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

AUG 7 1984

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Cutter Evergreen Scent Insect Repellent Pump Spray

TO: Tim Gardner (PM-17)
Registration Division (TS-767)

FROM: Byron T. Backus B.T. Backus 07-27-84 7/27/84
Toxicology Branch
HED (TS-769)

THROUGH: William Butler, Head William Butler 8-1-84
Review Section III
and
William Burnam, Chief
Toxicology Branch

Registration # 121-ET

Tox. Chem. 346

Registrant: Miles Laboratories, Inc.

Actives:

N,N-Diethyl-meta-toluamide	17.1%
Other Isomers	0.9%
Dimethyl phthalate	12%
Di-n-propyl isocinchomeronate	1.0%
N-Octyl bicycloheptene dicarboximide	1.0%

Action:

This product is a pump spray, proposed for use as an insect repellent, to be applied to clothing and human skin.

Acute oral LD_{50}, dermal LD_{50}, inhalation LC_{50}, primary eye and dermal irritation studies have been submitted for the following formulation:

N,N-Diethyl-meta-toluamide	22.95%
Dimethyl phthalate	15.30%
Di-n-propyl isocinchomeronate	1.275%
N-Octyl bicycloheptene dicarboximide	1.275%

An dermal sensitization study has been submitted for a formula-

tion with the following percentages of actives:

N,N-diethyl-m-toluamide.....35%
Dimethyl phthalate.....13%
Di-n-propyl isocinchomeronate.....1%
N-Octyl bicycloheptene dicarboximide.....1%

Conclusions:

1. The acute oral LD_{50}, inhalation LC_{50}, dermal sensitization and primary eye and dermal irritation studies are acceptable. These studies were conducted on formulations that were similar enough to the proposed product so that the findings adequately define the potential acute hazards associated with use and exposure to this product.

2. The dermal LD_{50} study has been classified as Supplementary Data, as 3 animals died during the course of the study. In any study in which 3 mortalities occur at a single dose level it cannot be stated with 95% confidence that the LD_{50} is greater than that dose level.

   It is not expected that this product can cause mortality by this exposure route at a dosage of 2 g/kg. However, this expectation is based on information that has been derived from other dermal LD_{50} studies on Deet formulations, rather than this one particular study.

3. The product is in toxicity category III on the basis of oral LD_{50} and eye irritation hazard potential. Labeling should include the appropriate statements of practical treatment ("If Swallowed..." and "If in Eyes..."), as well as such cautions as "Harmful if swallowed," and "Causes eye irritation."

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Data Evaluation Report

Compound:

N,N-diethyl-m-toluamide (DEET)

Citation:

Kowalski, R.L. and Hartnagel, R.E. The Toxicity of Cutter Pump Spray Non-Aerosol Insect Repellent Formulation RB10199-82 (9/9/83): Acute (14 day) Oral Toxicity in the Rat. Report No. 28; issued December 20, 1983. Study conducted by Miles Laboratories, Inc., Elkhart, IN 46515. Study received at EPA 02-28-84; in Acc. 254183.

Reviewed by:

Byron T. Backus B.T. Backus 7-27-84
Toxicologist

Core Classification: Minimum

Product Classification: Tox. Cat. III

Conclusion:

1. The study adequately demonstrates the product is in toxicity category III by the oral exposure route.

Discussion:

The toxic effects of this product appear to be primarily due [redacted] present in this formulation as an "inert."

Materials:

Charles River Crl:CD®(SD)BR rats of both sexes
Cutter Pump Spray Non-Aerosol Insect Repellent (CIR-PS)

Procedure:

The rats were randomly assigned to groups of 5 males and 5 females. Groups received 1, 3.5, 6, 8.5 or 11 g/kg of test material orally by catheter, or (controls) received distilled water. There was subsequent 14-day observation. Survivors were sacrificed at 14 days. Rats which died during the 14-day observation period, as well as those which were sacrificed at 14 days, were grossly necropsied.

Results:

For males, at least one death occurred in each of the groups which were exposed to the test material. For females, there was no mortality at 1 g/kg, but at least one mortality occurred at each of the other dosage levels. There were no mortalities among control animals.

Oral LD_{50} (male) with 95% confidence limits = 4550(3434-6029) mg/kg.
Oral LD_{50} (female) with 95% C.L. = 5450(3759-7903) mg/kg

Symptoms (in all exposed groups): Hypoactivity, ptosis, ataxia, salivation. At 3500 mg/kg and above there was also loss of righting reflex, prostration, bradypnea. Survivors appeared normal two days after exposure.

"Necropsy of animals that died during the study and animals that survived to termination did not reveal any test article related changes."

