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

008117

OCT 3 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: DEET: Reviews of a teratology study in rats and an oncogenicity study in mice

Caswell No. 346 HED Project No. 0-0837
EPA Record No. 260700
MRID No. 413515-01 (Mouse oncogenicity study)
413514-01 (Developmental toxicity study in rats)

TO: Jane Mitchell, PM Team (17)
Special Review and Re-registration Division (H7508C)

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

THROUGH: K. Clark Swentzel, Section Head K Clark Swentzel 9/18/90
and
Marcia van Gemert, Ph.D. Marcia Gemert 9/25/90
Branch Chief
HFAS/Tox. Branch II/ HED (H7509C)

Toxicology Branch II has been requested to review a developmental toxicity study in rats, an oncogenicity study in mice, a reproduction study in rats, and a 90-day feeding study in hamsters under EPA record No. 260700 by Special Review and Re-registration Division. The 2-generation reproduction study in rats was previously reviewed and transmitted to P. Hutton/J. Tavano, PM Team 17, on Dec 13, 1989 (Tox. Doc. No. 007645). The results from the 90-day feeding study in hamsters were to be used for selecting the appropriate test animals and dose levels for a chronic feeding study. To facilitate the initiation of the long term study, the 90-day feeding study in hamster had been reviewed earlier, and its data evaluation report was transmitted to Donna Williams.

Presently, the mouse oncogenicity and the rat developmental toxicity studies have been reviewed. The data evaluation reports of the rat developmental toxicity and the mouse oncogenicity studies are attached, and the conclusions are presented below. For reasons of completeness, the conclusions of the rat reproduction study and the 90-day feeding hamster day are also included.

1). Rat developmental toxicity study (MRID No. 413514-01):

Groups of mated female rats (25/group/dose) received Deet at doses of 0, 125, 250, and 750 mg/kg/day from gestation days 6 to 15. The maternal toxicities such as clinical signs (hypoactivity, ataxia, decreased muscle tone, and foot splay), mortality, reduced body weight, decreased food consumption, and increased mean liver weights were seen in 750 mg/kg dams. The only compound-related developmental toxicity was a statistically significant decrease in the mean fetal body weight of the high dose group relative to that of the controls. No teratogenic effects was found under these testing conditions.

Based upon these results, the maternal NOEL was 250 mg/kg; maternal LEL, 750 mg/kg. The developmental NOEL was 250 mg/kg; developmental LEL, 750 mg/kg. The study is classified as core minimum, and it satisfies the data requirements for a teratology study in rats (Guidelines No. 83-3).

2). Mouse oncogenicity Study (MRID No. 413515-01)

Groups of mice (60/sex/dose) received Deet at dietary concentrations of 0, 250, 500, or 1000 mg/kg/day for 78 weeks. No treatment-related effects were found in behavior, physical appearance, hematology, gross pathology or histopathology at any dose level. However, statistically significant decreases in mean body weight, body weight gains, and food consumption for both male and female mice were seen in the 1000 mg/kg group. The neoplastic and the non-neoplastic findings were comparable between the treated mice and the control mice. Therefore, Deet was not carcinogenic in male or female mice under the testing conditions, and a NOEL for systemic toxicity was established as 500 mg/kg/day; LEL, 1000 mg/kg/day.

This study is classified as core minimum, and it fulfills the data requirements for a mouse oncogenicity study (Guidelines No. 83-2).

3). 2-generation reproduction study in rats (MRID No. 409790-01):

The study was evaluated by Dynamac Corp.. The HFAS/Tox. Branch II does not agree with certain scientific judgments made by Dynamac. This reviewer has prepared an addendum reflecting the scientific opinions of the Branch. The addendum is attached to the data evaluation report of this study.

Groups of rats (28/sex/dose) received DEET at dietary concentrations of 0, 500, 2000, and 5000 ppm for two consecutive generations. Based upon the results presented in the study, the NOEL for parental toxicity could not be

established, and the LOEL was 500 ppm which was the lowest tested dose. The 500 ppm males showed signs of kidney effects which included mottling, inflammation, presence of hyaline droplets, granular cast formation, and tubular regeneration.

No reproductive or developmental toxicity was found, and the NOEL for reproductive toxicity was 5000 ppm (highest tested dose).

This study satisfies the data requirements for a 2-generation reproduction study (Guideline No. 83-4) and is classifies as core minimum.

4). 90-day feeding hamsters study (MRID No. 413441-01):

Groups of hamsters (15/sex/dose) received 0, 1,000, 5,000, 10,000, and 15,000 ppm of DEET (technical grade) in the diet for 90 days. Compound-related effects were seen in animals which received 5,000 ppm DEET or above. At 5,000 ppm in males, there was a consistent drop in food consumption and body weight. The decrease in body and food consumption was more marked in 10,000 and 15,000 ppm males and females. The increase in the incidence of gross pathologic and histologic changes in testes and epididymides were found in 10,000 and 15,000 ppm males. The gross pathologic changes were small testes and epididymides, and microscopically these changes were degeneration of the testes and cellular debris in the epididymal tubules. At 15,000 ppm, there were deaths in both males and females. Based upon these observations, the NOEL was 1,000 ppm; LEL, 5,000 ppm.

The results of the study clearly demonstrated that the renal lesion seen in the DEET treated male rats was not found in the hamsters which received DEET up to 15,000 ppm. This study satisfies data requirements for a 90-day feeding study in rodent (Guideline No. 82-1) and is classified as core minimum.

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PRIMARY REVIEWER: Jess Rowland, M.S., Toxicologist 9/12/90
Section II, Tox. Branch II (H7509C)

SECONDARY REVIEWER: K.Clark Swentzel, Section Head
Section II, Tox. Branch II (H7509C) 9/13/90

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity Study in Mice GUIDELINE: 83-2

TOX.CHEM.No.: 346 MRID No.: 413515-01 PROJECT No.: 0-0837

TEST MATERIAL: DEET (N,N-diethyl-m-toluamide)

STUDY NUMBERS: 555-005

SPONSOR: DEET Joint Venture / Chemical Specialties Manufacturing Association, Washington, D.C.

TESTING LABORATORY: International Research and Development Corp.

TITLE OF REPORT: Evaluation of DEET in an Eighteen Month Dietary Oncogenicity Study in Mice.

