Proposed Registration Decision PRD2010-21

# d-Limonene

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# Table of Contents

# Overview

## Proposed Registration Decision for d-Limonene

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 d-Limonene Technical, MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer, containing the technical grade active ingredient d-limonene, to control cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles on contact.

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

This Overview describes the key points of the evaluation, while the Science Evaluation section provides detailed technical information on the human health, environmental and value assessments of d-Limonene Technical, MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer.

## What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to 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 (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pest Management portion of Health Canada's website 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 d-limonene, 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 d-limonene, 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 d-Limonene?

d-Limonene is a chemical compound found in citrus fruits. Direct contact with d-limonene kills certain insects and arthropods.

## Health Considerations

### Can Approved Use of d-Limonene Affect Human Health?

**d-Limonene is unlikely to affect human health when used according to label directions.**

Exposure to d-limonene may occur when applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The technical grade active ingredient, d-limonene, is of low acute toxicity by the oral and dermal routes, slightly irritating to eyes, and moderately irritating to skin. Due to the irritative nature of d-limonene, inhalation exposure may cause respiratory irritation. There is potential for skin sensitization to occur when skin is repeatedly exposed to d-limonene. Due to the irritative and sensitizing nature of d-limonene, hazard statements alerting users are required on the product labels. Based on the available toxicological information, there is no evidence to suggest that d-limonene is carcinogenic to humans, neurotoxic, genotoxic, teratogenic, or a reproductive toxicant.

[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*.

### Residues in Water and Food

**Dietary risks from food and water are not of concern.**

End-use products containing d-limonene are not applied directly to food or feed crops, therefore residues on food are expected to be negligible.

### Risks From Handling MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer

**Risks are not of concern when MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer are used according to label directions, which include protective measures.**

As the end-use products are ready-to-use cans, exposure to applicators, domestic users and bystanders is minimal and likely mainly to be from spot treatments when individuals may be exposed via the inhalation route from spray drift or volatile vapours. Dermal exposure is also possible via direct contact with spray drift or with freshly sprayed surfaces.

Significant risks to humans from occupational/residential exposures are not anticipated due to the low toxicity of the formulations and additional precautionary measures on the product labels that are aimed at mitigating exposure, including restrictions on entry to freshly-treated sites and the wearing of personal protective equipment (PPE) for commercial applicators.

Exposure is expected to be brief, and not likely to result in unacceptable risks to commercial applicators, other workers, domestic users, or bystanders if the end-use products are used according to label directions, including mitigative measures.

## Environmental Considerations

### What Happens When d-Limonene Is Introduced Into the Environment?

**d-Limonene is a highly volatile insoluble terepene that naturally occurs in fruits, vegetables, meats and spices. It is used as an additive in a variety of foods and beverages.**

d-Limonene Technical is highly volatile and insoluble in water, therefore it is not expected to leach into ground water or be persistent in water or soil. Non-target organisms could be exposed by consumption of contaminated food items, such as insects. However, d-limonene is also registered by the EPA as a mammal repellent, therefore, contaminated food items are not likely to be consumed by mammals. The exposure of non-target terrestrial organisms to d-limonene under the operational conditions of these products is considered to be negligible.

The use of ProCitra-DL Botanical Crawling Insect Killer and MotherEarth Botanical Crawling Insect Killer is not expected to pose a risk to non-target organisms.

## Value Considerations

### What Is the Value of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer?

MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer are products that are for commercial and domestic use respectively. Both products contain 10% d-limonene that kills cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles on contact. These products provide users with an alternative to conventional pest control products. d-Limonene represents a new mode of action for use against labelled pests and therefore provides an additional tool for resistance management in integrated pest management (IPM) programs.

## Measures to Minimize Risk

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

The key risk-reduction measures being proposed on the label of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer to address the potential risks identified in this assessment are as follows.

### Key Risk-Reduction Measures

**Human Health**

- The signal words "POTENTIAL SKIN SENSITIZER" and "WARNING- SKIN IRRITANT" on the principal display panels and the precautionary statements "Potential skin sensitizer", "Causes skin and mucous membrane irritation", and "Do not get in eyes, on skin or on clothing" on the secondary display panels are required of both the technical label and the end-use product labels.

- The proposed commercial label for MotherEarth Botanical Crawling Insect Killer directs applicators to not apply the product to classrooms when in use, to remove patients before using in nursing homes and hospitals, and not to apply to institutions (including libraries, sport facilities, etc.) in the vicinity of people. The proposed label also recommends that after application in nursing homes and hospitals, the rooms be ventilated for 30 minutes before returning the patients. Furthermore, the proposed label instructs applicators to not remain in the treated area, ventilate the area after treatment is completed, not contaminate water, food, or food stuffs, cover or remove exposed food in the treatment area, remove all pets and birds, and cover fish tanks or remove before spraying. The inclusion of the following precautionary statements are also required: "Indoor application of the product should be performed only when commercial facilities are not in operation."; "Vacate indoor areas during application."; and "When applying and during clean-up, applicators and related workers are required to wear long pants, a long-sleeved shirt, shoes plus socks,

goggles or face shield, and chemical-resistant gloves. Wear a NIOSH approved respirator with an organic vapour cartridge or canister with any R or P prefilter when working in enclosed or confined spaces or when exposure to vapour or spray mist is expected."

- The proposed label for the domestic product, ProCitra-DL Botanical Crawling Insect Killer, includes the precautionary statements: "Apply only in well-ventilated areas."; and "For spot treatment, apply close to the surface and do not spray in the air." The following additional precautionary statements are also required: "Avoid breathing vapours or spray mists."; "Do not enter or allow re-entry of people/children/pets to treated areas until surfaces are dry and the areas are thoroughly ventilated."; "Do not apply in the immediate vicinity of people or pets."; and "Do not remain in freshly treated area, and ventilate the area thoroughly after the treatment is completed."

## Next Steps

Before making a final registration decision on d-limonene, 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.

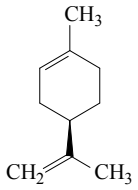
## Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on d-Limonene (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

## 1.0 The Active Ingredient, Its Properties and Uses

### 1.1 Identity of the Active Ingredient

| | |
|---|---|
| **Active substance** | d-Limonene |
| **Function** | Insecticide |
| **Chemical name** | |
| **1. International Union of Pure and Applied Chemistry (IUPAC)** | (*R*)-4-isopropenyl-1-methyl-1-cyclohexene |
| **2. Chemical Abstracts Service (CAS)** | Cyclohexene, 1-methyl-4-(1-methylethyl)-, (*4R*)- |
| **CAS number** | 5989-27-5 |
| **Molecular formula** | $C_{10}H_{16}$ |
| **Molecular weight** | 136.23 |
| **Structural formula** |  |
| **Purity of the active ingredient** | 95.9% nominal |



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

**Technical Product—d-Limonene Technical**

| Property | Result |
|---|---|
| Colour and physical state | Colourless to pale yellow liquid |
| Odour | Citrus aroma |
| Melting range | N/A |
| Boiling point or range | 176°C |
| Density at 20°C | 0.838 to 0.843 g/cm$^3$ |
| Vapour pressure at 20°C | < 2 mmHg |

| Property | Result |
|---|---|
| Henry's law constant at 20°C | N/A |
| Ultraviolet (UV)-visible spectrum | Not required for the food grade d-limonene |
| Solubility in water | Insoluble in water |
| Solubility in organic solvents at 20°C | N/A |
| *n*-Octanol-water partition coefficient ($K_{OW}$) | Not required for the food grade d-limonene |
| Dissociation constant (p$K_a$) | N/A |
| Stability (temperature, metal) | Not required for the food grade d-limonene |

