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

FEB 10 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: DEET: Review of Three 90-Day Toxicity Studies

Caswell No.: 346 Record No.: 206238

TO: Joseph Tavano
Product Manager
Registration Division (TS-767c)

FROM: Whang Phang, Ph.D. Whang Phang 5/5/88
Pharamcologist
Toxicology Branch / HED (TS-769c)

THROUGH: Marcia van Gemert, Ph.D. M. van Gemert 2/5/88
Head, Section III
and
Theodore M. Farber, Ph.D. 2/10/88
Branch Chief
Toxicology Branch / HED (TS-769c)

Chemical Specialties Manufacturers Association submitted the final reports of a 90-day oral dose range finding study in rats, a 90-day dermal toxicity study in rats, and a 90-day oral dose range finding study in mice. These studies have been reviewed, and the data evaluation reports are attached. The conclusion of each study is summarized in the following:

I. 90-Day Dermal Toxicity Study in Rats

When groups of rats (15/sex/dose) were dermally applied DEET at dose level of 0, 100, 300, and 1000 mg/kg; the following effects were observed:

1. Increased incidence of acanthosis and hyperkeratosis on the dermal application sites of all compound-treated rats.

2. Decreased body weights of high dose males.

3. Increased absolute and relative kidney weights (kidney/body & kidney/brain) in mid and high dose males and in relative kidney weights in high dose females.

4. Increased incidence of renal lesions which included granular casts, inflammation, tubular regeneration, hyaline droplets in all treated males; marginal renal effect in high dose females.

The study has been well conducted, and the report is well written However, based on the renal lesions in all treated males and dermal toxicity in all treated rats, a NOEL can not be established. According to the Subdivision F Guidelines, this study is classified as Supplementary.

II. 90-Day Oral Dose Range Finding Study in Rats

When groups of rats (15/sex/dose) were fed DEET at dietary concentrations of 0, 100, 500, 1000, 2000, and 4000 mg/kg, the following effects were observed:

1. Decreased food consumption and body weight and also deaths in 4,000 mg/kg animals. All the animals in this dose level were sacrificed at week 13.

2. Decreased body weight and food consumption in all treated males and females in 500 mg/kg and above.

3. Increased absolute kidney weight in 500 mg/kg males and increased absolute and relative liver weights in all treated groups except 100 mg/kg females.

4. Increased incidence of renal lesions which included granular casts, inflammation, regeneration, and hyaline droplets in all treated males.

The study has been well conducted, and the report is well written However, based on the renal lesions in all treated males and liver weights in all treated rats, a NOEL can not be established. According to the Subdivision F Guidelines, this study is classified as Supplementary.

III. 90-Day Oral Dose Range Finding Study in Mice

When groups of CR CD-1 mice (15/sex/dose) were fed DEET at dietary concentrations of 300, 1000, 3000, 6000, and 10000 mg/kg for 13 weeks, the following effects were observed:

1. Markedly decreased food intake and body weight and death during the first week of the study in 6000 and 10000 mg/kg mice which were removed from the study at week 3.

2. Decreased body weights in 3000 mg/kg males and females.

3. Increased absolute and relative liver weights in 1000 and 3000 mg/kg mice and relative liver weights in 300 mg/kg females.

4. Increased incidence of liver hypertrophy in 3000 mg/kg males and females and in 1000 mg/kg females.

The study has been well conducted, and the report is well written. However, based on liver weight increase in all treated females, a NOEL can not be established. In addition, this study was a dose range finding study. According to the Subdivision F Guidelines, this study is classified as Supplementary.

DISCUSSION

The crucial point in these study is the renal lesions which were found in all treated male rats of the 90-day dermal and oral toxicity studies. The DEET Steering Committee of CSMA believes that this finding is unique to male rats because similar renal lesions have been reported in male rats which were treated with other xenobiotics. The cause of these renal lesions has been reported to be mediated through stimulation of the synthesis of alpha 2u-globulin by the liver. The synthesis of this protein was thought to be under androgenic control. Therefore, the DEET Steering Committee has offered to conduct additional studies to show that the renal lesions observed in male rats are sex and species specific. The proposed studies are 90-day dermal toxicity studies in miniature swine and castrated male rats and a 90-day oral toxicity study in hamsters.