REPORT AUTHOR: Edwin P. Goldenthal, Ph.D

REPORT DATE: January 4, 1990

SUMMARY: Groups of 60 male and 60 female CD-1 mice were fed diets containing DEET at 0, 250, 500, or 1000 mg/kg/day for 78 weeks. Animals were observed daily for mortality, moribundity, and once weekly for clinical signs of toxicity. Body weights and food consumption were measured weekly for the first 14 weeks and once every two weeks thereafter. Hematology tests were conducted from control and high dose mice during study months 12 and 18. At termination gross necropsy was performed on all animals and brain, kidney, liver and testes were weighed. Histopathological examination was conducted on all tissues from the control and high-dose groups, and on gross lesions, masses and selected organs (liver,lungs, and kidneys) from the low- and mid-dose groups.

No treatment-related effects were seen in behavior, survival, physical appearance, hematology, or gross or histopathology at any dose level. No adverse effects were observed on body weights or food consumption of mice fed the 250 or 500 mg/kg/day diets. Treatment-related effects observed in both sexes of mice at the 1000 mg/kg/day dose level were statistically ($p < 0.05$ or $p < 0.01$) significant decreases in mean body weights, decreases in body weight gain, and a concomitant reduction in mean food consumption. The absolute and relative liver weights were increased in mice fed 1000 mg/kg/day diet; however, since no collaborative histopathological changes were seen in the liver, the increase was considered to be a consequence of adaptation rather than compound induced.

4

Under the conditions of this study DEET was not carcinogenic in male or female mice; neoplasms were not increased at any site. A NOEL of 500 mg/kg/day was established for systemic toxicity.

CORE CLASSIFICATION; Minimum; 82-3

I. INTRODUCTION

This Data Evaluation Report summarizes the experimental procedures and results of an 18-month dietary oncogenicity study of DEET in mice.

II. MATERIALS AND METHODS

1. Test Material

Common Name: DEET

Chemical Name: N, N-diethyltoluamide

Composition: 100% [redacted]

Purity: 98.301% [redacted]

Batch/Lot No.: A-1-96; S9401-45B

Identification No.: IRDC 8812B

Description: Pale yellow liquid

2. Test Animals

Species: Mice
Strain: Charles River CD-1
Sex: Males and females

Age: Approximately 35 days old
Weight at initiation: males, 26-31 g; females, 21-26 g Identification: Toe clip and cage card
Acclimation: 21-days
Health Status: Good

Housing: Individually in wire-mesh cages
Food: Control and test article mix given ad libitum
Water: ad libitum
Environment: Temperature- 72 ± 3 F; Humidity- 55 ± 15%; Air exchange- 6-10 changes/hour
Light / dark cycles:12 hr. light/dark cycle

3. Study Design

Mice were acclimated to laboratory conditions for 21 days, and were assigned randomly by sex to the following test groups using a computer-generated randomization procedure:

Test Group	Dose level (mg/kg/day)	No./sex/group
1 Control	0	60 M & 60 F
2 Control	0	60 M & 60 F
3 Low	250	60 M & 60 F
4 Mid	500	60 M & 60 F
5 High	1000	60 M & 60 F

4. Test Material Formulation

A premix for each concentration was prepared by mixing the total required amount of DEET with a portion of the required amount of powdered feed (Certified Rodent Chow #5002) in a Hobart food mixer for 5 minutes. Final diets were prepared by mixing the premixes with additional powdered feed in a twin shell blender for 20 minutes to achieve the appropriate concentration. Fresh diets were prepared weekly with the concentrations adjusted based on mean weekly food consumption measurement to maintain a constant mg/kg/day intake. The stability and homogeneity analyses of the premixes were performed before the start of the study, and concentration analysis of samples from the top, middle, and bottom of each diet mix was conducted weekly during study weeks 1 through 4 and every four weeks thereafter (through week 76).

5. Treatment

Animals were fed diets containing DEET at 250, 500, or 1000 mg/kg/day for 78 weeks; two groups of mice receiving the basal diet and served as controls. Concentrations were adjusted based on the most recent body weight and food consumption values.

6. Experimental Procedures

Parameter	Time measured
Mortality & moribundity	daily
General observations	daily
Clinical signs	once weekly
Body weight and food consumption	Weekly for the first 4 weeks and every 2 weeks thereafter.

Hematology	**At 12 and 18 months**
	10 mice/sex from
Erythrocyte count	**both control groups**
Leucocyte count	**and the high dose**
Hemoglobin	**group.**
Hematocrit	
Platelet count	
MCV, MCH,MCHC	
Differential count	

7. Termination

All animals that died and those sacrificed on schedule were subjected to gross necropsy and organs and tissues were preserved in formalin.

8. Histopathology

Tissues listed below from both control groups and the high-dose group were trimmed and processed for histopathological evaluation. Checked (X) tissues were collected for histological examination and the organs (XX) in addition were weighed.

Digestive system	Respiratory system	Urogenital system
x Salivary glands*	x Trachea*	xx Kidneys*
x Esophagus*	x Lung*	x Urinary bladder*
x Stomach*	Cardio vasc.Hematol	xx Testes*
x Duodenum*	x Aorta*	x Epididymis
x Jejunum*	x Heart*	x Prostate
x Ileum*	x Bone marrow*	x Seminal vesicle
x Cecum*	x Lymph nodes*	x Uterus*
x Colon*	x Spleen*	x Ovaries
x Rectum*	x Thymus*	
xx Liver/gall bladder*		
x Pancreas*		Other
		x Bone*
		x Skeletal muscle*
Neurologic	Glandular	x Skin*
xx Brain*	x Adrenal*	x All gross lesions & masses*
x Pituitary*	x Lacrimal gland	
x Eyes (optic n.)*	x Thyroids*	
x Periph. nerve*	x Parathyroid*	
x Spinal cord (3 levels)*	x Thyroids*	

*= EPA Guideline requirements.

In addition, sections were prepared of all tissue masses with regional lymph nodes, all gross lesions, and the liver, lungs, and kidneys of mice in the low and mid-dose groups.

9. Statistical Analyses

The following procedures were utilized in analyzing the numerical data: Bartlett's test was used to analyze homogeneity of variances. One-way analyzes of variance (ANOVA) was used for data with homogeneous variance, and if significant differences between groups were found, pairwise comparison with controls using Dunnett's test was performed. Tumor incidences were analyzed as described by Huff. Statistical procedures included the life table test, Hoel-Walburg "incidental tumor"test, Fisher's exact and Cochran-Armitage trend test.