**End-Use Products— MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer**

| Property | Result |
|---|---|
| Colour | Clear |
| Odour | Petroleum odour |
| Physical state | Liquid |
| Formulation type | Pressurized product |
| Guarantee | 10% nominal (limits: 9.5% - 10.5%) |
| Container material and description | 0.497 – 0.567 g metal aerosol cans |
| Density | 0.8012 g/cm$^3$ |
| pH of 1% dispersion in water | 7.73 at 24.6°C |
| Oxidizing or reducing action | The products do not contain any oxidizing or reducing agents |
| Storage stability | Study in progress |
| Corrosion characteristics | Not corrosive to the container material |
| Explodability | The products are not potentially explosive |

## 1.3 Directions for Use

MotherEarth Botanical Crawling Insect Killer is a commercial class end-use product to be used in apartments, food storage areas, homes, hospitals, hotels, meat packing and food processing plants, motels, nursing homes, resorts, restaurants and other food handling establishments, schools, supermarkets, transportation equipment (e.g. buses, boats, ships, trains, trucks), utilities, warehouses and other commercial and industrial buildings. ProCitra-DL Botanical Crawling Insect Killer is a domestic class end-use product to be used in apartments and homes.

Both products are for use to control cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles.

MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer kill pests on contact. For light crack and crevice infestations, either product should be applied by moving the injector tip along cracks while treating at a rate of 1 metre/second (m/s). For heavier crack and crevice infestations, MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer should be applied at a rate of 0.33 m/s. To treat closed voids, the approximate size of the void in cubic metres should be measured and applications of either product made within a rate range of 1-5 $s/m^3$. Spot treatments must be made with the injector nozzle approximately 30 cm from the surface or pest to be treated. Reapply as needed.

### 1.4 Mode of Action

d-Limonene affects the sensory nerves of the peripheral nervous system by causing spontaneous stimulation of nerves which results in muscle twitching, convulsions and eventual paralysis in listed arthropods.

## 2.0 Methods of Analysis

### 2.1 Methods for Analysis of the Active Ingredient

A well established Food Chemicals Codex method was used to analyse the product. The requirement for submission of the validation data has been waived.

### 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.

## 3.0 Impact on Human and Animal Health

### 3.1 Integrated Toxicology Summary

The PMRA conducted a detailed critical review of the toxicological database available for d-limonene, which consisted mainly of information obtained from the open scientific literature. The database is sufficiently complete to define the majority of toxic effects that may result from exposure to d-limonene when the pest control product is used as intended.

The applicant did not submit toxicology test data on the technical grade active ingredient (TGAI), but instead submitted information from published sources on the acute, short-term and chronic effects of d-limonene to address the requirements of registration. Included in the submission package was the United States Environmental Protection Agency's (USEPA) Reregistration Eligibility Decision document and the Tolerance Reassessment Eligibility Decision document, as well as various Material Safety Data Sheets (MSDSs) for the end-use

products and their associated formulants. Additional references obtained by the PMRA from the open scientific literature on d-limonene included the World Health Organization (WHO) Food Additives Series 30 document, International Agency for Research on Cancer (IARC) Monograph Volume 73, Concise International Chemical Association Document (CICAD) number 5 document, National Industrial Chemicals Notification and Assessment Scheme document (NICNAS), and the USEPA Integrated Risk Information System document (IRIS).

To address the data requirements in support of the associated end-use product registrations, the applicant submitted acute toxicity (oral and dermal), irritation (ocular and dermal), and sensitization studies conducted with TC-232 (10% d-limonene), as well as having provided the MSDSs for the end-use products. The submitted studies are sufficient to address the end-use product registration requirements for both products. In addition, information on formulants and impurities available from the scientific literature, MSDSs, and toxicology databases were also considered in the review.

The active ingredient, d-limonene, is absorbed by the gastrointestinal tract. Two male human volunteers when given 1.6 g [$^{14}$C] d-limonene orally, excreted 52–83% of the radiolabel in their urine within 48 hours. In another study involving healthy human volunteers (five women and two men), blood samples were drawn at 0 and 24 hours for blood chemistry, and at 0, 4 and 24 hours for metabolite analysis, after the subjects had ingested 100 mg/kg bw of d-limonene in custard. Results of the analysis demonstrated the presence of five metabolites of d-limonene in the sampled plasma, and in all of the test subjects, the metabolite concentrations were higher at 4 hours than at 24 hours after dosing. The investigators did not calculate a metabolic half-life value for d-limonene.

In male Wistar rats, [$^{14}$C] d-limonene was rapidly absorbed following administration of 800 mg/kg bw (4.15 µCi/animal) by gavage. The radiolabel concentration in blood was at a maximum after 2 hours and large amounts of radiolabel were also detected in the liver (maximum concentration after 1 hour) and kidneys (maximum concentration after 2 h). Negligible concentrations were found in blood and organs after 48 h. Urinary recovery of [$^{14}$C] d-limonene was 77–96% within 3 days in rats, guinea pigs, hamsters and dogs. Fecal recovery was reported to be 2–9% within 3 days of administering the test substance.

When [$^{14}$C] d-limonene was administered orally to male and female Sprague Dawley rats at a dose of 409 mg/kg bw, the renal concentration of d-limonene equivalents was about 2.5 times higher in males than females, and approximately 40% of the radiolabel in male rats was bound reversibly to renal proteins. The major metabolite bound to the renal protein fraction was identified as d-limonene-1,2-epoxide (> 80%), with parent d-limonene and the 1,2-diol adduct as minor components of the protein-bound moieties. The renal protein to which these metabolites bound was identified as α 2µ-globulin.

Acute toxicity of d-limonene by oral and dermal routes is low based on the oral $LD_{50}$ > 5000 mg/kg bw (in rabbits and rodents) and dermal $LD_{50}$ > 5000 mg/kg bw (in rabbits), respectively.

Publicly available information regarding the acute inhalation toxicity of limonene includes supplemental human exposure data. The sensory irritation threshold in humans was reported to be above 80 ppm (0.45 mg/L). Based on an $RD_{50}$ > 1 g/kg (concentration that depresses respiration rate by 50% > 5.57 mg/L) when tested on mice, d-limonene is likely to be of low toxicity. The American Industrial Hygiene Association (AIHA) has set a standard 8 h Time Weighted Average (TWA) of 30 ppm (0.17 mg/L) for d-limonene. The 8 h time weighted exposure limit for d-limonene is 25 ppm (0.14 mg/L) in Sweden and Norway, and the short-term (15 minute) exposure limit (STEL) in Sweden is 50 ppm (0.28 mg/L). Inhalation of d-limonene is likely to result in irritation of nose, throat and respiratory tract.

Based on studies in guinea pigs and rabbits, d-limonene is a skin irritant. In rabbits, d-limonene was classified as moderately irritating to skin based on the primary irritation index score of 3.5/8.0. Although there is insufficient information to grade the ocular irritancy of d-limonene, eye irritation in rabbits has been reported. Therefore, d-limonene is likely to cause ocular irritation in humans.

d-Limonene is a skin sensitizer in humans and is usually included among the fragrance allergens. According to a comprehensive study in guinea pigs, including a variety of methods for sensitization (e.g. open Epicutaneous Test and Guinea Pig Maximization Test), d-limonene exhibited sensitization potential in all but one of the tests. In a study on guinea pigs, allergenicity of d-limonene was found to be caused by the oxidation products of d-limonene. d-Limonene of high purity gave no significant allergic reactions, while d-limonene exposed to air for two months sensitized animals. The study concluded that allergenic compounds are formed from d-limonene upon prolonged air exposure.

