Citriodiol Active Ing. file

New York State Department of Environmental Conservation
Division of Solid & Hazardous Materials
Bureau of Pesticides Management
Pesticide Product Registration Section
625 Broadway, Albany, New York 12233-7257
Phone 518-402-8768 FAX 518-402-9024
Website: http://www.dec.state.ny.us/website/dshm
E-Mail: ppr@gw.dec.state.ny.us

Erin M. Crotty
Commissioner

May 16, 2002

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ms. Jean Killoren
WPC Brands, Inc.
1 Repel Road
Jackson, Wisconsin 53037

Dear Ms. Killoren:

Re: Registration of the Formulated Product Repel Lemon Eucalyptus (EPA Reg. No. 305-56) and the Manufacturing Use Product (MUP) (EPA Reg. No. 305-59) Containing the New Active Ingredient Citriodiol.

The New York State Department of Environmental Conservation (Department) has completed the evaluation of your application and data package, received April 11, 2001, additional information, received July 11, 2001, additional information received on November 13, 2001, and further additional information, received on April 5, 2002, submitted in support of the registration of the referenced product and the manufacturing use product (MUP) containing the new active ingredient **Citriodiol.**

Repel Lemon Eucalyptus Insect Repellent Lotion (EPA Reg. No. 305-56) is labeled for application to exposed skin to repel mosquitoes and deer ticks for up to six hours. The Repel product may be re-applied once for a maximum number of applications of two per day.

The subject application and data package received July 11, 2001, were deemed complete for purposes of technical review on August 22, 2001, following one determination of incompleteness dated June 5, 2001. Pursuant to the review time frame specified in ECL §33-0704.2, a registration decision date of January 18, 2002 was established. By mutual agreement, the registration decision date was subsequently waived to allow WPC Brands, Inc. to respond to issues raised by the New York State Department of Health (NYSDOH). A conference call between the registrant, NYSDOH and the Department was held on December 14, 2001 to discuss these issues. The registrant agreed to provide further data including a four day dermal irritation study to address concerns presented by the NYSDOH with regard to dermal effects noted in the United States Environmental Protection Agency (USEPA) study reviews.

The registration package for the active ingredient citridiol and the formulated product, Repel Lemon Eucalyptus (EPA Reg. No. 305-56) and the Manufacturing Use Product (MUP) (EPA Reg. No. 305-59) were reviewed by this Department and the NYSDOH. The final use product is applied directly to human skin and therefore, did not require a review of effects to non-target organisms or environmental fate.

Human Health Effects Review:

The Repel Lemon Eucalyptus product contains 30 percent of the active ingredient Citriodiol which contains about 65 percent p-menthane-3,8-diol as the primary repellent active ingredient and 35 percent co-extracts. The MUP is labeled for the manufacture of repellent products and contains 100 percent Citriodiol. Both of these products are classified as biopesticides and as such the USEPA required only limited toxicity data for federal registration.

The active ingredient Citriodiol was not very toxic in acute oral or dermal exposure studies in laboratory animals and did not cause skin sensitization in guinea pigs. The USEPA allowed the registrant to bridge these data on Citriodiol to the Repel Lemon Eucalyptus product and as a result, product specific data are not available. The requirement to conduct an acute inhalation study was waived for both Citriodiol and the Repel product. Acute eye and dermal irritation studies on Citriodiol and Repel Lemon Eucalyptus showed that both were corrosive to the eyes, and whereas the active ingredient was a moderate skin irritant, the formulated product was a mild skin irritant. Given the general use pattern of insect repellents, however, repeat applications to skin are likely and could result in more skin contact and possibly reactions than were identified in the acute exposure studies.

The USEPA also required the registrant to submit a 28-day dermal toxicity study, a dermal developmental toxicity study and a battery of genotoxicity studies. The genotoxicity studies with the active ingredient Citriodiol gave negative results. Also, the 28-day dermal toxicity study and the dermal developmental toxicity study in rats reported no systemic or developmental effects at the only Citriodiol dose tested, which was 1,000 milligrams per kilogram body weight per day (mg/kg/day) in both studies. Therefore, the no-observed-effect level (NOEL) for systemic effects was equal to or greater than 1,000 mg/kg/day. On the other hand, in both these studies a significantly increased incidence of animals with slight to mild dermal irritation (edema, erythema, flaking of the skin) at the application site was noted. Since only one dose (1,000 mg/kg/day) was tested, the NOEL for these dermal irritation effects could not be determined. The USEPA apparently has not developed a reference dose for Citriodiol or its constituents. Also, no toxicokinetic, reproductive, subchronic feeding or chronic feeding/oncogenicity studies were required.