10. Quality Assurance

A quality assurance statement was signed and dated January 8, 1990.

III. RESULTS

1. Analysis of Diet Mix

Homogeneity analysis indicated the diet mix to be homogeneous; 10 randomly analyzed batches of diet mix contained 89 to 100% of the target concentrations. The means (± S.D) of the 10 values/batches were 98 ± 2.1, 95 ± 2.8, and 95 ± 3.8 percent of the 250, 500, and 1000 mg/kg/day dosage levels respectively. Results of the stability analysis showed that test diets contained 95 to 97% of initial concentration after a 10 day storage interval at room temperature. Test diets prepared for use during study weeks 1-4 and once every 4 weeks through week 76 were found to contain average concentrations ranging from 90 to 107% of the desired levels. Mean concentrations for the entire study are as follows:

Nominal (mg/kg/day)	Sex	Mean Analyzed Concentration (% of Nominal ± S.D)
250	M	97 ± 3.8
	F	98 ± 3.4
500	M	99 ± 3.1
	F	99 ± 3.3
1000	M	99 ± 2.8
	F	99 ± 3.6

2. Survival

As shown below in Table 1, survival was comparable between treated and control animals.

Table 1. Survival of Mice Fed DEET in the Diet for 78 weeks.

Dose Level (mg/kg/day)	No.Surviving/No.Initiated (%) Male	Female
Control 1	46/60 (77)	43/60 (72)
Control 2	46/60 (77)	44/60 (73)
250	44/60 (73)	44/60 (73)
500	45/60 (75)	48/60 (80)
1000	51/60 (85)	50/60 (83)

3. Clinical Signs

No compound-related clinical signs of toxicity were observed. Pharmacotoxic signs observed were those commonly seen in this strain of mice in long-term studies and their incidence was similar in treated and control groups.

4. Body Weight

Selected group mean body weights are presented in Table 2 and the percent differences from control values at study week 78 are presented in Table 3. Mean body weights of mice at the low-dose (250 mg/kg/day) was comparable to the controls. Although statistically significant differences were observed in mean body weights of mice at the mid-dose (500 mg/kg/day), the differences were sporadic and showed no consistent pattern. Statistically significant ($p < 0.05$ or $p < 0.01$) decreases in mean body weights were observed for both males and females at the 1000 mg/kg/day group at all intervals. The decreases in body weights in treated mice were <10% when compared to percent differences from controls.

Table 2. Mean Body Weight Values (grams) of Mice Fed DEET in the Diet for 78 weeks.

Week of Study	Control 1 (0 ppm)	Control 2 (0 ppm)	250 ppm	500 ppm	1000 ppm
		Males			
Allocation	28/60a	28/60	28/60	28/60	28/60
13	36/60	35/60	34/59	35/59	34/59 b
28	38/59	38/59	36/59	37/59 d,e	36/58 b,c
40	39/59	39/59	37/58	38/58 d,e	37/58 b,c
52	40/59	39/56	38/57	38/56 d	37/57 b,c
64	40/52	39/54	38/55	39/53 d	38/54 b,d
78	40/46	39/45	38/44	38/45	37/51 b,e
		Females			
Allocation	24/60	24/60	24/60	23/60	24/60
13	29/59	29/60	30/60	29/59	29/60
28	31/58	32/60	32/60	30/59 c,d	31/60 c
40	33/58	33/60	33/60	32/59 c	32/60 c
52	33/56	34/58	34/60	33/58 e	32/60 c
64	34/54	35/56	35/56	34/58	33/58 c
78	35/43	35/44	36/44	34/47	33/50 c,d

a= Group mean body weight/Number of survivors.
b= Significantly different from control 1; p <0.01
c= Significantly different from control 2; p <0.01
d= Significantly different from control 1; p <0.05
e= Significantly different from control 2; p <0.05

Table 3. Mean Body Weights of Mice at Termination (Week 78) Following Dietary Administraton of DEET .

	Mean Body Weight (g) (% difference from control groups)					
Dose Level (mg/kg/day)	Male			Female		
	Mean	A	B	Mean	A	B
Control 1	40	-	+2.6	35	-	0
Control 2	39	-2.5	-	35	0	-
250	38	-5.0	-2.6	36	+2.9	+2.9
500	38	-5.0	-2.6	34	-2.9	-2.9
1000	37	-7.5	-5.1	33	-5.7	-5.7

A= % difference from Control 1
B= % difference from Control 2

Body weight gain data are presented in Table 4. Males, exhibited decreases in body weight gain at all dose levels when compared to control group 1 and 2. The decreases were -17%, -17%, and -25% at the low-, mid-, and high-dose groups,respectively, when compared to control group 1. The decreases were -9%, -9%, and -25% at the respective doses as compared to control group 2. In females decreases in body weights were seen only at the high dose; -18% when compared to either control group 1 or 2. Body weight data show a definite treatment-related effect in both sexes at the high-dose, namely, statistically significant decreases in mean body weights as well as decreases in body weight gain. The sporadic differences at the mid-dose were not considered to be treatment related.

Table 4. Mean Body Weight Gain (grams) of Mice Fed DEET in the Diet for 78 Weeks.

Week of Study	Control 1 (0 ppm)	Control 2 (0 ppm)	250 ppm	500 ppm	1000 ppm
		Males			
At allocation	28	28	28	28	28
At termination	40	39	38	38	37
Body weight gain	12	11	10	10	9
Difference from Control 1 (%)	-	-8	-17	-17	-25
Difference from Control 2 (%)	+9	-	-9%	-9%	-18%
		Females			
At allocation	24	24	24	23	24
At termination	35	35	36	34	33
Body weight gain	11	11	12	11	9
Difference from Control 1 (%)	-	0	+9	0	-18
Difference from Control 2 (%)	0	-	+9	0	-18

5. Food Consumption and Compound Intake

Average food consumption values (weeks 1-78) on a g/animal/day basis with the percent difference from the control groups are presented Table 5. Average food consumption values (g/animal/day and g/kg/day) during the course of the study was similar between the treated and the control groups. Sporadic, statistically ($p < 0.05$ or 0.01) significant decreases in food consumption (g/animal/day and g/kg/day) were observed at all dose levels throughout the study with the most frequent significance occurring in both males and female at the 1000 mg/kg/day dose level.