Based on the studies provided by the applicant using the TC-232 test substance, the end-use products are likely to be of low toxicity by oral ($LD_{50}$ > 5000 mg/kg bw), dermal ($LD_{50}$ > 5000 mg/kg bw) and inhalation ($LC_{50}$ > 2.05 mg/L) routes of exposure. There were no mortalities or abnormalities noted in any of the acute studies in rats.

TC-232 is minimally irritating to the eyes and moderately irritating to skin in New Zealand White rabbits based on MAS (Maximum Average Score) of 0.44/110 and 3.8/8.0, respectively.

TC-232 is not a dermal sensitizer when topically applied in Hartley-Albino guinea pigs by the Buehler method. Although this study indicates that the end-use products are unlikely to be dermal sensitizers, based on the sensitization potential of d-limonene, which is considered a human skin sensitizer, it is likely that repetitive dermal contact to the end-use products may result in dermal sensitization. Therefore, the formulations are classified as potential skin sensitizers.

In a short-term oral study, groups of five male and five female mice ($B6C3F_1$) were administered d-limonene by gavage at doses of 0, 413, 825, 1650, 3300 or 6600 mg/kg bw/d in 10 mL/kg bw corn oil for 5 days/week over a 16 day period (12 total dosings). All mice (5/5) exposed to 6600 mg/kg bw/d, 4/5 males and 5/5 females exposed to 3300 mg/kg bw/d, and 1/5 males and 1/5 females exposed to 1650 mg/kg bw/d died before study termination. In mice that received 1650 mg d-limonene/kg bw/d and survived, there were no compound-related clinical or histopathological findings.

Daily administration of d-limonene at 277–2770 mg/kg bw/d to male and female Sprague-Dawley rats for one month resulted in a slight decrease in body weight and food consumption at the highest dose tested. On histological examination, granular casts were observed in the kidney of males at the highest dose tested but no significant change was observed in other organs.

In male Fischer 344 rats, d-limonene administered at 150 mg/kg bw/d increased renal cell proliferation, particularly in the $P_2$ segment of the renal proximal tubular epithelium after 4 or 31 weeks of exposure. Fischer 344 rats (male), when dosed orally for 91 days at 0, 5, 30, 75 or 150 mg/kg bw/d, exhibited increased renal cell proliferation in response to hyaline droplet formation. At the lowest dose, neither formation of hyaline droplets nor an increase in proliferating cell nuclear antigen-labelled renal proximal tubular cells was noted. At doses of 30 mg/kg bw/d of d-limonene and higher, both hyaline droplet formation and the percentage of labelled cells increased. At the highest dose, the percentage of antigen-labelled cells was increased by about six times over that of the control group, and the cells were localized to the $P_2$ segment of the renal proximal tubule.

In male NCI Black Reiter rats (NBR), when given orally for four days at 1650 mg/kg bw, d-limonene caused no renal toxicity. NBR rats do not synthesize the α 2μ-globulin that is normally present in hyaline droplets found in male Fischer 344 rats associated with d-limonene-induced nephrotoxicity.

In adult beagle dogs, oral administration of d-limonene at 100 or 1000 mg/kg bw/d (maximum tolerated does for emesis) administered by gavage twice daily for 6 months increased kidney weights, but there were no histopathological changes, hyaline droplet accumulation, or nephropathy.

Effects of d-limonene on the central nervous system have been reported in animal studies, but it is not known whether these effects were from general intoxication or a more direct effect of the chemical. In rats and mice, peroral administration of d-limonene (3 mL) showed decreased motor activity. Similar effects were observed when limonene was administered to mice (1000 mg/kg bw/d for 13 weeks).

Studies were unavailable regarding the reproductive toxicity of limonene, and there is no evidence that limonene is teratogenic or embryotoxic in the absence of maternal toxicity. The developmental toxicity of d-limonene has been studied in mice, rats, and rabbits.

In a mouse study, 15 pregnant mice per group were administered 0, 591, or 2363 mg/kg bw/d d-limonene by gavage on gestation days 7–12. In the animals administered 2363 mg/kg bw/d, maternal toxicity (significant reduction in body weight) and developmental toxicity (significant increase in the number of fetuses with skeletal abnormalities, including lumbar ribs, fused ribs, and delayed ossification of several bones in the paws) were observed. At the low dose, no maternal or fetal effects were noticed. This study is limited because of the small sample size, only two doses were tested, and dosing did not cover the entire period of organogenesis.

In a rabbit study, 10–18 pregnant Japanese white rabbits were dosed with 0, 250, 500, or 1000 mg/kg bw/d d-limonene by gavage on days 6–18 of gestation. Maternal toxicity occurred at exposure doses of 500 or 1000 mg/kg bw/d, there were significant reductions in food consumption and body weight at both doses, and mortality occurred in the highest dose tested (6/21). Developmental toxicity was not observed at any dose. This study is limited by the small sample size.

In a rat developmental toxicity study, a no observed effect level (NOEL) of 250 mg/kg bw/d for maternal and developmental toxicity was determined. At 500 and 1000 mg/kg bw/d, a small decrease in maternal body weight gain, as well as excessive salivation, were observed at 1000 mg/kg/d. At 500 and 1000 mg/kg bw/d, slight but statistically significant and dose-dependent increases in the number of litters and fetuses with 14 ribs instead of 13 were observed. These effects were considered to be variations in skeletal formation, were secondary to maternal toxicity and were not accompanied by other effects; therefore, there is no evidence of sensitivity in the young.

d-Limonene and its metabolites are unlikely to be genotoxic or mutagenic. In *Salmonella typhimurium*, d-limonene was not mutagenic with or without exogenous metabolic activation. It did not induce sister chromatid exchange, chromosomal aberrations, trifluorothymidine resistance or transformation of rodent cells *in vitro*. Negative results were observed in the mammalian spot test, even at doses considered to be toxic. In the SOS chromotest, the metabolite, d-limonene-1, 2-oxide tested negative. The metabolite was not mutagenic in *Salmonella typhimurium* and did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro*. Essential oils containing d-limonene did not induce differential toxicity in *Bacillus subtilis*, nor did they induce reverse mutation in *Salmonella typhimurium*.

In a 2-year study, 50 animals/species/sex/dose were administered 0, 75, or 150 mg/kg/d (male rats); 0, 300, or 600 mg/kg/d (female rats); 0, 250, or 500 mg/kg/d (male mice); or 0, 500, or 1000 mg /kg/d (female mice) d-limonene by gavage in corn oil once a day for 5 days/week. Male rats at 150 mg/kg/d had slightly decreased body weight, and developed α 2μ-globulin-induced nephropathy and renal adenoma/adenocarcinoma. Female rats showed no effects at 300 mg/kg/d but at 600 mg/kg/d had slightly decreased body weight and increased mortality. Female mice at 1000 mg/kg/d dose had decreased body weight. No treatment-related nephropathy or renal adenomas/carcinomas were observed in either sex in the mice.

d-Limonene is reported to have produced hyaline droplet nephropathy and caused renal tubular tumours only in adult male rats through an α 2μ-globulin-associated response. Male rats are unique in that they exhibit a background of spontaneous protein droplets in the proximal tubule, particularly within the cells of the $P_2$ segment. d-Limonene increases the formation of these droplets, and it was shown by two-dimensional gel electrophoresis that the only protein accumulating was α 2μ-globulin. Alpha α 2μ-globulin is synthesized in the liver of adult male rats, secreted into the general circulation and reabsorbed by the renal proximal tubule cells. The critical role of this protein in renal effects of d-limonene is demonstrated by the absence of histopathological changes in female rats and in species that do not synthesize α 2μ-globulin. Therefore, d-limonene did not show renal toxicity in female rats, in male NBR rats or in other species studied, including male and female mice and dogs, but transgenic mice that synthesize α 2μ-globulin have been shown to develop these lesions.