The registrant submitted summaries from an oral developmental toxicity study (required as a condition of federal registration) and a 14-day dermal toxicity study that exposed animals to Citriodiol. In the oral developmental toxicity study, transient clinical effects (e.g., ataxia, impaired righting reflex) and increased absolute and relative liver weights were reported in maternal animals at dose levels of 300 and 1,000 mg/kg/day.

One maternal animal in the 100 mg/kg/day also had these effects. No effects on fetal malformations/variations or on litter parameters were noted for any dose group. In the dermal study, rats were administered Citriodiol to occluded skin at doses of either 0, 3,000 or 5,000 mg/kg/day (equivalent to 0, 7.5 or 12.5 mg/cm^2 skin). Due to clinical signs and deaths, the 5,000 mg/kg/day group was terminated after 7 days of treatments. Rats in the 3,000 mg/kg/day group experienced sporadic clinical effects (e.g., lacrimation, hypoactivity, eye and nasal discharge) as well as erythema and/or desquamation at the exposure site.

The registration package contained a USEPA review of a post-marketing surveillance study conducted outside the United States. The products considered in this survey were not the Repel product, but contained p-menthane-3,8-diol and were formulated as sprays, gels and sticks. Of the 1,093 recent users of these products surveyed, four percent experienced some rash. A slightly higher proportion of rashes were reported among children ages 0 to 9 years old than among older users. Apart from the survey, the formulator also received 20 complaints from users of the p-menthane-3,8-diol products over the period of July 1994 to August 1997. Of these 20 complaints, 9 involved burning sensation or irritation, 5 reported a rash, 4 involved a respiratory effect (e.g., wheezing, sinus congestion) and 2 reported either an unspecified allergic reaction or contact dermatitis. These 20 complaints reportedly represent less than 0.007 percent of the estimated 300,000 users of these products. The complaints received by the formulator most likely represents only a fraction of those that have experienced problems with using the products. Consequently, the survey of recent users may more accurately reflect dermal irritation potential among users.

The registration package contains a risk assessment for the Repel product based on data for the insect repellent DEET. The exposure assessment included acute dermal contact by adult females, teenagers (13-17 years of age) and children 12 and under. The estimated average daily exposures of these groups to Citriodiol in the Repel product, based on two applications per day (the label directions state to not apply more than twice a day), were 9.0, 9.8 and 20.0 mg/kg, respectively. When the acute dermal exposures are compared to the NOEL (1,000 mg/kg/day or greater) from the dermal toxicity and dermal developmental toxicity studies, the respective margins of exposure (MOEs) are 111, 102 and 50. Generally, MOEs of 100-fold or greater are considered adequate by the USEPA.

The registrant also submitted a subchronic exposure assessment for the Repel product. For adult females, teenagers and children, the respective MOEs were about 1,700, 2,270 and 1,090 for mean population usage of repellents. These MOEs were calculated using a NOEL of 1,000 mg/kg/day and respective time-weighted daily exposure doses of 0.59, 0.44 and 0.92 mg/kg. For the 95th percentile population frequency of usage, MOEs were estimated to be about 520, 800 and 300 for adult females, teenagers and children, respectively. The respective time-weighted daily exposures for the two month period of highest use (June and July) were 1.92, 1.25 and 3.36 mg/kg. These MOE assessments evaluate the likelihood of systemic effects from Repel use. However, both the subchronic (28-day) dermal toxicity study and the dermal

developmental toxicity study suggest that repeated dermal application of Citriodiol could cause skin irritation characterized by edema, erythema and flaking of skin in humans at doses of 1,000 mg/kg/day. The data from the survey of recent users of p-menthane 3,8-diol products appears to support this potential.

The potential for dermal and systemic effects to result from the use of the Repel product can also be evaluated in another manner. The application rates of the active ingredient in the 28-day dermal toxicity study were not provided in terms of mg/cm^2, but if application practices were the same as those in the 14-day study, the dose of 1,000 mg/kg/day would be equivalent to about 2.5 mg/cm^2. At this application rate, no systemic effects were noted, but dermal irritation was reported. In the 14-day dermal study, both dermal and systemic effects were reported at an application rate of about 7.5 mg/cm^2. The efficacy studies submitted in the registration package (see below), and which form the basis of the efficacy claims, generally used an application rate of about 1.6 mg/cm^2 product (equal to about 0.48 mg/cm^2 Citriodiol for the Repel product). This application rate is only about 5-fold less than the rate that caused dermal effects in a 28-day dermal toxicity study and only about 16-fold lower than the dose level that caused both dermal and systemic effects in a 14-day dermal study. This comparison does not take into account the repeat applications of the Repel product that may occur during each day of use.

