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CASWELL FILE

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

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APR 28 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: DEET: Review of a teratology study in rabbits

Caswell No. 346 **HED Project No.** 2-1737
MRID No. 421411-01 **EPA ID No.** 080301
DP Barcode: D175752

TO: Jane Mitchell, PM Team (71)
Special Review and Re-registration Division (H7508C)

FROM: Whang Phang, Ph.D. 4/21/92
Pharmacologist
HFAS/Tox. Branch II/ HED (H7509C)

THROUGH: James Rowe, Ph.D. James Rowe 4/21/92
Section Head, Section III
and
Marcia van Gemert, Ph.D. Marcia van Gemert 4/24/92
Branch Chief
HFAS/Tox. Branch II/ HED (H7509C)

Toxicology Branch II has been requested to review a rabbit teratology study on DEET. The review of this study is completed, and the conclusions is the following:

Chun, J. S. and Neeper-Bradley, T. U. (1991) Developmental toxicity evaluation of DEET administered by gavage to New Zealand white rabbits. Study conducted by Bushy Run Research Center; Study No. 54-597. (12/6/91). Submitted to EPA by DEET Joint Venture/Chemical Specialties Manufacturers Association. EPA MRID No. 421411-01.

Groups of presumed pregnant female rabbits (16/group) received DEET at doses of 30, 100, and 325 mg/kg b.w. from gestation day (gd) 6 to 18. No compound-related maternal clinical signs were observed. There was a periodic decrease in body weight gains in all treated does during the dosing period, but that of 325 mg/kg group was more noticeable. However, this decrease did not show a

consistent statistical significance. There was a statistically significant ($p<0.01$) decrease in the mean food consumption (≈30%) in 325 mg/kg group relative to that of the controls during the treatment period. During the post treatment period, the food consumption of all the treatment groups returned to the level of the controls. Under the conditions of the study the decrease in food consumption in 325 mg/kg does could not be considered as a toxicological effect.

The maternal gross pathology results showed no evidence that DEET produced an effect in any of the treated rabbits. DEET did not show any evidence of developmental toxicity under the conditions of the study.

The NOEL for maternal and developmental toxicity was 325 mg/kg (HDT). The results indicate that the test animals could have tolerated higher dose levels. The report also fails to present any explanation for dose selection.

The current study is classified as **supplementary**, and it provides useful information in confirming some of the results of a previous rabbit teratology study which did not show any evidence of developmental toxicity in rabbits which received DEET by dermal application with doses as high as 5000 mg/kg b.w..

2

CASWELL FILE

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Reviewer: Whang Phang, Ph.D. 4/21/92
HFAS/Tox. Branch II (H7509C)

Secondary Reviewer: Susan Makris, M.S. 4/21/92
HFAS/Tox. Branch II (H7509C)

DATA EVALUATION REPORT

Study Type: Teratology study-rabbits

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

Caswell No.	346	**HED Proj. No.**	2-1737
MRID No.	421411-01	**EPA Case No.**	819244
EPA ID No.	080301	**DP Barcode:**	D175752

Sponsor: DEET Joint Venture/Chemical Specialties Manufacturers Association

Testing Facility: Bushy Run Research Center
6702 Mellon Rd
Export, PA

Citation: Chun, J. S. and Neeper-Bradley, T. U. (1991) Developmental toxicity evaluation of DEET administered by gavage to New Zealand white rabbits. Study conducted by Bushy Run Research Center; Study No. 54-597. (12/6/91). Submitted to EPA by DEET Joint Venture/Chemical Specialties Manufacturers Association. EPA MRID No. 421411-01.

Conclusion: Groups of presumed pregnant female rabbits (16/group) received DEET at doses of 30, 100, and 325 mg/kg b.w. from gestation day (gd) 6 to 18. No compound-related maternal clinical signs were observed. There was a periodic decrease in body weight gains in all treated does during the dosing period, but that of 325 mg/kg group was more noticeable. However, this decrease did not show a consistent statistical significance. There was a statistically significant ($p<0.01$) decrease in the mean food consumption (≈30%) in 325 mg/kg group relative to that of the controls during the treatment period. During the post treatment period, the food consumption of all the treatment groups returned to the level of the controls. Under the conditions of the study the decrease in food consumption in 325 mg/kg does could not be considered as a toxicological effect.

The maternal gross pathology results showed no evidence that DEET produced an effect in any of the treated rabbits. DEET did not show any evidence of developmental toxicity under the conditions of the study.

