fetuses/dam, ↓defecation, bw loss, ↓fc, and dark red areas in stomach	300
Long-term dermal[2]	Rat 2-year chronic/carcinogenicity	NOAEL: 2 mg ISL/kg bw/day; based on ↓ bw, bwg and fc, various signs of irritation of stomach	100

Short-term inhalation	Rat 90-day inhalation toxicity	NOAEC: 0. 34 µg/L (≈0. 06 mg ISL/kg bw/day); based on nasal cavity rhinitis	100
Long-term inhalation	Rat 90-day inhalation toxicity	NOAEC: 0. 34 µg/L (≈0. 06 mg ISL/kg bw/day); based on nasal cavity rhinitis	100
Non-dietary oral ingestion (short-term)	Rabbit developmental toxicity	NOAEL: 10 mg ISL/kg bw/day; based on ↓ defecation, bw loss, ↓ fc and dark red areas in stomach	100
Dermal sensitization	See Dermal sensitization Section for EC3 values for quantitative risk assessment		
Cancer	**A quantitative cancer risk assessment was not required**		

[1]MOE refers to a target MOE for occupational and residential assessments

[1]Since an oral NOAEL was selected, a dermal absorption factor was used in a route-to-route extrapolation

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