Nephrotoxicity was induced in the rat but was not considered to be a relevant endpoint for human risk assessment purposes. Binding of d-limonene, and particularly the 1, 2-epoxide, to α 2μ-globulin is the requisite step in the development of α 2μ-globulin nephropathy. However, the protein content of human urine is very different from that of rat urine, since humans excrete very little protein (about 1% of the concentration found in urine of male rats). Also, human urinary protein is predominantly a species of high molecular mass, and there is no protein in human plasma or urine identical to α 2μ-globulin. As such, the information suggests that the renal tumours caused by d-limonene in male rats are not relevant to humans.

Based on a critical review of published scientific literature on the acute and short-term toxicity of d-limonene, coupled with a long history of use as an ingredient in cosmetics, essential oils, and other consumer goods, there is no conclusive evidence to suggest that d-limonene is carcinogenic to humans, genotoxic, teratogenic or a reproductive toxicant.

## 3.2 Occupational/Residential Exposure and Risk Assessment

The end-use products are packaged in 496 to 567 g ready-to-use pressurized metal cans intended for cracks, crevices, or void spaces, where insects may be living and breeding, or for spot treatment applications on insects, both indoors and outdoors.

The commercial product is to be hand applied with the supplied actuators and injection tubes or using a piece of injector equipment, called Whitmire Micro-Gen Equipment™ System III® for crack and crevice treatments, and also by spot treatment. The domestic product is to be applied with the supplied actuators and injection tubes for crack and crevice treatment or by spot treatment in and around the home.

For crack and crevice treatment, the injector tip is to be placed into cracks, crevices, holes and other small openings and the product is released approximately for 1 second. The recommended maximum rate of application for light infestations is 1m/s, i.e., move injector tip along cracks while treating; for heavy infestations 35 cm/s; for closed voids, the void's cubic area is to be calculated and treated at the rate of 1 – 5 s/$m^3$. Several holes need to be treated in long-running voids. For spot treatment directly on insects, the product is to be sprayed approximately 30 cm from the target for one second.

A one second application from the ready-to-use container results in 1.4 grams of the formulation (0.147 g a.i.) being applied with injector or direct spray, and 1 gram (0.105 g a.i.) with the Whitmire Micro-Gen Equipment™ System III®. The labels recommend to repeat application as needed.

On average, 26 applications are expected to be done per treatment site per year. Based on the information provided by the applicant, a commercial applicator will use approximately 1 can of product per day (60 g of a.i.).

Crack and crevice application is meant for cracks, crevices and void spaces where insects may be present, including openings around pipes, and sinks, under refrigerators, behind baseboards, washing machines, stoves, cabinets, sewers, floor drains, meter boxes, baseboards, around door and window frames, wall voids, structural cracks and crevices, bed frames, box springs, inside empty dressers and clothes closets, carpet edges, high and low wall moldings, wall paper edges, under siding, in machinery, and cracks and crevices in cabinets and pantries, weep holes, soffits, and around attic vents. Although use against bed bugs is proposed, the end-use product is not proposed to be used in/on mattresses.

Spot treatment includes application mainly outdoors, in commercial kitchens, garages, attics or unfinished basement areas, to pet bedding and under furniture.

Indoor treatment sites include apartments, food storage areas, homes, hospitals, hotels, meat packing and food processing plants, motels, nursing homes, resorts, restaurants and other food handling establishments, schools, supermarkets, transportation equipment (buses, boats, ships, trains, trucks), utilities, warehouses, and other commercial and industrial buildings.

Treatment sites in food areas include areas for receiving, storage, packing, preparing, edible waste storage and enclosed processing systems, and serving areas.

Non-food treatment sites include areas such as garbage rooms, lavatories, floor drains (to sewers), entries and vestibules, offices, locker rooms, machine rooms, boiler rooms, garages, mop closets and storage areas (after canning or bottling), wall voids, baseboards, and construction sites.

Outdoor treatments are proposed for use around apartments, campgrounds, homes, hospitals, hotels, motels, nursing homes, resorts, schools, supermarkets, utilities, warehouses, and other commercial and industrial buildings which include perimeter treatment and treatment for in-ground service boxes.

### 3.2.1 Occupational/Domestic-user

Since the proposed end-use products are ready-to-use cans, there is no mixing or loading involved before application. Therefore, occupational and domestic user exposure is limited to individuals during application and clean-up activities. Inhalation of d-limonene is likely to result in irritation of the nose, throat and respiratory tract. Review of oral toxicity, dermal toxicity, eye irritation, dermal irritation, and dermal sensitization studies submitted for formulation and

review of the toxicological information on d-limonene indicate that the formulations are likely to be of low toxicity irrespective of the route of exposure, are likely to be minimally irritating to eyes, and moderately irritating to skin and dermal sensitizers.

In general, exposure by users is expected to be minimal. The only exposure scenario of concern being from spot treatment, when applicators spraying at the target from a distance may be exposed through inhalation of aerosolized sprays or volatile vapours, and also possible dermal exposure from spray drift or on contact with sprayed wet surfaces.

Inhalation exposure can be minimized if commercial applicators/domestic users do not remain in the recently treated area, as is recommended on the proposed labels. Warning statements indicating the skin irritation, dermal sensitization potential, respiratory irritation potential and other mitigative measures, such as, “avoid breathing vapour or spray mists”, “do not get in eyes, on skin or on clothing” are also required on the product labels.

Commercial applicators, and workers involved in clean-up activities, are required to wear long pants, long-sleeved shirt, shoes plus socks, goggles or face shield and chemical-resistant gloves as well as a NIOSH approved respirator with an organic vapour cartridge or canister with any R or P prefilter when working in enclosed or confined spaces or when there is prolonged exposure to the vapours or spray mists.

There is minimal maintenance and clean-up associated with this product. The only post-application activity expected is the clean-up required to remove pesticide from non-target areas caused from excessive or careless pesticide applications; therefore, there is minimal post-application exposure.

### 3.2.2 Bystander

Bystander exposure from the commercial and domestic applications is expected to be minimal and of short term duration based on the methods of application and adherence to use precautions. Bystander exposure is negligible from crack and crevice treatment, and only spot treatment is anticipated to result in bystander exposure of concern when bystanders may be exposed to spray drift resulting in inhalation, dermal and ocular exposure. However, if label use directions are followed, the bystander exposure from spot treatment is expected to be minimal as the product is to be applied by directing the nozzle approximately 30 cm from surface to be treated.

As the commercial application involves only authorized personnel and bystanders are not expected to remain in the treatment area, bystander exposure is expected to be negligible when the commercial product is used according to label directions. The commercial label has use directions that the product not be applied to classrooms when in use and not applied in institutions (including libraries, sport facilities, etc.) in the immediate area of occupants. To protect bystanders from pesticide application to commercial use sites, precautionary measures require that the product not be applied in the immediate vicinity of people/pets, and indoor application of the product to commercial facilities be restricted to when they are not in operation.