Table 5. Average Food Consumption of Mice Fed DEET in the Diet for 78 weeks.

	Average Food Consumption, g/animal/day (% difference from control groups)					
Dose Level	Male			Female		
(mg/kg/day)	Mean	A	B	Mean	A	B
Control 1	4.9	-	+2.1	5.0	-	-2.0
Control 2	4.8	-2.0	-	5.1	+2.0	-
250	4.7	-4.1	-2.1	5.1	+2.0	0
500	4.7	-4.1	-2.1	5.0	0	-2.0
1000	4.6	-6.1	-4.2	4.8	-4.0	-5.9

A= % difference from Control 1
B= % difference from Control 2

The calculated intakes of DEET were 251, 501, and 1004 mg/kg/day for males at dietary levels of 250, 500, or 1000 mg/kg/day and 250, 502, and 1005 for females at the same doses.

6. Hematology

No treatment-related effects were observed on any hematological parameter for mice at the 1000 mg/kg/day group at the 12 or 18 month interval.

7. Gross Pathology

No compound-induced gross pathological changes were seen at any dose level. Macroscopical changes observed in treated and control groups included: liver masses, nodules, or foci in males; lung nodules; enlarged seminal vesicles; ovarian cysts or hematocyst; enlarged spleens; uterine cysts or distended lumen; hydronephrosis, pale, or discolored kidneys, renal cysts; enlarged livers, liver with discoloration or foci; enlarged lymph nodes; hair loss or thinning; erosions in the stomach; small or soft testes; distended urinary bladders and other miscellaneous lesions.

8. Organ Weights

Table 6 summarizes the statistically significant ($p < 0.01$ or <0.05) differences observed in organ weights.

Table 6. Mean Organ Weights of Mice Fed DEET in the Diet for 78 Weeks.

Parameters Measured (g)	Control 1	Control 2	mg/kg/day 250	500	1000
	Mean S.D	Mean S.D	Mean S.D	Mean S.D	MeanS.D
Males					
Body Weight	40 ± 4	39 ± 4	38* ± 4	38 ± 4	37* ± 3
Kidney	0.98±0.23	0.94± 0.15	0.88*±.17	0.94± 0.14	0.87*±.13
Liver	2.6±0.42	2.5±0.36	2.6±0.45	2.8*±0.37	3.0*±0.43
Liver/B.W %	6.5±0.83	6.3±0.79	6.8±1.0	7.5*±0.80	8.2*±1.1
Females					
Body Weight	35 ± 4	35 ± 4	36 ± 3.6	34*± 3	33* ± 3.2
Liver	2.4± 0.52	2.3±0.31	2.5*±0.49	2.5*±0.44	2.5*±0.40
Liver/B.W %	6.7±1.3	6.5±0.80	7.0*±0.96	7.3*±1.2	7.5*±1.1

* Significantly different from control groups 1 or 2.

The decreases in absolute kidney weights observed in males at the 250 and 1000 mg/kg/day groups were not considered to be biologically significant since such an effect did not occur in a dose dependent manner nor were they found in females at any level. The increases in absolute and relative liver weights observed in a dose-related manner in males and females were considered to be significant. However, these increases were considered to be adaptive in nature rather than compound related since no collaborative histopathological changes were seen in the liver at any dose level.

9. Histopathology

No treatment-related histopathological changes were seen in mice at any dose level. A variety of non-neoplastic and neoplastic lesions seen in both treated and control groups were considered to be incidental and consistent with commonly occurring spontaneous lesions in this strain of mice.

Nonneoplastic Lesions: The nonneoplastic lesions included various inflammatory lesions in a number of organs, amyloidosis in several tissues and organs, subcapsular cell hyperplasia in the adrenal gland, chronic nephritis, hyperplastic nodules in the liver (more common in males), lymphoid or reticuloendothelial hyperplasia in various lymph nodes and spleen, testicular degeneration, dilation of the urinary bladder (males), ovarian cysts or hematocyst, uterine cystic glandular hyperplasia and other lesions.

Neoplastic Lesions: Statistical analyses showed no significant increases in any tumor type at any site in treated mice when compared to controls (Appendix 1). In both the control and treated animals, the frequently occurring neoplastic lesions included malignant lymphoma, hepatocellular adenomas and carcinomas (most common in males) and alveolar/bronchiolar adenomas. Other neoplasms that were seen both in the treated and control groups were: adrenal pheochromocytoma; Harderian gland cystadenoma; renal adenoma; hepatic hemangioma; mammary adenocarcinoma; pituitary adenoma; uterine leiomyoma and leiomyosarcoma and neoplasms commonly seen in mice of this age/strain.

10. Protocol Deviations

a. Temperature and humidity values deviated from the protocol specification in range from -2°F to +2° F and -22% to +20% respectively.

b. Tissues of 48 animals (listed below) were inadvertently placed in water instead of formalin for approximately 1 to 23 hours.

Group	No.of animals	
	Males	Females
1	5	4
2	6	5
3	5	6
4	4	5
5	4	4

These tissues were processed and examined for quality and acceptability by an independent pathologist. The independent pathologist stated that most of the tissues were in excellent condition and only a few were completely destroyed by autolysis. The pathologist concluded that " In my opinion, the condition of the tissues should not be a major factor in histopathologic interpretation and should not affect the validity of the study".

11. Data Discrepancies

Table 2, Page 43 (Males: Summary of Survival): Control 2, at study week 80, the number of survivors should be 7 not 13 as reported.

Table 3, Page 91 (Summary of Clinical Findings) Control 1, at interval 66-78 week, the number of found dead animals should be 4 not 5 as reported.

Table 3, Page 131 (Summary of Clinical Findings) Control 2, at interval 66-78 week, the number of moribund animals should be 3 not 2 as reported.

IV. DISCUSSION

No treatment-related mortality was seen during the study; survival among the treated and the control groups was comparable. No treatment-related clinical signs of toxicity were seen at any dose levels. Hematology parameters showed no effects of treatment at any level.

