UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

MAY 2 1 2007

DATE: May 21, 2007

SUBJECT: Science Review of Product Performance in Support of the Registration.

Decision Number: 371862
DP Number: 338694
EPA File Symbol Number: **71654-ER and 71654-EG**
Chemical Class: Biochemical
PC Code: **004801**
CAS Number: **8023-84-5**
Active Ingredient Tolerance Exemptions: No tolerance exemption. Non- food product.
MRID Numbers: 469774-24, 469774-25 and 470156-02

FROM: *Clara Fuentes, Ph. D. Biologist*
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TO: Raderrio Wilkins, Regulatory Action Leader
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~~**THE FOLLOWING CONTAINS CONFIDENTIAL BUSINESS INFORMATION**~~

ACTION REQUESTED

DuPont Chemical Solutions Enterprise requests registration of end-use products, *Refined Oil of Nepeta Cataria 15% Lotion* (EPA Reg. No. 71654-ER), and *Refined Oil of Nepeta Cataria 7 % Lotion* (EPA Reg. No. 71654-EG), containing 15 % w/w and 7 % w/w of new active ingredient, respectively, of hydrogenated catmint oil (also known as refined oil of *Nepeta cataria*). The new products proposed for registration are intended for use as personal skin-applied insect repellents against mosquitoes and black flies. In support of this registration, the registrant has submitted copies of product labels, CSFs and *MRIDs 469774-24, 469774-25, and 470156-02.*

1. Product chemistry data (CSF) are acceptable pending resolution of the deficiencies identified below:

1a. Deficiency #1: The CAS number, [redacted] respectively, are unknown to the Agency.

2. Product Performance data are acceptable pending clarification on the following items:

2a. The study report needs to provide a detailed discussion on the statistics employed to analyze the data.

2b. There is no written study report for these studies, except a brief summary of results and conclusions. The description of the study methods are referenced back to the original protocol. Protocol deviations are not addressed.

2c. The inconsistencies concerning amount of test material applied to subjects need to be resolved (Refer to "Reviewer's comments" at the end of this memo).

2d. It is not clear whether the landing rates for the whole body counts are based on 1 minute exposure taken hourly for 1. This information on landings rate does should appear on the results table (Appendix IV).

2e. The test sites were not monitored for incidence of mosquito-borne diseases prior to testing there. Although this is not a scientific issue, it has ethical implications.

2f. Complete Protection Time can be estimated from landings rather than bites, to minimize subjects' exposure to mosquito bites in the field. It is reported in these studies that the endpoint was bites, and subjects were continuously exposed to mosquitoes throughout the entire duration of the test. Although this approach does not compromise the scientific validity of the data, it has ethical implications.

STUDY SUMMARIES

Product Chemistry

The only product chemistry reviewed herein is the information provided on the CSF dated 4/12/06. No inert ingredient is in list 1. [redacted]

[redacted] This is a non-food product to be used as insect repellent. The lower and upper certified limits are within acceptable range. The active ingredient statement on the label matches the CSF. pH = 6.09 at 25°C for product 71654-EG, and pH = 5.54 at 25°C. Flash point/flammability > 97°C for both products.

Product Performance

MRDs *469774-24 and 469774-25, and 470156-02*

Introduction

The objective of studies 469774-24 and -25 is to evaluate the efficacy of 4 repellent formulations, containing different concentrations of the same active ingredient, *hydrogenated catmint oil* (CAS #8023-84-5; PC Code: 004801, also known as *Nepeta catia*) against mosquitoes in the field. The test sites were at Nicatous Lodge, Maine, and Collier Seminole State Park, Florida. The type of habitat at these sites are not described in the study reports. The main species of mosquitoes found in Maine was *Ochlerotatus intrudens*. The primary mosquito species found at the Florida site were: *Ochlerotatus atlanticus, O. taenior.hynchus, Psorophora ferox and Culiseta melanura.* Environmental conditions recorded during the studies were within acceptable limits.

The objective of study MRID 470156-02 is to evaluate the efficacy of 4 repellent formulations, containing different concentrations of the same active ingredient, *hydrogenated catmint oil* (CAS #8023-84-5; PC Code: 004801, also known as *Nepeta catia*) against black flies in the field. The test site was at Nicatous Lodge, Maine. The type of habitat at this site was not described in the study report. The main species of black flies found at the study site was *Simulium decorum.* The Environmental conditions recorded during the study were within acceptable limits

Results and Conclusions

MRID 469774-24:

The average number of landings on each control subjects were 14.6 and 17.1 per 5 minutes exposure, ranging from 5 to 43. The average count of landings on whole body suit was 20.4 landings, ranging from 11 to 41 landings. These whole body suit counts were taken hourly during 8 hours of intermittent exposure. (Appendix IV: statistics. Page 66 of 104). The duration of whole body suit's exposure periods are not specified in the report.