Bystander exposure is likely from domestic uses, primarily when the product is used for spot treatment, resulting in inhalation and dermal exposures of spray drift. Therefore, the domestic label includes a precautionary statement that the product should not be applied in the immediate vicinity of people/pets.

To minimize post-application exposure in nursing homes and hospitals, the commercial label recommends that after treatment, the rooms need to be ventilated for 30 minutes before returning the patients.

Post-application exposure risks are further diminished if applicators/users or others re-enter the freshly sprayed area after the spray residues are dried and the treated areas are thoroughly ventilated. For domestic uses, children may be exposed if they enter freshly treated areas with wet surfaces, thus exposure from dermal and hand-to-mouth contact, as well as inhalation of vapours, is possible. To avoid such exposure, both the commercial and domestic labels contain statements restricting entry or re-entry to freshly treated areas following end-use product applications. Restricted entry is also applicable to pets. Adherence to these label directions is expected to not only adequately protect commercial applicators and domestic users from post-application exposures, but residential bystanders as well.

### 3.3 Food Residue Exposure Assessment

d-Limonene products are not applied directly to food and when applied in homes, apartments, meat packing and food processing plants, supermarkets, restaurants and food handling establishments, exposed food in the treatment area must be covered or removed. Consequently, the risk from dietary exposure is considered negligible.

### 3.4 Aggregate Exposure

The potential for exposure of the general public to d-limonene resulting from its use in the control of insects is not expected to be of concern, considering the background levels currently in the environment, as well as exposure from a variety of commercial and domestic products, such as citrus oils, fragrances, cleaners, as a food flavouring agent, and other sources. Significant exposure via drinking water is not expected to occur from the use in and around structures, in human habitat and recreational areas, empty food storage areas, and in residential outdoor areas, because it is not anticipated that the concentrations of d-limonene will exceed current background levels in the environment or from the use of other consumer products in commercial and residential settings. Non-occupational (i.e., residential) exposure is expected to occur as a result of the use of d-limonene as a pesticide, but is not considered a significant risk because of the generally low toxicity of d-limonene and the current levels which occur naturally in the environment or from use of other consumer products that contain d-limonene.

The general public is exposed to d-limonene by virtue of its occurrence in citrus oils, its use as a fragrance, its use in household cleaning products, and other commercial and domestic uses. Given that no appreciable increase in dietary or residential exposure relative to background levels is expected to occur from the use of either the commercial or domestic product, the PMRA has determined that there is no unacceptable risk expected from the aggregate exposure to d-limonene.

# 4.0 Impact on the Environment

## 4.1 Fate and Behaviour in the Environment

d-Limonene is insoluble in water, and it is somewhat resistant to aerobic and anaerobic biodegradation in water and soil. Based on its water solubility and estimated octanol/water partition coefficient (4.2), its predicted soil adsorption coefficient indicates that it will display low mobility in soil. However, it is expected to rapidly volatilize from both dry and moist soil to the atmosphere, although adsorption to soil may attenuate the rate of this process. Once in the atmosphere, d-limonene is expected to rapidly undergo gas-phase oxidation reactions with photochemically produced hydroxyl radicals, ozone, and at night with nitrate radicals, with calculated half-lives for these processes on the order of two hours or less.

Because the limonene molecule does not have functional groups for hydrolysis, and its cyclohexene ring and ethylene group are known to be resistant to hydrolysis, the compound is expected to be stable in water.

## 4.2 Environmental Risk Characterization

Due to the proposed use pattern (spot treatment) and that d-limonene is insoluble in water; aquatic organisms are not expected to be exposed to this product. Moreover, d-Limonene is a food grade chemical that is practically non toxic to terrestrial vertebrates. As such, an environmental risk assessment to either aquatic or terrestrial non-target organisms was not required, thus not conducted.

### 4.2.1 Risks to Terrestrial Organisms

d-Limonene is considered to be practically non-toxic to birds and mammals. Information regarding toxicity of d-limonene to terrestrial plants was not found.

The use of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer is considered to pose negligible risks to non-target terrestrial organisms.

### 4.2.2 Risks to Aquatic Organisms

d-Limonene is considered to be slightly toxic to rainbow trout and to *Daphnia*. Given the proposed method of application of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer and that d-limonene is insoluble in water, it is unlikely that aquatic organisms will be exposed to significant levels of d-limonene. The use of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer is considered to pose negligible risks to aquatic organisms

## 5.0 Value

### 5.1 Effectiveness Against Pests

### 5.1.1 Acceptable Efficacy Claims

In the five submitted efficacy trial reports, mortality reached 100% for all insects tested by 24 hours or less after application. Therefore, the use of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer to kill cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles on contact was supported. Listed use sites were accepted for MotherEarth Botanical Crawling Insect Killer, the commercial class end-use product. Use in apartments and homes was accepted for ProCitra-DL Botanical Crawling Insect Killer, the domestic class end-use product.

### 5.2 Adverse Effects

Although d-limonene is not expected to damage most substrates, it is recommended that it be tested in a small, inconspicuous area prior to treating an entire area.

### 5.3 Sustainability

### 5.3.1 Survey of Alternatives

The availability of alternative insecticides varies depending on the pest and product class (Appendix I, Table 3). Some of the currently available alternatives are older classes of chemistry (e.g., organophosphates). Some of these compounds are in the process of being removed from the Canadian market and will no longer be available for use in the future. No other domestic class products are available for control of Asian lady beetle.

### 5.3.2 Compatibility with Current Management Practices Including Integrated Pest Management

Both MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer may be used in an IPM program that includes monitoring and good cultural practices. d-Limonene may impact some beneficial arthropod predators and parasitic arthropods if they come in direct contact with either of these products during application.

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

d-Limonene represents a new mode of action and therefore provides an additional tool for resistance management in an IPM program to control cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles.

## 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., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, d-limonene was 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:

- d-Limonene does not meet the Track 1 criteria and will not form any transformation products which meet the Track 1 criteria. d-Limonene is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.

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

### 6.2 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 d-limonene and the end-use products ProCitra-DL Botanical Crawling Insect Killer and MotherEarth Botanical Crawling Insect Killer do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette.*

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[9].

## 7.0 Summary

### 7.1 Human Health and Safety

The available information for d-limonene is adequate to qualitatively identify the toxicological hazards that may result from exposure to d-limonene. d-Limonene is of low acute toxicity by oral and dermal routes. d-Limonene is moderately irritating to skin and is likely to cause ocular irritation in humans. d-Limonene is considered a skin sensitizer and repeated dermal exposure to the end-use products can result in skin sensitization. Due to the irritative nature of d-limonene, inhalation exposure is likely to cause irritation of the respiratory tract. Based on available toxicological information, there is no evidence to suggest that d-limonene is carcinogenic to humans, genotoxic or a teratogen/reproductive toxicant nor is it likely to present a neurotoxicity concern.

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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.

9 DIR2006-02, PMRA Formulants Policy.

Occupational/residential exposure is expected to be minimal if measures are taken to limit exposure during and after application, including the wearing of PPE for commercial applications, and ensuring that bystanders are not present during applications and that suitable re-entry intervals are followed in hospitals, nursing homes and in other institutions, including schools.