No statistically significant differences on body weight or food consumption were observed in mice fed the 250 mg/kg/day diet when compared to control. The sporadic, statistically significant differences seen in mean body weights of both sexes of mice fed the 500 mg/kg/day diet were not considered to be treatment related. Both male and female mice at the 1000 mg/kg/day dose exhibited statistically significant ($p < .05$ or $p < 0.1$) decreases in mean body weight, decreases in body weight gain and a concomitant reduction in food consumption. The decrease in body weight gain was -18% and -25% compared to control groups 1 and 2, respectively, in males and -18% compared to control groups 1 or 2 in females. The decrease in the average food consumption was -6.1% and -4.2% compared to control groups 1 and 2, respectively, in males and -4% and -5.9% compared to control groups 1 and 2, respectively, in females. The decrease in food consumption coincide with the decrease mean in body weights and body weight gains observed at the high dose.

The increases in absolute and liver weights observed at the 500 and 1000 mg/kg/day were not accompanied by any histopathological correlates in the liver, therefore the effect was considered to be adaptive in nature rather chan compound related.

No treatment-related gross or histopathological changes were seen in male or female mice at any dose level. Statistical analyses showed no increase for any tumor type at any site in treated mice compared to controls. Non neoplastic or neoplastic lesions observed in the treated animals were not increased at any site when compared to controls. These changes were considered to be consistent with commonly occurring spontaneous lesions in mice in long-term studies.

V. CONCLUSION

The dose levels tested appear to be adequate to evaluate the carcinogenic potential of DEET when administered in the diet of mice. This is based on decreases in mean body weights as well as body weight gain observed in both sexes at the highest dose (1000 mg/kg/day) tested. In addition, HED considers 1000 mg/kg/day to be a limit dose for a carcinogenicity study.Under the conditions of this study, DEET was not carcinogenic in male and female mice at doses including and up to 1000 mg/kg/day. A no-effect-level of 500 mg/kg/day was established for systemic toxicity.

VI. CORE CLASSIFICATION

Minimum; this study satisfies the toxicology testing requirements for an oncogenicity study in mice (83-2) and is acceptable for regulatory purposes.

APPENDIX. 1

DEET toxicology review

Page _____ is not included in this copy.

Pages 18 through 25 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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Review by: David S. Liem, Ph.D. David Sheem 8/21/90
Section II, Tox. Branch II/HED (H7509C)
Secondary Reviewer: Whang Phang, Ph.D. 8/22/90
Section II, Tox. Branch II/HED (H7509C)
Tertiary Reviewer: K. Clark Swentzel, Section Head K. Clark Swentzel 8/27/90
Section II, Tox. Branch II/HED (H7509C)

DATA EVALUATION RECORD

Study Type: Teratology - Developmental Toxicity
Species: Rat Guideline: 83-3

EPA Identification No.s: EPA MRID (Accession) No.: 413514-01
Caswell No.: 346 ID No.: CSMA-TF
HED Project No.: 0-0837

Test Material: Deet Synonyms: N-N'-Diethyl-m-Toluamide

Sponsor: DEET Joint Venture/Chemical Specialties Manufacturers Association, Suite 1120, 1001 Connecticut Ave., N.W., Washington DC 20036

Study Number: 52-603; BRRC No. 88-44-58002

Testing Facility: Bushy Run Research Center, R.D. No. 4, Mellon Rd., Export, PA 15632

Title of Report: Developmental Toxicity Evaluation of DEET Administered by Gavage to CD^{r} (Sprague-Dawley) Rats

Author: T.L. Neeper-Bradley, Ph.D.

Report Issued: January 4, 1990

Conclusions: Four groups of 25 mated female CD^{r} (Sprague-Dawley) rats were given oral administration of 0, 125, 250, and 750 mg/kg/day of DEET from days 6 to 15 of gestation. According to the data submitted, administration of DEET produced the following maternal toxicity: adverse clinical signs (including possible neurotoxic effects), mortality, reduced maternal body weight gain and food consumption values, and increased mean liver weight in the high dose group (750 mg/kg/day) as compared to the control. In the high dose group, the percent postimplantation loss was slightly increased (not statistically significant) as compared to the control. The only treatment related developmental toxicity in the fetal data was the statistically significant decrease in the mean fetal body weight of the high dose group as compared to the control. No other fetal data are considered related to treatment. No teratogenic effect was observed at dosages employed.

Maternal toxicity NOEL = 250 mg/kg/day; LOEL = 750 mg/kg/day
Developmental toxicity NOEL = 250 mg/kg/day; LOEL = 750 mg/kg/day

Core Classification: Minimum

A. Materials

Test Compound: Purity: 98.301% [redacted]
Description: DEET(N-N'-Diethyl-m-Toluamide); clear tinged-yellow, very slightly viscous liquid
Lot No.: A-1-96
Contaminant: Not specified in the report
Source: Morflex Chemical Company, Inc., Greensboro, NC 27403
Storage: In closed container at room temperature.

Vehicle: Certified Mazola® Corn Oil obtained from Best Foods, Inc., CPC International, was administered to the control group rats.

Test Animal(s): Species: Rat
Strain: Sprague-Dawley Crl:COBS CD® (SD)BR
Source: Charles River breeding Laboratories, Inc., Kingston, N.Y.
Acclimation period: Approximately 14 days
Age: Females 56 days old (on arrival)
Females 93 days old (on Day 0 of gestation)
Males 63 days old (on arrival)
Weight: Females 175-200 grams (on arrival)
Females 197-256 grams (on Day 0 of gestation)
Males 250-300 grams (on arrival)

B. Environmental Parameters

- o Ventilation: A minimum of 12 room air changes per hour
- o Room Temperature: 60 to 73° F
- o Relative Humidity: 40 to 60%
- o Light/Dark Cycle: 12 hours light/dark cycle
- o Animal Feed: Purina Certified Rat Chow # 5002 (batch Nos. FEB 10 89 1D and FEB 11 89 1A) and municipal potable water were supplied ad libitum.
- o Caging: Pregnant female rats were kept individually in wire-bottomed cages.

C. Study Design

This study was designed to assess the developmental toxicity potential of technical DEET when administered by gavage to female rats on gestation days 6 through 15, inclusive.

Mating

Females were mated naturally; each female was kept in a cage with a male (1:1) during the cohabitation period.