The mean CPT for the Lotion (15 % w/w) was 8 hours with no deviations (n=10)
The mean CPT for the Liquid (15 % w/w) was 7.48 hours ± 0.26 (n=10)
The mean CPT for the Lotion (7 % w/w) was 7.33 hours ± 0.33 (n=5)
The mean CPT for the Lotion (7 % w/w) was 4.17 hours ± 1.58 (n=5)

MRID 469774-25:

The average number of landings on each control subjects were 12.1 and 20.4 per 5 minutes exposure, ranging from 5 to 43. The average count of landings on whole body suit was 20.9 landings, ranging from 7 to 49 landings. These whole body suit counts were taken hourly during 8 hours of intermittent exposure. (Appendix IV: statistics. Page 66 of 104). The duration of whole body suit's exposure periods are not specified in the report.

The mean CPT for the Lotion (15 % w/w) was 6.14 hours ± 1.05 (n=10)
The mean CPT for the Liquid (15 % w/w) was 5.14 hours ± 0.22 (n=10)
The mean CPT for the Lotion (7 % w/w) was 5.54 hours ± 1.34 (n=5)
The mean CPT for the Lotion (7 % w/w) was 4.17 hours ± 0.42 (n=5)

MRID 470156-02:

The mean number of landings on each control subjects were 21.7 and 29.6, ranging from 3 to 42 during session 1, and 20.3 and 24.3, ranging from 1 to 56, during session 2. These counts are per 5 minutes exposure. The mean count of landings on whole body suit was 26.3, ranging from 14 to 47 landings during session 1, and 27.2 landings, ranging from 2 to 37, during session 2. These whole body suit counts were taken hourly during 8 hours of intermittent exposure (Appendix IV: statistics. Pg. 99 of 140). The duration of the whole body suit exposure periods are not specified in the report.

Session 1 and 2: Mean CPT for the Lotion (15 % w/w) = 7.31 (±0.56) hours (n=10)
Session 1 and 2: Mean CPT for the Liquid (15 % w/w) = 7.32 (±1.09) hours (n=10)

Session 1 and 2: Mean CPT for the Lotion (7 % w/w) = 6.59 (± 0.26) hours (n= 5)
Session 1 and 2: Mean CPT for the Liquid (7 % w/w) = 5.54 (± 2.28) hours (n=5)

Reviewer Comments:

MRIDs 469774-24 and 469774-25

The repellency of 4 products, 2 lotion and 2 liquid formulations differing in their concentrations of the same active ingredient, were tested in 2 field sites, one site in Maine and another site in Florida. The report does not describe the different habitat characteristics at these 2 test sites. The report provides information on the species, and abundance of mosquito species found at each site. The environmental data shows that the weather was cloudy, humid and on the cold side in Maine (average temperature was high fifties and low sixties ° F); RH was between 80 and 94; and the wind speed was less than 1 MPH. The weather data from Florida shows that it was sunny for the first 4 hours of the test, and then it became cloudy with 100% cloud cover. Raw

data collection sheet indicates that it started raining at the last 2 hours of the test. Apparently, this did not interfere with mosquito activity. The temperature was between 75 and 90 ° F, and RH was between 70 and 96. The wind speed was less than 1 MPH. These environmental conditions are within acceptable limits.

Neither Maine nor the Florida site was monitored for incidence of mosquito borne diseases prior to conducting the study. Site selection was based solely on unobstructed space, abundance and diversity of mosquito species, and mosquitoes' landing rate. All the mosquito species identified at these sites are potential vectors of WNV. While this is not a scientific issue, it has ethical implications.

The informed consent document states that subjects will be treated with less than 1 teaspoon full of formulation, which is the amount that would normally be applied to consumers. This study provides no indication of measuring a typical consumer dose to determine that the amount applied to subjects was the dose normally applied by consumers. The report shows some inconsistencies concerning the amount of test material applied to subjects. On page 7 of 104, it is stated that the lotions will be applied at 0.63 and 0.64 g./ 250 sq. cm skin surface area for the 15% and 7% formulations, respectively. On pages 13 and 16 of 104, the application rate for the 15% lotion is 62g/ 250 sq. cm., and 0.4 g/ 250 sq. cm. for the liquid 15% formulation. However, the report also states that the liquid formulation was applied by volume using a syringe, and the volume will be determined based on the specific gravity of the material. The reported applications for the liquid formulations on page 7 of 104 are given in units of volume, ml., instead of grams as reported on pages 13 and 16.