## 7.2 Environmental Risk

The use of ProCitra-DL Botanical Crawling Insect Killer and MotherEarth Botanical Crawling Insect Killer is not expected to pose a risk to non-target organisms. d-Limonene occurs naturally in citrus and certain other fruits, vegetables, meats and spices.

## 7.3 Value

MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer kills cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles on contact. It is applied at a rate of 1 m/s for light and 1/3 m/s for heavy crack and crevice infestations and at a range of 1-5 $s/m^3$ for closed voids. For direct contact, treatment must be made from a distance of 30 cm. MotherEarth Botanical Crawling Insect Killer, a commercial class end-use product, is for use in listed sites. ProCitra-DL Botanical Crawling Insect Killer, a domestic class end-use product, is for use in apartments and homes. Both end-use products provide users with an alternative option to conventional pest control products. d-Limonene represents a new mode of action for use against labelled pests and therefore, provides an additional tool for resistance management in IPM programs.

## 7.4 Unsupported Uses

The proposed use of MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer to kill ants, boxelder bugs, carpenter bees, chocolate moths, clover mites, dermestids, drug store beetles, earwigs, elm leaf beetle, grain weevils, scorpions, silverfish, sowbugs, springtails, termites (drywood), trogoderma (cabinet, Khapra and warehouse beetles) and wood-infesting borers and beetles was not supported due to lack of supporting data or rationale and/or the use was not relevant to Canada.

The use site categories of campgrounds, hospitals, hotels, motels, nursing homes, resorts, transportation equipment (buses, boats, ships, trains, and trucks), utilities, warehouses and other commercial and industrial buildings were not supported for the domestic class end-use product, ProCitra-DL Botanical Crawling Insect Killer.

## 8.0 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 d-Limonene Technical, MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer, containing the technical grade active ingredient d-Limonene, to control cockroaches, spiders, crickets, millipedes, centipedes, flour beetles, cluster flies, ticks, fleas, bed bugs and Asian lady beetles on contact.

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 | micrograms |
| a.i. | active ingredient |
| AIHA | American Industrial Hygiene Association |
| bw | body weight |
| CAS | Chemical Abstracts Service |
| CICAD | Concise International Chemical Association document |
| cm | centimetres |
| d | day(s) |
| DNA | deoxyribonucleic acid |
| g | gram |
| h | hour(s) |
| Hg | mercury |
| IARC | International Agency for Research on Cancer |
| IPCS | International Program on Chemical Safety |
| IPM | integrated pest management |
| IRIS | Integrated Risk Information System |
| IUPAC | International Union of Pure and Applied Chemistry |
| kg | kilogram |
| $K_{ow}$ | *n*–octanol-water partition coefficient |
| L | litre |
| $LC_{50}$ | lethal concentration 50% |
| $LD_{50}$ | lethal dose 50% |
| m | metre(s) |
| mg | milligram |
| mL | millilitre |
| mm | millimetre(s) |
| MAS | maximum average score |
| MIS | maximum irritation score |
| MSDS | material safety data sheet |
| N/A | not applicable |
| NBR | NCI Black Reiter rats |
| NICNAS | National Industrial Chemicals Notification and Assessment Scheme |
| NIOSH | National Institute of Occupational Safety and Health |
| NOEL | no observed effect level |
| p*K*a | dissociation constant |
| PMRA | Pest Management Regulatory Agency |
| PPE | personal protective equipment |
| ppm | parts per million |
| $RD_{50}$ | concentration that depresses respiration by 50% |
| RED | Reregistration Eligibility Decision |
| s | second(s) |
| STEL | short-term exposure limit |
| TGAI | technical grade active ingredient |
| TSMP | Toxic Substances Management Policy |
| TWA | time weighted average |

| | |
|---|---|
| USEPA | United States Environmental Protection Agency |
| UV | ultraviolet |
| WHO | World Health Organization |

# Appendix I Tables and Figures

## Table 1 Acute Toxicity of d-Limonene and Its Associated End-use Product (MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer)

| Study Type | Species | Result | Comment | Reference |
|---|---|---|---|---|
| **Acute Toxicity of d-Limonene (Technical)** | | | | |
| Oral | Rabbit | $LD_{50}$ > 5000 mg/kg bw | Low acute toxicity | 1617315 |
| Dermal | Rabbit | $LD_{50}$ > 5000 mg/kg bw | Low acute toxicity | 1617315 |
| Inhalation | Mice | $RD_{50}$ > 1 g/kg | Low acute toxicity | 1617315<br>1902787 |
| Skin irritation | Rabbits | Irritation index score = 3.5/8 | Skin irritant | 1902789 |
| Eye irritation | Rabbits | From published information | Slightly irritating | 1902789 |
| Skin sensitization | Guinea Pig | Positive results | Skin sensitizer | 1902789<br>1902785 |
| **Acute Toxicity of End-Use Products: MotherEarth Botanical Crawling Insect Killer and ProCitra-DL Botanical Crawling Insect Killer** | | | | |
| Oral | Rat | $LD_{50}$ > 5000 mg/kg bw | Low acute toxicity | 1617334 |
| Dermal | Rat | $LD_{50}$ > 5000 mg/kg bw | Low acute toxicity | 1617335 |
| Inhalation | Rat | $LC_{50}$ > 2.05 mg/L | Low acute toxicity | 1617336 |
| Skin irritation | Rabbit | MAS[1] = 3.8/8 (24, 48, & 72 h)<br>MIS[2] = 4/8 (1 h). | Moderately irritating | 1617338 |
| Eye irritation | Rabbit | MAS[1] = 0.44/110 (24, 48, & 72 h)<br>MIS[2] = 4/110 (at 1 h) | Slightly irritating | 1617337 |
| Skin sensitization[3] | Guinea Pig | Negative results | Negative skin sensitizer | 1617339 |

1 Maximum average score according to the method of Draize (MAS)
2 Maximum irritation score according to the method of Draize (MIS)
3 Buehler method.

## Table 2 Short-term Toxicity, Prenatal Development Toxicity, and Genotoxicity Profile of d-Limonene Technical

| Study Type | Species | Results (mg/kg/day in M/F ) | Reference |
|---|---|---|---|
| Short-term oral toxicity | B6C3F1 mice | Dose: 0, 413, 825, 1650, 3300, or 6600 mg/kg bw/day for 5 days a week for 16 days (12 doses total)<br><br>Mortality at 6600 mg/kg bw/day was 5/5 for males and 5/5 for females. At 3300 mg/kg bw/day, 4/5 males and 5/5 females died. At 1650 mg/kg bw/day, 1/5 males and 1/5 females died.<br><br>No treatment-related findings were observed in the surviving animals. | 1902789 |
| | Sprague-Dawley rat | Dose: 277-2770 mg/kg bw/day for 1 month<br><br>No treatment-related findings observed. | 1902790 |
| | Beagle dog | Dose: 100 or 1000 mg/kg bw twice daily for 6 months<br><br>↑ kidney weights. No other treatment-related findings were observed. | 1902790 |
| Prenatal developmental toxicity | Rat | Dose: 250, 500, and 1000 mg/kg bw/day on unknown gestation days.<br><br>↑ number of litters containing pups with extra ribs (500 and 1000 mg/kg bw/day). Likely secondary effects of maternal toxicity.<br><br>Maternal or developmental toxicity was not observed below 500 mg/kg bw/day. | 1644188 |
| | Japenese white rabbit | Dose: 0, 250, 500, or 1000 mg/kg bw/day administered by gavage on gestation days 6-18.<br><br>↓ food consumption and body weight at 500 and 1000 mg/kg bw/day. Death occurred in 6/21 animals at 1000 mg/kg bw/day. No adverse fetal development was noted.<br><br>Maternal or developmental toxicity was not observed below 500 mg/kg bw/day. | 1902784 |
| Reverse gene mutation assay | *S. typhimurium* (TA98, TA100, TA1535, TA1537, and TA1538) | Mutagenicity was not observed in the absence or presence of S9 metabolic activation at 2720 µg/plate. | 1902790 |
| | *S. typhimurium* (TA98, TA100, TA1535, and TA1537) | Mutagenicity was not observed in the absence or presence of S9 metabolic activation at 3333 µg/plate. | 1902790 |

| Study Type | Species | Results (mg/kg/day in M/F ) | Reference |
|---|---|---|---|
| Gene mutations in mammalian cells in vitro | Mouse lymphoma L5178Y cells, *tk* locus | Gene mutations were not induced at 60 µg/mL, with and without S9 metabolic activation. | 1902790 |