Data Evaluation Report

Compound:

N,N-diethyl-m-toluamide (DEET)

Citation:

Kowalski, R.L. and Hartnagel, R.E. The Toxicity of Cutter Pump Spray Non-Aerosol Insect Repellent Formulation RB10199-82 (9/9/83): Acute (14 day) Dermal Toxicity in the Rabbit. Report No. 31; issued December 20, 1983. Study conducted by Miles Laboratories, Elkhart, IN 46515. Study received at EPA 02-28-84; in Acc. 254183.

Reviewed by:

Byron T. Backus B.T. Backus 7-27-87
Toxicologist

Core Classification: Supplementary

Product Classification: (Tox. Cat. III)

Conclusion:

1. Since three deaths occurred at the one dosage level given, this study is classified as Supplementary. In any study in which 3 mortalities (even accidental) occur at a single dose level it cannot be stated with 95% confidence that the LD_{50} value is greater than that dose level.

2. It is not expected that this product will cause mortality by this exposure route at this dosage level. However, this is information that has been derived from other dermal LD_{50} studies on Deet formulations, rather than this one particular study.

Discussion:

Three deaths occurred in this study. According to the information given the animals had broken their backs during the 24-hr restraining period in plastic stocks, and were subsequently found dead during the 14-day observation period. While this reviewer agrees that the deaths were probably not caused by the toxicity of the test material, the study in itself cannot be considered as showing that the dermal LD_{50} is greater than 2 g/kg.

Materials:

New Zealand White SPF rabbits, both sexes, weighing 2.0-2.2 kg at the start of the study.
Cutter Pump Spray Non-Aerosol Insect Repellent (CIR-PS)

Procedure:

Five male, 5 female rabbits received 24-hr occluded dermal exposure to 2000 mg/kg of the test material with subsequent 14-day observation. Survivors were sacrificed at 14 days. All mortalities and sacrificed animals received a gross

postmortem examination.

Results:

Two males died, one on day 3 and one on day 8. One female died on day 10. These deaths were not considered to be related to the exposure to the test material, as the animals had incurred broken backs during the 24-hr restraining period.

Although the report states that no body weight changes were observed, the data indicate that only one animal gained a small (0.1 kg) amount of weight; most of the others had small weight losses or remained the same.

There was no sign of dermal irritation in any subject.

Necropsy findings report there were no apparent test article related changes in any animal.

Data Evaluation Report

Compound:

N,N-diethyl-m-toluamide (DEET)

Citation:

Collins, C., Breckenridge, C., Tellier, P., Hamelin, N., Procter, B., and Osborne, B. The Acute Toxicity of Inhaled Base Formula Cutter Insect Repellent in the Albino Rat. Project No. 81774; dated Dec. 27, 1983. Study conducted by Bio-Research Laboratories Ltd, Montreal, Quebec. Received at EPA 02-28-84; in Acc. 254183.

Reviewed by:

Byron T. Backus B.T. Backus 7-27-84
Toxicologist

Core Classification: Minimum

Product Classification: Tox. Cat. IV

Conclusion:

1. The study adequately demonstrates the formulation is in toxicity category IV by the inhalation exposure route.

Discussion:

This study shows that the rat inhalation LC_{50} (4-hr exposure) is greater than 5 mg/L. It is doubtful whether the concentration and length of exposure of this study could be attained with normal product use.

Materials:

Crl:CD^R(SD)BR rats of both sexes, 175-200 g, approximately 7 weeks old, of both sexes, obtained from Charles River Canada, Inc.
Evergreen Aerosol Concentrate Normalized to 100%.

Procedure:

A randomly selected group of 5 male and 5 female rats received a 4-hr exposure to a nominal concentration of 39.1 mg/L. The actual product concentration was 5.3 mg/L, and the mass median diameter was 3.1 um. A minimum of 94% of the particles were estimated to be less than 9 um in diameter. A control group of 5M, 5F were exposed for 4 hrs to air on the following day. Animals were subsequently observed for 14 days. Survivors were sacrificed on day 14. All mortalities and sacrificed animals were grossly necropsied. The lungs of all animals sacrificed at 14 days were weighed.

Results:

The animals exposed to the test material could not be observed during the exposure period because of the dense atmosphere.

Symptoms shown by most exposed rats included ataxia, lethargy, salivation, and respiratory distress. Some also showed nasal discharge and unkempt fur. All exposed animals showed weight losses on the day following exposure. Almost all symptoms were gone by day 4.

One exposed animal (female) died on day 4. Gross necropsy showed changes in the stomach and intestine suggesting hemorrhage involving gastric and jejunal mucosal erosion. Nothing remarkable was found in the survivors.

Although some control animals showed weight losses, these were less than those of exposed animals. Two female controls showed salivation, eye discharge and redness of the extremities following removal from the exposure chamber.

There was no significant difference between control and exposed rats with respect to lung weights.

The inhalation LC_{50} is greater 5.3 mg/L.