Group Arrangement

Twenty-five pregnant female rats were assigned to each dose group by computerized randomization procedure, stratified by body weight on day 0 so that all groups were similar in both mean body weight and body weight range as follows:

Test Group	Dose Level (mg/kg/day)	No. Rat Assigned
Control	0	25
Low Dose	125.0	25
Mid Dose	250.0	25
High Dose	750.0	25

Dosing

Pregnant rats were dosed daily with DEET or vehicle control (corn oil) on days 6 to 15, inclusive. The test liquid was administered by gavage to the three groups of 25 female rats each, at dosages of 125, 250, and 750 mg/kg/day or equivalent to 0.128, 0.255, and 0.766 ml/kg/day of test liquid. The control group was dosed with certified corn oil by gavage at the highest volume in the high dose group (0.766 ml/kg/day).

Test material was administered undiluted and the volume administered depended on the dosage selected and was adjusted, based on the individual animal's most recent weight. The dosing liquid was not analyzed for concentration, stability, and homogeneity since the test liquid was dosed undiluted.

Observations

The animals were checked daily for clinical signs of toxicity (twice daily during the dosing period) and twice daily for mortality and morbidity throughout the study.

Maternal body weights were recorded on days 0, 6 (prior to dosing), 9, 12, 15, 18, and 21 of gestation.

Food consumption was determined at three-day intervals from days 0 to 21 of gestation.

Dams were sacrificed on day 21 of gestation using CO_2 gas. Examinations at sacrifice consisted of: ovaries and/or uterine contents, number of corpora lutea, number and placement of implantations, presence of early or late resorptions and the number of live and dead fetuses. Maternal liver and gravid uterine weights were measured.

The fetuses were examined as follows: Approximately one-half of the fetuses in each litter were examined for soft tissue malformations and variations, and then the head of these fetuses was decapitated, fixed in Bouin's solution, serially sectioned and were then examined for craniofacial malformations and variations. The remaining fetuses in each litter were examined for skeletal alterations following alizarin red-S staining.

Statistical Analysis

The litter was the unit of comparison. Results of the quantitative continuous variables (e.g. maternal body weights, organ weights, fetal weights, etc.) were intercompared with the three treated groups and the control group by using Levene's test for equal variances, analysis of variance (ANOVA), and t-tests with Bonferroni probabilities for pairwise comparisons. When Levene's test indicated homogenous variances, and the ANOVA was significant, the pooled t-test was used. When Levene's test indicated heterogenous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by the separate variance t-test.

Nonparametric data were statistically treated using the Kruskal-Wallis test followed by the Mann-Whitney U test when appropriate. Incidence data were compared using Fisher's Exact Test. For all statistical tests, the fiducial limit of 0.05 (two-tailed) was used as the criterion for significance.

Compliance

- o A signed Statement of Confidentiality Claim was provided.
- o A signed Statement of compliance with EPA GLP's was provided.
- o A signed Quality Assurance Statement was provided.

RESULTS AND DISCUSSIONS

A. Dosing Analysis

Since the test material was administered undiluted, the concentration, stability, and homogeneity of the dosing solutions were not determined. However, the report should contain the actual chemical stability data besides the general information provided in the Material Safety Data Sheet.

B. Clinical Observations

As compared to the controls the only statistical significant adverse maternal clinical signs were observed in the high dose group during the dosing period (days 6-15 of gestation). These included hypoactivity (14/24 rats), ataxia (11/24 rats), decreased muscle tone (12/24 rats), urine stain (13/24 rats), foot splay (8/24 rats), perinasal encrustation (10/24 rats) and perioral wetness (17/24 rats). The above clinical signs were considered compound-related effects. While some of these clinical signs were sporadically seen in other treated groups, none of them were observed in the controls (Table 3 on p.20-21 of the study report). High incidences of hypoactivity, ataxia and decreased muscle tone in the high dose dams during the dosing period suggest a possible neurotoxic effect.

C. Maternal mortality

Two high dose dams were sacrificed on day 7 of gestation. Gross examination revealed that these rats exhibited ulceration (one of which exhibited sloughing) of the glandular portion of the stomach and distended urinary bladder.

D. Maternal Body Weight

During pre-dosing period, both the mean maternal body weight and body weight gains were comparable among the four dose groups. From day 6 onwards, the high dose maternal body weights were lower as compared to the control. This decrease was statistically significant on day 18 of gestation (Table 2, p.18 of report).

The body weight gain can be summarized as follows:

Summary Mean Body Weight Gain and Net Body Weight Gain@

Dose Groups	Control	Low Dose	Mid Dose	High Dose
#Pregnant/Total	22/25	23/25	23/25	24/25
# Rats Used for BW Calculations	22	22a	23	22
Days 0 to 6	30.1±6.6	29.7±5.6	33.0±7.4	31.5±7.3b
Days 6 to 9	11.4±4.1	8.0±6.8	5.7±15.2	-0.47±11.4**
Days 6 to 15	47.1±9.2	44.1±9.2	40.2±10.6	30.73±12.2**
Days 15 to 21	92.2±11.2	94.7±10.8	92.8±15.5	90.0±16.9
Days 0 to 21	169.4±19.2	168.5±16.6	165.9±26.1	152.8±29.8
Corrected BW	291.8±18.1	290.6±15.0	294.5±20.7	283.0±19.4
Net BW Gain	59.7±14.3	57.1±9.2	60.4±12.4	50.1±16.4

a = one dam delivered early was excluded from BW calculations
b = mean of a total of 24 dams prior to 2 deaths on day 7
BW = Body Weight; @ = derived from Tables 2 and 7, p. 18 & 25.
* = $P < 0.05$; ** = $P < 0.01$

As seen from the above table, three days after dosing (days 6 to 9) the body weight gain was reduced in all treated groups, but only the high dose group was statistically significant as compared to the control. The mean body weight gain for the high dose rats as compared to the control was significantly ($P < 0.01$) lower throughout the dosing period. During the post-dosing (days 15 to 21) period, the body weight gains were similar among the four groups and they were not significantly different.

The reduced body weight gain in the high dose group dams that occurred during the dosing period (days 6 to 15), was reflected in the mean body weight gains reduction throughout the remainder of the gestation period. Maternal body weight gain decrease is considered a dose-related effect.

The corrected maternal body weight (BW minus gravid uterine weight) and the net maternal body weight gain (corrected BW minus BW on day 0) of the high dose group were decreased as compared to the control, but they were not statistically significant.

