Health Canada Santé Canada

Section 12 Notice **Additional Information Required to Fulfill the Terms of Registration**

Product Name: Insect Repellent Moisturizing Milk Citronella Essential Oil
Registration Number: 25447
Application Number: 2017-0867
PMRA # : 2766737

PART 0 INDEX

DACO: 0
Title: Index

Required Data: Please submit an electronic index of the data package submitted in response to this letter. Please refer to Regulatory Directive 2006-05, Requirements for Submitting Data Index, Documents and Forms, for additional information.

PART 2 PRODUCT CHEMISTRY (Citronella Oil TGAI)

During the registration period, the PART 2 information is to be generated and must be provided to the Agency **by September 1, 2018**, and should indicate the DACO numbers specified below. A partial response to the outlined Requirements of Registration will not be accepted.

DACO	Requirement
DACO 2.11 (Manufacturing process and starting materials)	A description of the manufacturing process of the citronella oil would be required including all raw materials used in the process (type and part of plant, solvents, etc.)
DACO 2.12/0.1.6003 (Specification form)	A SPSF of the TGAI would be required which would include specifications for any impurity of concern.
DACO 2.13.1 (Methodology/Validation)	A method would be required to determine the composition of the product – literature method would be acceptable. The major components of the oil must be determined and quantitated. Major components of citronella oil may include citronellal, geraniol, geranyl acetate and limonene.
DACO 2.13.2 (Confirmation of Identity)	
DACO 2.13.3 (Batch data)	

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DACO 2.13.4 (Impurities of concern)	5-Batch data would be required for any impurity of concern. A description of the method used and validation data (linearity, % recovery, %RSD, & LOD) would also be required.
DACO 2.14 (Chemical and physical properties)	Chemical and physical properties obtained from public sources would be acceptable.

PART 4 TOXICOLOGY

The following information is to be generated and must be provided to the Agency **by September 1, 2019**, and should reference the DACO numbers specified below. A partial response to the outlined Requirements of Registration will not be accepted.

A formal commitment to generate the required toxicology data (for example, provide proof of the contract with the laboratory conducting study) with a detailed study plan/protocol (e.g. start/end time, detailed steps, etc.) must be submitted within **90 days** from the date of this letter for review by PMRA before initiation of the study.

The following is required to be submitted by **September 1, 2019**. Detailed progress reports with respect to the study plan/protocol must be submitted every **6 months** from the start date of the study.

DACO	**Requirement**
DACO 4.5.1 (Reproductive and Developmental Toxicity)	One-generation reproduction study with developmental toxicity endpoints by the dermal route with whole citronella oil. A study of dermal dosing tolerance may be necessary to ensure it is possible to conduct the main study without having to remove animals due to adverse skin irritations. ▪ The PMRA recommends that the test substance (the "active ingredient") should be a mixture of citronella oil and citronella terpenes as presented in currently registered products. ▪ A dermal tolerance study is recommended as a first screening step. The goal of this study is to determine the maximum concentration of whole citronella oil that can be applied to animal skin for the duration of the reproduction study. The results of this study are critical as it will help select the appropriate dose range for the reproduction study. ▪ Afterwards, a modified extended one-generation reproductive toxicity study (OECD Test No. 443) is required. In this study, the parental generation (P and F1) should be exposed as indicated in OECD Test No. 443 for the reproduction cohort only (cohort 1). This cohort should subsequently be extended to produce pregnant females for the assessment of developmental toxicity as per OECD Test No. 414.

Toxicology studies must be conducted according to current OECD study protocols with the modifications listed in the table above and be in compliance with GLP requirements. The applicable OECD study protocols are listed below:

OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects
http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

Test No. 443: Extended One-Generation Reproductive Toxicity Study
http://www.oecd-ilibrary.org/environment/test-no-443-extended-one-generation-reproductive-toxicity-study_9789264122550-en

Test No. 414: Prenatal Development Toxicity Study
http://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820-en