To this end, the NYSDOH reviewed the study report entitled "Primary Skin Irritation Screen of Repel Lemon Eucalyptus Insect Repellent Lotion in Human Volunteers" submitted by WPC Brands, Inc. on April 5, 2002. This study was conducted in response to concerns expressed above. These concerns resulted from the fact that the Repel Lemon Eucalyptus product is labeled for direct application to human skin and that skin irritation has been noted in laboratory animal studies using Citriodiol and in humans from using products containing *p*-menthane-3, 8-diol, a major component of Citriodiol.

The currently submitted study involved the application of repellents to the inner forearm of 32 adult human test subjects (31 subjects completed the study) three times a day for a period of four consecutive days. For each subject, the Repel Lemon Eucalyptus insect repellent product was applied to a section of one forearm and a similarly-formulated repellent containing DEET instead of Citriodiol was applied to a section of the other forearm to serve as a control. The report states that "there was no evidence of erythema or other skin irritation observed at any time during the study" and presents the results that serve as the basis for this conclusion. The NYSDOH reviewed these results and accept this conclusion.

The registrant submitted data from several efficacy studies using Repel Lemon Eucalyptus. According to the registrant, the Repel product was 95 percent effective in repelling deer ticks from humans in a laboratory setting for six hours, 99.9 percent effective in reducing mosquito bites in the field over this same time period and showed a comparable efficacy to a major alternate repellent, 20 percent N,N-diethyl-m-toluamide (DEET).

There are no chemical specific federal or State drinking water/groundwater standards for p-menthane-3,8-diol or the other co-extracts of Citriodiol that were identified in the registration package. Based on their chemical structures, these compounds fall under the 50 microgram per liter (µg/L) general New York State drinking water standard for "unspecified organic contaminants" (10 NYCRR Part 5 – Public Water Systems) with the exception of citronellal which is a "principal organic contaminant" with a standard of 5 µg/L. The New York State drinking water standard for the sum of "unspecified organic compounds" and "principal organic compounds" is 100 µg/L.

Limited data are available on the toxicity of Citriodiol, containing p-menthane-3,8-diol. There are no studies on chronic toxicity, oncogenicity, multi-generation reproductive toxicity or toxicokinetics. Acute and subchronic toxicity studies alone are not adequate to fully characterize the toxic potential of a pesticide. This is a particular concern given that the pesticide in this case, Repel Lemon Eucalyptus (and products formulated with Citriodiol), is applied directly to the skin. Furthermore, the limited available data indicate some potential for local and systemic toxicity.

Given the limited database for the active ingredient and the use pattern of the formulated product, i.e., direct application to human skin, there were several issues that needed to be addressed. The primary concerns were possible skin irritation following repeated use and the potential effects from exposure to very young children.

WPC Brands, Inc. has submitted an acceptable skin irritation study which has shown no evidence of skin irritation to 31 human test subjects over a four day period, using greater than labeled use rates of the Repel product. The Department is satisfied that labeled use of the Repel product will not cause excessive skin irritation and is acceptable for use by the general population above the age of three years.

In recognition of the data gap for studies that address the potential for risks to very young children from exposure to citridiol, WPC Brands, Inc. proposed to mitigate potential concerns by changes/additions to the label text. The proposal included addition of the statement "Do not use on children under the age of three years" under the Precautionary Statements section of the labeling. Please also note that optional label claims referring to use by the whole/entire family will not be acceptable for this product/active ingredient in New York State. An application for amendment to revise the Repel Lemon Eucalyptus Insect Repellent Lotion federal label was filed March 5, 2002. The USEPA approved the label amendment on May 8, 2002.

The Department hereby accepts Repel Lemon Eucalyptus Insect Repellent Lotion for Registration in New York State. Enclosed for your files are the Certificate of Pesticide Registration and New York State stamped "Accepted" labeling.

Please note that a proposal by WPC Brands, Inc. or any other registrant, to register a product that contains *citriodiol*, and whose labeled uses are likely to increase the potential for significant impact to humans, non-target organisms, or the environment, would constitute a major change in labeled (MCL) use pattern. Such an application must

be accompanied by a new application fee and meet the requirements listed in Appendix 1.B. of "New York State Pesticide Product Registration Procedures" (August 1996). Such information as well as forms can be accessed at our website as listed in our letterhead.

If you have any questions on this matter, please contact Ms. Paula McBath, of my staff, at (518) 402-8768.

Sincerely,

Maureen Serafini

Maureen Serafini
Director
Bureau of Pesticides Management

Enclosures

cc: w/enc. - N. Kim/D. Luttinger - NYS Dept. of Health
R. Zimmerman/ R. Mungari - NYS Dept. of Ag. & Markets
G. Good/W. Smith - Cornell University, PMEP