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3

tolerated higher dose levels. The report failed to present any explanation for dose selection.

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Methods and Materials

Test Article: DEET (N,N-diethyltoluamide); 98.7% purity. The test article was a mixture of equal parts of 4 representative production runs supplied by McLaughlin Gormley King Co. (Lot No. 20111), Miles Laboratories (Lot No. 90003), Virginia Chemical Co. (Lot No. 85227), and Morflex Chemical Co. (Lot No. N61214-S9401). The test chemical was described as a pale yellow, slightly viscous, and translucent liquid. It was assigned BRRC No. 54-68 A through H.

Test Animals: Female New Zealand White rabbits were obtained from Hazleton Lab., Inc. (Denver, PA). These rabbits were 5.5 to 6 months old and weighed 2.8-4.6 kg within 3 days of receipt.

Study design

a. Mating: The test "females were mated on a 1:2 basis to 'proven' males from the BRRC breeding colony". The date of copulation was designated as gestation day (gd) 0. After successful mating, the 64 does were randomly assigned to 4 dose groups (16 does/group).

b. Treatment: The does were treated daily with DEET or Mazola^{R} corn oil by gavage. The dosage levels were 0, 30, 100, and 325 mg/kg b.w./day, and the treatment period was from gd 6 to 18.

c. Observations: All does were observed daily for signs of toxicity, morbidity, and mortality.

d. Body weights: The does were weighed on gd 0, 6, 9, 12, 15, 18, 24, and 29.

e. Food consumption was measured daily.

f. Sacrifice: On gd 29, all surviving does were sacrificed by i.v. administration of sodium pentobarbital. The gravid uterus, ovaries, cervix, vagina, and peritoneal and thoracic cavities were examined grossly. The maternal liver was weighed. Ovarian corpora lutea of pregnancy were counted. Each uterus was weighed and dissected longitudinally to expose the contents. All live and dead fetuses and

resorption sites (early and late) were recorded.

g. Fetal examinations: After the fetuses were removed from the uterus, they (live or dead) were weighed, and the live ones were euthanized by intraperitoneal injection of sodium pentobarbital. They were examined externally for variations and malformations including cleft palate. All live fetuses were examined for thoracic and abdominal visceral abnormalities. The gender of each fetus was determined. For the examinations of craniofacial structures, one half of the live fetuses in each litter were sacrificed, and their heads were separated from the body and fixed in Bouin's solution. For the evaluation of skeletal malformations and variations, all fetuses in each litter were eviscerated, air-dried, and processed for skeletal staining with alizarin red S.

h. Statistical analysis: Levene's test of variances, analysis of variance, t-test, Kruskal-Wallis test, and Fisher's exact test were employed. A probability value of 0.05 (2-tailed) was used as the critical level of significance.

i. A quality assurance statement was signed and included in the report.

Results

1. Observations and mating results: Compound-related clinical observations were not noted. No early delivery nor abortion were seen in any test animals. One doe of the 325 mg/kg group was found dead on gd 16 due to dosing error and removed from the study (Table 1). The pregnancy rates were 16/16, 14/16, 13/16, 14/15 in 0, 30, 100, and 325 mg/kg groups, respectively. All pregnant females had viable fetuses (Table 1).

2. Maternal body weights and body weight gains: No statistically significant decrease in body weight was seen in any treatment group (Table 2). The body weight change (gain) in the 325 mg/kg group was statistically significantly decreased during gd 6 to 9 relative to that of the controls, but this decrease did not persist through the treatment period as indicated by the greater body weight gain than the controls in the interval of gd 15 to 18 (Table 2). After the treatment was stopped, the body weight gain of the 325 mg/kg was comparable to that of the controls. Although, during the entire treatment period (gd 0-29), a decrease in the mean body weight gains was seen in the 325 mg/kg females, it did not show a statistically significant difference from the controls (Table 3).

5

3. Food consumption: During the treatment period (gd 6 to 18), food consumption in the 325 mg/kg group was significantly decreased ($p<0.01$) (Table 4). After cessation of compound treatment, the food consumption was comparable between the treated and the control does. In general, there appeared to be a slight drop in food consumption in the 30 and 100 mg/kg groups during the treatment period, and occasionally the decrease showed a statistical significance the in 30 mg/kg group. The sporadic decrease in food consumption in the 30 mg/kg does was not considered a compound-related effect.

4. Laparotomy and gross examination of does: The results of gross examination did not revealed any compound-related effects in treated does. The gravid uterine weights, corrected body weights (body weight at sacrifice minus gravid uterine weight), corrected body weight changes, liver weights, and relative liver weights were comparable between the treated and the control does (Table 5).