**Table 3 Alternative Insecticide Active Ingredients**

| ***Commercial Class Products*** | |
|---|---|
| **Pest** | **Alternative Insecticide Active Ingredients Include** |
| Cockroaches[1] | Abamectin, boric acid, chlorpyrifos, cyfluthrin, diatomaceous earth, d-trans allethrin, disodium octaborate tetrahydrate, german cockroach extract, hydramethylnon, imidacloprid, lambda-cyhalothrin, malathion, permethrin, propoxur, pyrethrins, resmethrin and silica aerogel. |
| Spiders | Boric acid, chlorpyrifos, cyfluthrin, d-trans allethrin, diatomaceous earth, lambda-cyhalothrin, malathion, permethrin, propoxur, pyrethrins and resmethrin. |
| Crickets | Boric acid, chlorpyrifos, cyfluthrin, d-trans allethrin, diatomaceous earth, lambda-cyhalothrin, malathion, permethrin, propoxur and pyrethrins. |
| Millipedes | Boric acid, carbaryl, chlorpyrifos, lambda-cyhalothrin, malathion, propoxur and pyrethrins. |
| Centipedes | Boric acid, chlorpyrifos, d-trans allethrin, lambda-cyhalothrin, permethrin, propoxur and pyrethrins. |
| Flour beetles[2] | D-trans allethrin, boric acid, diatomaceous earth, malathion, permethrin, propoxur and pyrethrins. |
| Cluster flies | Chlorpyrifos, lambda-cyhalothrin, permethrin, propoxur and pyrethrins. |
| Ticks | Carbaryl, chlorpyrifos, d-trans allethrin, lambda-cyhalothrin, malathion, permethrin, pyrethrins, rotenone and tetrachlorvinphos. |
| Fleas | D-trans allethrin, permethrin, propoxur, pyrethrins and pyriproxyfen. |
| Bed bugs[3] | Boric acid, carbaryl, cyfluthrin, diatomaceous earth and permethrin. |
| Asian lady beetles | Cypermethrin and malathion. |

| *Domestic Class Products* | |
|---|---|
| **Pest** | **Alternative Insecticide Active Ingredients Include** |
| Cockroaches[1] | Abamectin, boric acid, chlorpyrifos, diatomaceous earth, d-trans allethrin, d-phenothrin, disodium octaborate tetrahydrate, german cockroach extract, imiprothrin, permethrin, propoxur, pyrethrins, resmethrin, silica aerogel and tetramethrin. |
| Spiders | D-trans allethrin, diatomaceous earth, malathion, permethrin, propoxur, pyrethrins, resmethrin and tetramethrin. |
| Crickets | Boric acid, carbaryl, d-trans allethrin, diatomaceous earth, permethrin, propoxur, pyrethrins, rotenone and tetramethrin. |
| Millipedes | Carbaryl, d-trans allethrin, diatomaceous earth, malathion, permethrin, propoxur, pyrethrins and tetramethrin. |
| Centipedes | D-trans allethrin, diatomaceous earth, permethrin, propoxur, pyrethrins, resmethrin and tetramethrin. |
| Flour beetles[2] | Imiprothrin, permethrin and pyrethrins. |
| Cluster flies | D-trans allethrin, permethrin and pyrethrins. |
| Ticks | Carbaryl, d-trans allethrin, imidacloprid, permethrin, pyrethrins, (s)-methoprene and tetrachlorvinphos. |
| Fleas | D-trans allethrin, permethrin, propoxur, pyrethrins and tetrachlorvinphos. |
| Bed bugs[3] | D-trans allethrin, diatomaceous earth, permethrin, pyrethrins and tetramethrin. |

[1] Other control methods for cockroaches include prevention of the infestation, reducing clutter, good sanitation practices, vacuuming, trapping and cold treatments.

[2] Other control methods for flour beetles include prevention of the infestation, good sanitation practices and temperature (hot or cold) treatments.

[3] Other control methods for bed bugs include prevention of the infestation, reducing clutter, mattress encasements, vacuuming, heat, steam and laundering.

# References

## A. List of Studies/Information Submitted by Registrant

### 1.0 Chemistry


PMRA 1617274 2008, Product Chemistry Report for AI, DACO: 2.1,2.11,2.11.1,2.11.2, 2.11.3,2.11.4,2.12,2.13,2.13.1,2.13.2,2.13.3,2.13.4,2.14,2.14.1,2.14.10,2.14. 11,2.14.12,2.14.13,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9

PMRA 1617275 2005, A procedure for the safety evaluation of natural flavor complexes used as essential oils, DACO: 2.16

PMRA 1644191 2008, Complete Product Chemistry Report for AI, DACO: 2.1,2.11,2.11.1,2.11.2,2.11.3,2.11.4,2.12,2.13,2.13.1,2.13.2,2.13.3,2.13.4,2.1 4,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2 .14.7,2.14.8,2.14.9

PMRA 1664391 Certificate of Analysis, DACO: 2.16

PMRA 1755979 Description of Starting Materials and Detailed Production Process Description, DACO: 2.11.2,2.11.3

PMRA 1755980 2009, Testing of Registered Grade d-Limonene, DACO: 2.13.1,2.13.2, 2.13.3, 2.14 CBI

PMRA 1617331 2008, Product Identification, DACO: 3.1,3.1.1,3.1.2,3.1.3,3.1.4

PMRA 1617332 2008, Summary of Product Chemistry, DACO: 3.2,3.2.1,3.2.2,3.2.3,3.3.1,3.4,3.4.1,3.4.2,3.5,3.5.1,3.5.10,3.5.11,3.5.12,3.5.1 3,3.5.14,3.5.15,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.9

PMRA 1617333 2001, Physical and Chemical Characteristics of TC 232, DACO: 3.2

PMRA 1641703 2008, Product Identification, DACO: 3.1,3.1.1,3.1.2,3.1.3,3.1.4

PMRA 1641704 2008, Summary of Product Chemistry, DACO: 3.2,3.2.1,3.2.2,3.2.3, 3.3.1, 3.4,3.4.1,3.4.2,3.5,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3, 3.5.4,3.5.5,3.5.6,3.5.7,3.5.9

PMRA 1641705 2001, Physical and Chemical Characteristics of TC 232, DACO: 3.2

PMRA 1641706 Analytical Procedures, DACO: 3.5.8

PMRA 1641707 2008, Oxidizing or Reducing Action (Chemical Incompatibility), DACO: 3.5.8