E. Maternal Food Consumption

The maternal food consumption data can be summarized as follows:

Mean Food Consumption Data (g/rat/day)@

Dose Groups	Control	Low Dose	Mid Dose	High Dose
#Pregnant/Total	22/25	23/25	23/25	24/25
# Rats Used for FC Calculations	22	22	23	21-24
FC (g/rat/day)				
Days 0 to 6	23.5±1.8	23.6±1.4	23.7±2.4	23.5±2.1a
Days 6 to 9	24.0±1.6	22.5±2.8	21.4±4.3*	19.5±3.9**[b]
Days 6 to 15	24.9±1.3	24.4±1.7	23.9±3.1	22.0±2.3**[c]
Days 15 to 21	27.8±2.0	27.8±1.8	28.4±2.6	28.2±3.7[b]

a = mean of a total of 24 dams prior to 2 deaths on day 7; b = mean of 22 dams; c = mean of 21 dams; FC= Food Consumption; @ derived from table 4, p. 22; * = $P < 0.05$; ** = $P < 0.01$;

The mean maternal food consumption values (g/rat/day) during the pre-dosing (days 0 to 6) and post-dosing (days 16-20) periods were comparable among the four groups.

As compared to the control, the high dose group mean food consumption values were significantly lower during the dosing period ($P < 0.01$). The decreased food consumption value of the mid dose group was statistically significant ($P < 0.05$) during the days 6-9 interval, but was essentially unaffected throughout the remaining period. The food consumption reduction is considered a dose related effect. The overall mean maternal food consumption (days 0-21) was not calculated by the investigator, hence comparison among the dose groups can not be made.

The relative food consumption data (computed in g/kg body weight/day) were not calculated nor were they presented in the report. Therefore, comparison of the net food consumption among the dose groups can not be made.

F. Maternal Gross Pathology

No treatment related lesions were observed in dams necropsied at the time of C-section on day 21 of gestation (table 5 p.23 of the report). The two high dose dams which were sacrificed on day 7 of gestation exhibited ulceration (one of which exhibited sloughing) of the glandular portion of the stomach and distended urinary bladder (Table 6 on p.24 of the report).

G. Pregnancy Rate

The pregnancy rate was relatively high, 22/25 (88%) for the control, 23/25 (92%) for the low and mid dose, and 24/25 (96%) for the high dose groups. The two high dose dams that were sacrificed on day 7 of gestation were also pregnant.

One low dose dam delivered early on day 21 of gestation prior to the scheduled sacrificed that day. No dams aborted and all surviving pregnant dams had one or more live fetuses at scheduled sacrifice.

H. Caesarean Section Observations

a. Maternal Liver Weight at Terminal Sacrifice

The maternal mean liver weight and the maternal relative mean liver weight (based on the percentage of corrected body weight) were significantly increased in the high dose group as compared to the control. They are summarized as follows:

	Control	Low Dose	Mid Dose	High Dose
Liver weight (g)	13.5±1.4	13.5±0.9	14.2±1.2	14.5±1.6*
Rel. Liver weight	4.6±0.3	4.0±0.4	4.8±0.3	5.1±0.4**

* = $P < 0.05$; ** = $P < 0.01$; values derived from Table 7 on p. 25 of the study report

The liver weight increase is considered a treatment related effect.

b. Delivery Data

Caesarean-delivery data reveal that the mean numbers of corpora lutea, total implantations, live fetuses and resorptions, incidences of dams with resorptions and of dams with viable fetuses did not differ among all four groups (see attached Appendix A).

The percent preimplantation loss [(corpora lutea - total implants)/corpora lutea) X 100%] was increased (but not statistically significant) in the high dose group as compared to the control. This observation is not considered a treatment-related effect.

More male fetuses were born in the mid dose as compared to the control ($P < 0.01$). This difference is within the normal variation range and it is not considered a compound-related effect (see attached Appendix A).

c. Fetal Body Weight Data

The reduction of the mean fetal body weight/litter of the high dose group as compared to the control was statistically significant (see attached Appendix A). The fetal body weight decrease in the high dose group is a compound-related effects.

I. Gross Fetal External (Pathological) Alterations

Six external fetal malformations and variations were observed during gross macroscopic examination. One control and two high dose fetuses (of 2 litters) had bent tail, and two low dose (of two litters) and 1 mid dose fetuses had a thread-like tail. One low dose fetus was edematous, and two low dose (of 2 litters) and one mid dose fetuses had an imperforate anus (Table 9 on p. 27 of the study report). Ecchymosis (subepidermal hematomas) of the trunk was observed in all four dose groups and ecchymosis of the head was observed in all treated groups (Table 10 on p. 31 of the study report). All these incidences are not considered dose-related effects.

J. Soft Tissue (Visceral) Alterations

A total of seven visceral malformations were observed, which included dilated lateral ventricle, missing innominate artery, ventricular septal defect, uni- or bi-lateral hydronephrosis, and uni- or bi-lateral hydroureter (Table 9 on p. 28 of the study report).

A total of 16 soft tissues variations were observed. Only the litter incidence of dilated lateral ventricle was significantly increased in the low dose group as compared to the control (Table 10 on p. 32 of the study report).

Incidences of soft tissue variations and malformations are not considered treatmert related effects, as the fetal and litter incidences were infrequent, and/or there was no clear trend of increased incidences in the treated groups as compared to the control.

K. Fetal Skeletal Alterations

The significant fetal and litter incidences of fetal skeletal alterations and malformations, and skeletal ossifications can be summarized as follows:

Summary of Fetal Skeletal Alterations and Malformations and Bone Ossifications@ (fetuses/litters)

	Control	Low Dose	Mid Dose	High Dose
Fetuses/Litters Evaluated	159/22	165/22	159/23	159/22
Cervical Centra #1,#2,#3, and/or #4 bilobed	9/7	4/4	5/4	2/1*
Thoracic Centrum #10 Bilobed	5/3	13/10*	7/6	6/5
Thoracic Centrum #13 Poorly Ossified	3/3	13/10*	5/4	12/8
Hyoid Poorly Ossified	11/4	15/12*	14/7	11/8
Some Hindlimb Metatarsal Poorly Ossi.	47/21	29/14*	30/17	43/18
Majority Proximal Phalanges (Hindlimb)				
o Poorly Ossified	10/10	5/5	3/3*	3/3*
o Unossified	28/21	23/13**	26/14*	17/10**

@ = derived from Tables 9 & 10 on p. 29 & 34-41 of the report
* = $P < 0.05$; ** = $P < 0.01$

Out of the total of 93 skeletal variations, seven were worth noting. The thoracic centrum #10 bilobed, thoracic centrum #13 poorly ossified and the hyoid poorly ossified, exhibited statistically increased incidences ($P < 0.05$) in the low dose group as compared to the control.