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Data Evaluation Report

Compound:

N, N-diethyl-m-toluamide (DEET)

Citation:

Kowalski, R.L. and Hartnagel, R.E. The Toxicity of Cutter Pump Spray Non-Aerosol Insect Repellent Formulation RB10199-82 (9/9/83): Primary Ocular Irritation in the Rabbit. Report No. 18; issued Nov. 18, 1983. Study conducted by Miles Laboratories, Inc. Elkhart, IN 46515. Study received at EPA 2-28-84; in Acc. 254183.

Reviewed by:

Byron T. Backus
Toxicologist

B.T. Backus 7-27-87

Core Classification: Minimum

Product Classification: Tox. Cat. III

Conclusion:

1. The study adequately demonstrates the product is in toxicity category III on the basis of eye irritation potential.

Discussion:

The eye irritation potential of this formulation is probably due to the [redacted] is present as an "inert."

Materials:

New Zealand White SPF rabbits,
Cutter Pump Spray Non-Aerosol Insect Repellent (CIR-PS).

Procedure:

0.1 ml test material was instilled into one eye of each of 9 rabbits. Three eyes were washed by water for one minute starting 20-30 seconds after instillation of the test material. The remaining six eyes were unwashed. Eyes were examined and scored (Driaize) at 24, 48, and 72 hrs, and at 4 and 7 days after instillation of the test material.

Results:

All eyes showed some irritation. Some subjects showed some corneal involvement which in two cases persisted through day 4. All eyes scored zero by day 7.

Data Evaluation Report

Compound:

N,N-diethyl-m-toluamide (DEET)

Citation:

Kowalski, R.L. and Hartnagel, R.E. The Toxicity of Cutter Pump Spray Non-Aerosol Insect Repellent Formulation RB10199-82 (9/9/83): Primary Dermal Irritation in the Rabbit. Report No. 27; issued Dec. 20, 1983. Study conducted by Miles Laboratories, Inc., Elkhart, IN 46515. Study received at EPA 02-28-84; in Acc. 254183.

Reviewed by:

Byron T. Backus B.T.B. 7-27-84
Toxicologist

Core Classification: Minimum

Product Classification: Tox. Cat. IV

Conclusion:

1. This study adequately shows the product is in toxicity category IV in terms of its dermal irritation hazard potential.

Discussion:

The product has an acceptably low dermal irritation potential.

Materials:

New Zealand White SPF rabbits.
Cutter Pump Spray Non-Aerosol Insect Repellent (CIR-PS)

Procedure:

0.5 mls of test material were applied to each of 2 sites, 1 intact, 1 abraded, on each of 6 rabbits, with 24-hr occluded dermal exposure, and scoring at 24 and 72 hrs. There were 2 additional sites (1 intact, 1 abraded) on each of these 6 rabbits which were similarly treated with 0.9% NaCl solution.

Results:

Three rabbits showed some erythema at 24 hrs at the abraded site which had been treated with the test material. All other sites were clear at 24 hrs; all sites were clear by 72 hrs. PDIS = 0.21. No irritation occurred at dermal sites treated with the physiologic saline solution.

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Data Evaluation Report

Compound:

N,N-diethyl-m-toluamide (DEET)

Citation:

Porter, M.C. and Hartnagel, R.E. The Toxicity of Cutter Pump Spray Non-Aerosol Insect Repellent Formulation 7422-83-6: Dermal Sensitization in the Guinea Pig. Report No. 20; issued Nov. 18, 1983. Study conducted by Miles Laboratories, Inc., Elkhart, IN 46515. Study received at EPA 02-28-84; in Acc. 254183.

Reviewed by:

Byron T. Backus
Toxicologist

B.T. Backus 7-27-87

Core Classification: Minimum

Product Classification: Non-sensitizing

Conclusion:

1. This study adequately demonstrates the product has an acceptably low dermal sensitization potential.

Materials:

Male albino guinea pigs

i-chloro-2,4-dinitrobenzene (DNCB) = positive control

Cutter Pump Spray Non-Aerosol Insect Repellent (CIR-PS), batch 7422-83-6 with the following composition:

Actives:

N,N-diethyl-m-toluamide	35%
Dimethyl phthalate	13%
Di-n-propyl isocinchomeronate	1%
N-Octyl bicycloheptene dicarboximide	1%

Procedure:

On day 0 10 guinea pigs received 0.05 ml intradermal injections of 5% test material in corn oil. Subsequently, they received 9 additional 0.1 ml intradermal injections of this mixture at 2-3 day intervals at new application sites. On the same schedule, 5 controls received the same amounts of 0.05% DNCB in 5% EtOH in normal saline. Two weeks after the last of the initial series of sensitizing injections, guinea pigs were challenged with a 0.1 intradermal injection of the appropriate formulation. The site was scored 24 and 48 hrs later.

Results:

There was no evidence of any dermal sensitization reaction with the insect repellent formulation. Scores at 24 and 48 hours after challenge were similar to those seen throughout the study. A reaction was elicited in all subjects with the DNCB.