   The parameters of corpora lutea, total implants, percent preimplantation loss, viable implants, non-viable implants, early resorptions, late resorptions, dead fetuses, and percent live fetuses were comparable between the treated and control does (Table 6).

5. Fetal examinations: The results of fetal body weights did not indicate any significant difference between the treated groups and the controls (Table 6). The fetal and litter incidences of external soft tissue and skeletal malformations or variations were comparable between the treated groups and the controls either measured by individual categories or by total, broad incidence (Tables 7 & 8).

Discussion

Groups of presumed pregnant female rabbits (16/group) received DEET at doses of 30, 100, and 325 mg/kg b.w. from gd 6 to 18. No compound-related maternal clinical signs or deaths were observed. There was a periodic decrease in body weight gain in all treated does during the dosing period, but that of 325 mg/kg group was more noticeable. However, this decrease did not show a consistent statistical significance. There was a statistically significant ($p<0.01$) decrease in food consumption in the 325 mg/kg group (≈30%) relative to that of the controls during the treatment period. During the post-treatment period, the food consumption of all the treatment groups returned to the level of the control.

The decrease in food consumption in 325 mg/kg does during the treatment period could not be considered as a toxicological effect since the decrease in body weight gains was inconsistent during that same period, and the value of the mean body weight gains did not show a statistically significant difference from the controls. In addition, the corrected maternal body weight (maternal body weights at sacrifice minus the gravid uterine weights) was not affected by DEET. The decrease in food consumption was probably due to the process of administration of the chemical.

The maternal gross pathology results showed no evidence that DEET produced an effect in any of the treated rabbits. DEET did not show any evidence of developmental toxicity under the conditions of the study.

Based upon the above discussion, the NOEL for maternal and developmental toxicity was 325 mg/kg (HDT). The does in the 325 mg/kg group could have tolerated higher dose levels. The report stated that the doses were selected by the sponsor, but the author of the report should have, at least, attempted to obtain and to present the rationale for dose selection.

The results of this study are consistent with those seen in a previous rabbit teratology study conducted by the U. S. Army in 1980 (MRID No. GS0002036). In that study, rabbits were dermally applied DEET at doses of 0, 50, 100, 500, 1000, or 5000 mg/kg b.w./day from day 0 through 29. No evidence of developmental toxicity was found (DEET Registration Standard, Dec. 1980).

Based upon the information in the Registrant Standard for DEET (1980), an adequate rabbit teratology study is available, and another study has not been requested. The current study is classified as **supplementary**, and it provides useful information in confirming the previous results at lower dose levels (less than 500 mg/kg b.w.).

7

80301 DEET RIN 8220-92

Page_____ is not included in this copy.

Pages 4 through 13 are not included.

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U.S. ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PESTICIDES/HED/SACB
TOX ONELINERS

CHEM NO. 346 DEET

FILE LAST PRINTED: 4/21/92

ATION	MATERIAL	ACCESSION/ MRID. NO.	RESULTS	TOX CAT	CORE GRADE/ DOCUMENT #
eratology-rabbit ushy Run Res. Center. tudy No. 54-597 12/6/91)	DEET 98.7%	421411-01	Groups of presumed pregnant female rabbits (16/group) received DEET at doses of 30, 100, and 325 mg/kg b.w. from gestation day (gd) 6 to 18. No compound-related maternal clinical signs were observed. There was a periodic decrease in body weight gains in all treated does during the dosing period, but that of 325 mg/kg group was more noticeable. However, this decrease did not show a consistent statistical significance. There was a statistically significant ($p<0.01$) decrease in the mean food consumption (=30%) in 325 mg/kg group relative to that of the controls during the treatment period. During the post treatment period, the food consumption of all the treatment groups returned to the level of the controls. Under the conditions of the study the decrease in food consumption in 325 mg/kg does could not be considered as a toxicological effect. The maternal gross pathology results showed no evidence that DEET produced an effect in any of the treated rabbit. DEET did not show any evidence of developmental toxicity under the conditions of the study. The NOEL for maternal and developmental toxicity was 325 mg/kg (HDT). The results indicate that the test animals could have tolerated higher dose levels. The report also fails to present any explanation for dose selection. The current study provides useful information in confirming some of the results of a previous rabbit teratology study which did not show any evidence of developmental toxicity in rabbits which received DEET by dermal application with doses as high as 5000 mg/kg b.w..		Supplementary

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