PMRA 1779650 2000, HPLC Method of Analysis for DeterminatIon of Limilin in Whitmire Micro-Gen Research Laboratories TC-232 (D-Limonene), DACO: 3.4.1

PMRA 1779651 2001, Characterization and Test Site Storage Stability for TC 232, DACO: 3.5.10

PMRA 1789817 2009, GC Method of Analysis of ProCitra, DACO: 3.4.1

PMRA 1789818 2009, Physical and Chemical Characteristics of Whitmire TC 232, DACO: 3.5,3.5.1,3.5.11,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9

PMRA 1789819 2009, Instrument Chromatogram for TC 232, DACO: 3.7

PMRA 1789820 2009, Corrosion Stability, DACO: 3.5.14

PMRA 1789821 2009, Analysis Results, DACO: 3.7 CBI

PMRA 1644958 2008, Product Identification, DACO: 3.1,3.1.1,3.1.2,3.1.3,3.1.4

PMRA 1644959 2008, Summary of Product Chemistry, DACO: 3.2,3.2.1,3.2.2,3.2.3,3.3.1, 3.4,3.4.1,3.4.2,3.5,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3, 3.5.4,3.5.5,3.5.6,3.5.7,3.5.9

PMRA 1644961 2001, Physical and Chemical Characteristics of TC 232, DACO: 3.2

PMRA 1644962 Peroxide Method, DACO: 3.5.8

PMRA 1644963 2008, Oxidizing or Reducing Action (Chemcial Incompatibility), DACO: 3.5.8

PMRA 1789806 2009, GC Method of Analysis of ProCitra, DACO: 3.4.1

PMRA 1789807 2009, Physical and Chemical Characteristics of Whitmire TC 232, DACO: 3.5,3.5.1,3.5.11,3.5.2,3.5.3,3.5.6,3.5.7,3.5.9

PMRA 1789808 2009, Instrument Chromatogram for TC 232, DACO: 3.7

PMRA 1789809 2009, Corrosion Stability, DACO: 3.5.14

PMRA 1789810 2009, Analysis Results, DACO: 3.7 CBI

## 2.0 Human and Animal Health

PMRA 1617275 2005, A procedure for the safety evaluation of natural flavor complexes used as essential oils, DACO: 2.16

PMRA 1644188 1994, EPA RED, DACO: 0.17.1

PMRA 1644190 Exposure and Risk Assessment on Lower Risk Pesticide Chemicals, DACO: 0.17.1

PMRA 1617269 2006, EPA Label for Florida Chemical, DACO: 0.14

PMRA 1617304 1994, d-Limonene - Tolerance Exemption 4/94, DACO: 0.14

PMRA 1617305 2004, d-limonene, DACO: 0.14

PMRA 1617334 2001, Acute Oral Toxicity Study in Rats - Limit Test, DACO: 4.6.1

PMRA 1617335 2001, Acute Dermal Toxicity Study in Rats - Limit Test, DACO: 4.6.2

PMRA 1617336 2001, Acute Inhalation Toxicity Study in Rats - Limit Test, DACO: 4.6.3

PMRA 1617337 2000, Primary Eye Irritation Study in Rabbits, DACO: 4.6.4

PMRA 1617338 2001, Primary Skin Irritation Study in Rabbits, DACO: 4.6.5

PMRA 1617339 2001, Dermal Sensitization Study in Guinea pigs (Buehler Method), DACO: 4.6.6

PMRA 1617340 2008, Product Summary and Use Description, DACO: 5.1, 5.2, 5.3

PMRA 1617341 2008, Waiver request for Post Application-Passive data and Dislodgeable Residues, DACO: 5.6, 5.9

PMRA 1617342 2008, Waiver Request for Mixer Loader applicator Data, DACO: 5.3

### 3.0 Environment

PMRA 1644188 U.S. EPA. 1994. Reregistration Eligibility Decision (RED): Limonene. Office of Prevention, Pesticides, and Toxic Substances (7508W). EPA 738-R-94-034.

PMRA 1644190 U.S. EPA. Reregistration Special Review and Reregistration Division: D-Limonene. Office of Pesticide programs.

### 4.0 Value

PMRA 1617319 2008, Value Summary, DACO: 10.1

PMRA 1617320 2008, Summary-802-T80-023, DACO: 10.2.3.1

PMRA 1617321 2001, Comparative Efficacy of Residual Treatments for Control of the Southeastern Drywood Termite Using a Laboratory Choice Bioassay, DACO: 10.2.3.2

PMRA 1617322 2008, Summary-Z90-034, DACO: 10.2.3.1

PMRA 1617323 2001, Efficacy Evaluations of TC 232 (d-Limonene) Against Selected Arthropod Pests in vitro, DACO: 10.2.3.2

PMRA 1617324 2008, Summary-907-PHP51-018, DACO: 10.2.3.1

PMRA 1617325 2006, Evaluation of TC 245(6% Py/60%PBO) 0.26%, TC 267 0.50%, Tc 252 2% Py, ProCitra Dl 10% when applied directly onto Adult Bed Bugs, DACO: 10.2.3.2

PMRA 1617326 2008, Summary-1934-Z95-011, DACO: 10.2.3.1

PMRA 1617327 2006, Evaluation of the Efficacy of 2 Formulations of several products when applied as Direct spray to Asian Lady Beetles, DACO: 10.2.3.2

PMRA 1617328 2008, Summary - 2039-Z95-027, DACO: 10.2.3.1

PMRA 1617329 2007, Laboratory evaluation of Cy-Kick CS, Pro-Citra Dl and TC 249 Dinotefuran Dust in the control of the millipede, DACO: 10.2.3.2

PMRA 1617330 2008, Summary-Non-Safety Adverse Effects, DACO: 10.3.1

PMRA 1617332 2008, Summary of Product Chemistry, DACO: 3.2,3.2.1,3.2.2,3.2.3,3.3.1,3.4,3.4.1,3.4.2,3.5,3.5.1,3.5.10,3.5.11,3.5.12,3.5.13,3.5.14,3.5.15,3.5.2,3.5.3,3.5.4,3.5.5,3.5.6,3.5.7,3.5.9

PMRA 1641688 2008, Mode of Action, DACO: 10.2.1

PMRA 1641689 2008, Description of Pest Problem, DACO: 10.2.2

PMRA 1641702 2008, Non-Safety Adverse Effects, DACO: 10.3.2

PMRA 1779651 2001, Characterization and Test Site Storage Stability for TC 232, DACO: 3.5.10

## B. Additional Information Considered

### i) Published Information

#### 1.0 Human and Animal Health

PMRA 1902783 IPCS INCHEM, 750. Limonene (WHO Food Additives Series 30), DACO: 4.8

PMRA 1902784 d-Limonene (CASRN 5989-27-5), IRIS, US EPA, DACO: 4.8

PMRA 1902785 1991, Animal Experiments on the Allergenicity of d-Limonene - The Citrus Solvent, Annals of Occupational Hygiene, 35(4), 419 – 426, DACO: 4.8

PMRA 1902787 2000, Effects of R-(+)-and S-(-)-limonene on the respiratory tract in mice Human & Experimental Toxicology 19, 457-466, DACO: 4.8

PMRA 1902789 1998, World Health Organization, Concise International Chemical Assessment Document 5 - LIMONENE, DACO: 4.8

PMRA 1902790 d-LIMONENE, IARC Monograph, Volume 73, DACO: 4.8

PMRA 1902791 2002, NICNAS, Limonene - Priority Existing Chemical Assessment Report No. 22, DACO: 4.8