The following fetal skeletal variations exhibited significant reduction in incidences as compared to the control: majority of proximal phalanges (hindlimb) unossified in all treated groups and poorly ossified in the mid and high dose groups; cervical centra #1, #2, #3, and/or #4 bilobed in the high dose group; and metatarsal of the hindlimb poorly ossified in the low dose group. Differences of these fetal skeletal variations data are not of toxicological significance, hence they are not considered treatment related effects. No other differences were considered treatment-related, as the values were within normal range and/or were not significantly different among the four dose groups.

CONCLUSIONS

According to the data submitted, oral administration of DEET by gavage to CD^{R} (Sprague-Dawley) rats during major organogenesis produced maternal toxicity. This included significant adverse clinical signs (hypoactivity, ataxia, decreased muscle tone, urine stain, foot splay, perinasal encrustation, and perioral wetness), mortality, reduced maternal body weight gain and food consumption values, and increased mean liver weight in the high dose group (750 mg/kg/day) as compared to the control. High incidences of hypoactivity, ataxia, and decreased muscle tone observed in the high dose dams during the dosing period suggest a possible neurotoxic effect.

In the high dose group, the percent postimplantation loss was slightly increased, but not statistically significant, as compared to the control.

The only treatment related developmental toxicity in the fetal data was the statistically significant decrease in the mean fetal body weight/litter of the high dose group as compared to the controls. No teratogenic effect was observed at dosages employed.

The relative food consumption data (computed in g/kg body weight/day) were not presented in the report, but they do not affect the interpretation of the results.

Although the investigator noted on p. 258 that a data base for historical controls was available for the rat strain studied in the test facility with regard to gestational indices and incidences of fetal malformations and variations, this data base was not submitted with this study report.

Maternal toxicity NOEL = 250 mg/kg/day; LEL = 750 mg/kg/day
Developmental toxicity NOEL = 250 mg/kg/day; LEL = 750 mg/kg/day

Core Classification: Minimum

008117

APPENDIX A
(Derived from Table 8 of the study report, MRID #413514-01)

DEVELOPMENTAL TOXICITY EVALUATION OF DEET ADMINISTERED BY GAVAGE TO CD® (SPRAGUE-DAWLEY) RATS
SUMMARY OF GESTATIONAL PARAMETERS

	FEMALES			
GROUP: MG/KG/DAY	0.0	125.0	250.0	750.0
CORPORA LUTEA				
MEAN	17.0	17.3	17.7	17.6
S.D.	1.91	1.61	2.27	2.32
N	22	22	23	22
TOTAL IMPLANTS				
MEAN	16.0	16.5	16.1	15.5
S.D.	1.36	1.50	2.51	3.60
N	22	22	23	22
PERCENT PREIMPLANTATION LOSS[a]				
MEAN	4.9	4.2	8.5	11.6
S.D.	6.31	7.05	12.76	20.27
N	22	22	23	22
VIABLE IMPLANTS				
MEAN	15.0	15.5	14.4	14.9
S.D.	1.53	2.04	3.45	3.58
N	22	22	23	22
NON-VIABLE IMPLANTS				
MEAN	1.0	1.0	1.7	0.6
S.D.	1.07	1.09	3.11	0.90
N	22	22	23	22
EARLY RESORPTIONS				
MEAN	0.7	0.9	1.6	0.5
S.D.	0.77	1.06	3.07	0.86
N	22	22	23	22
LATE RESORPTIONS				
MEAN	0.3	0.0	0.0	0.0
S.D.	0.77	0.21	0.21	0.21
N	22	22	23	22
DEAD FETUSES				
MEAN	0.0	0.0	0.1	0.0
S.D.	0.00	0.00	0.42	0.21
N	22	22	23	22
PERCENT LIVE FETUSES				
MEAN	93.9	94.0	90.1	96.0
S.D.	6.47	7.17	17.35	5.75
N	22	22	23	22
SEX RATIO (% MALE FETUSES)				
MEAN	49.8	48.7	61.6**	41.9
S.D.	13.75	12.69	12.52	15.53
N	22	22	23	22
FETAL BODY WEIGHTS PER LITTER (GRAMS)				
ALL FETUSES				
MEAN	5.328	5.225	5.348	5.067*
S.D.	0.2292	0.3328	0.2753	0.2946
N	22	22	23	22
MALE FETUSES				
MEAN	5.466	5.350	5.465	5.219*
S.D.	0.2484	0.3544	0.3000	0.2833
N	22	22	23	21[b]
FEMALE FETUSES				
MEAN	5.185	5.101	5.168	4.927*
S.D.	0.2248	0.3317	0.2645	0.3104
N	22	22	23	22

* Significantly different from control group ($p < .05$)
** Significantly different from control group ($p < .01$)
[b] Data not included for one animal due to weighing error.
[a] Percent preimplantation loss=[(corpora lutea - total implants)/corpora lutea] X 100.
[b] One litter consisted of female fetuses only.

Study/Lab/Study #/Date	Material	No.	LD50, LC50, PIS, NOEL, LEL	Category	Doc. No.
Mouse Oncogenicity Study Inter. Research. Develop. Corp. ~~[redacted]~~ 555-095. Lab Project ID. 1/4/90	Technical DEET 98.3%	41355-01	NOEL for Systemic tox. = 500 mg/Kg LEL " " " = 1000 mg/Kg (decr. in mean body wt., body wt. gains, and food consumption) No neoplastic or non-neoplastic findings. Doses Tested = 0, 250, 500, and 1000 mg/Kg		minimum
Developmental toxicity - Rats. Bushy Run Research center. ~~[redacted]~~ Lab. Proj. ID. 52-630	Technical DEET 98.3%	41357A-01	NOEL for Maternal tox. = 250 mg/Kg/day LEL " " " = 750 mg/Kg/day (Clinical signs, decr. maternal body wt. gain, food consumption, and incr. liver weight) ~~Dose~~ NOEL for Development tox. = 250 mg/Kg/day LEL for developmental tox. = 750 mg/Kg/day (decre. in mean fetal body wt) Doses Tested = 0, 125, 250, and 750 mg/Kg/day		minimum.