The whole body count of mosquito landings was taken hourly for unspecified exposure periods throughout the study. The table on page 66 of 104 shows hourly counts and the mean of those landings: 20.9 average landings. It is stated on page 8 of 104, that these counts are per minute. Also on page 8 of 104, it is reported that the landing counts on untreated skin of test subjects are recorded as number of landings per 5 minutes exposure. The information regarding landings rate should be reported on the table.

The endpoint in this study was the First Confirmed Bite, with subjects being continuously exposed to mosquitoes in the field. Frequency of mosquito landings is a good indicator of repellent breakdown. Risk to subjects from continuous exposure to mosquitoes in the field can be minimized by changing the endpoint from bites to landings, and exposing subjects to mosquitoes intermittently for short periods of time.

According to the study protocol, two test substances will be tested simultaneously on separate arms of the same subject. EPA specifically discourages testing more than one product on the same subject, unless the researcher can verify that the proximity of the 2 formulations on the same subject won't compromise the results.

Statistical data analysis is not discussed in any detail. The experimental design could have been analyzed as a 2 X 2 factorial (factors are 2 types of formulation – lotion and liquid - by 2

concentrations of active ingredient), for mean comparison with possible interaction or treatment main effect.

Lastly, the study report only provides a brief summary of the results and conclusion. The report is based entirely on the study protocol as amended. The actual study should be reported as conducted consistently with a copy of the study protocol.

MRID 470156-02

The repellency of 4 products, 2 lotion and 2 liquid formulations differing in their concentrations of the same active ingredient, were tested in 2 field sites, in Maine during 2 separate test sessions. Each test session lasted 8 hours. The report does not describe the different habitat characteristics at these 2 test sites. The predominant black fly species collected at these sites is *Simulium decorum*. The environmental data shows that the weather was sunny at the first day session, and cloudy the second. RH was not recorded the first day session; for the second day session, the RH was between 58 and 88, and the temperature was in the high fifties and seventies ° F. The wind speed was less than 1 MPH. These environmental conditions are within acceptable limits.

The informed consent document states that subjects will be treated with less than 1 teaspoon full of formulation, which is the amount that would normally be applied to consumers. This study provides no indication of measuring a typical consumer dose to determine that the amount applied to subjects was the dose normally applied by consumers. The report shows some inconsistencies concerning the amount of test material applied to subjects. On page 7 of 140, it is stated that the lotion formulations, 15% and 7% w/w of a. i. will be applied at 0.63 and 0.64 g./ 250 sq. cm skin surface area, respectively, and the liquids formulations will be applied as 43 g / 250 sq. cm. On pages 13 and 16 of 140, the application rate for the 15% lotion is 62g/ 250 sq. cm., and 0.4 g/ 250 sq. cm. for the 15 % liquid formulation. However, the report also states that the liquid formulation was applied by volume using a syringe, and the volume will be determined based on the specific gravity of the material. The reported applications for the liquid formulations on page 7 of 140 are given in units of volume, ml., instead of grams as reported on pages 13 and 16.

The endpoint in this study was the First Confirmed Landing, with subjects being continuously exposed to black flies in the field. To evaluate efficacy against black flies, landings will be used instead of bites due to the painful nature of black fly bites.

According to the study protocol, two test substances will be tested simultaneously on separate legs of the same subject. EPA specifically discourages multiple tests on the same subject unless the researcher can verify that the proximity of the 2 formulations on the same subject won't compromise the results.

The protocol, on page 15 of 140, states that if the period of black fly activity were less than 8 hours, subjects would be treated early enough before black fly activity began. The report does

not indicate that subjects were treated well in advance to initiation of the study because the landing rates were considered acceptable over the length of the study period (pg. 10 of 140). There were only 3 exposure periods during the study showing landing rates below 1 landing per minute. This occurred at 2 and 3 hours after test initiation. The conclusion is that if repellency lasted longer than that period, the products would have been effective during those periods as well.

Statistical data analysis is not discussed in any detail. The experimental design could have been analyzed as a 2 X 2 factorial (factors are 2 types of formulation – lotion and liquid - by 2 concentrations of active ingredient), for mean comparison with possible interaction or treatment main effect.

Lastly, the study report only provides a brief summary of the results and conclusion. The report is based entirely on the study protocol as amended. The actual study should be reported as conducted consistently with a copy of the study protocol.

cc: *Reviewer name*, Clara Fuentes
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Date: May 21, 2007