A discussion was held between Dr. Marcia van Gemert, Section Head and this reviewer. The results of the three 90-day toxicity studies and other alternative studies were considered. It was decided that the proposed studies might provide evidence to demonstrate whether or not the compound-related renal lesions were sex and species specific, and they should be conducted. However, if the data were inadequate to support the conclusion that the renal lesions were sex and species specific, further work in the rats at dosage levels below those used in the recent rat dermal toxicity study ought to be conducted.

In addition, the registrant is encouraged to discuss with Toxicology Branch about the dosage selection, specifically maximum tolerated dose, for chronic/oncogenicity studies on rats/mice after satisfactorily completing the proposed studies.

Reviewed by: Whang Phang, Ph.D. Whang Phang 1/27/88
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. M. van Gemert 2/3/88
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: 90-Day Dermal Toxicity Study-Rats

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

RECORD NUMBER: 206238 CASWELL NO.: 346

MRID No.: 40241702 EPA ID No.: 51147-1

SPONSOR: DEET Joint Venture/Chemical Specialties Manufacturers Association, Washington, DC.

TESTING FACILITY: International Research & Development Corp., Mattawan, Michigan.

CITATION: Johnson, D.E. Evaluation of DEET in 90-Day Subchronic Dermal Toxicity Study in Rats. International Research and Development Corp., Project No.: IRDC 555-003 (June 5, 1987). Submitted by DEET Joint Venture/Chemical Specialties Manufacturers Association. EPA MRID No.: 40241702.

CONCLUSIONS:

When groups of rats (15/sex/dose) were dermally applied DEET at dose level of 0, 100, 300, and 1,000 mg/kg; the following effects were observed:

1. Increased incidence of acanthosis and hyperkeratosis on the dermal application sites of all compound-treated rats.

2. Decreased body weights of high dose males.

3. Increased absolute and relative kidney weights (kidney/body & kidney/brain) in mid and high dose males and in relative kidney weights in high dose females.

4. Increased incidence of renal lesions which included granular casts, inflammation, tubular regeneration, hyaline droplets in all treated males; marginal renal effect in high dose females.

The study has been well conducted, and the report is well written However, based on the renal lesions in all treated males and dermal toxicity in all treated rats, a NOEL can not be established. According to the Subdivision F Guidelines, this study is classified as Supplementary.

A. MATERIALS:

1. Test compound: The details of N,N-diethyl-m-toluamide is presented in Appendix 1.

2. Test animals: 5-weeks old Charles Rivers CD rats were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan. The average weights were 280 gm for males; 180 gm, females.

B. STUDY DESIGN:

1. Animal assignment

Groups of rats (10/sex) were randomly selected for pretest health screen which included clinical pathology examinations, viral serology testing, and gross necropsy. Healthy animals were then assigned randomly to the following test groups:

Test Group	Dose in diet (mg/kg)	90-day dermal toxicity study male	female
1 Cont.	0	15	15
2 Low (LDT)	100	15	15
3 Mid (MDT)	300	15	15
4 High(HDT)	1000	15	15

2. Compound Administration

Approximately 24 hrs prior to study initiation, the hair on dorsal aspect of rats was clipped from the nape of the neck to the base of the tail. During the study, this process was was carried out on the last day of each week. The compound was dermally applied to the shaved area at volumes of 0.1, 0.3, and 1.0 ml/kg corresponding to the dose levels of 100, 300, and 1,000 mg/kg, respectively. For the controls, tap water at 1.0 ml/kg was applied.

It should be noted that the highest dose (1000 mg/kg) represented the maximum amount of the test compound which could be applied without significant runoff.

3. Animals received food and water ad libitum.

90-Day Dermal Toxicity Study - RATS (DEET)

TABLE 1. (Data TAKEN From Submission)

MALES: Summary of Clinical Findings
Total Incidence[a] (% Affected)[b]

Observation	Study Interval (Weeks)	0 mg/kg (Control)	100 mg/kg	300 mg/kg	1000 mg/kg
Red area, application site	1-14	0	13 (87)	14 (93)	12 (80)
Scabbed areas, application site	1-14	0	2 (13)	3 (20)	9 (60)
Abraded area, application site	1-14	0	1 (7)	1 (7)	1 (7)
Red and swollen, nasal region	1-14	0	2 (13)	0	0
Tip of tail, not evident	1-14	0	1 (7)	0	0
Scabbed areas[c]	1-14	1 (7)	1 (7)	1 (7)	1 (7)
Hair loss	1-14	0	1 (7)	3 (20)	1 (7)
Area around eye red and/or swollen	1-14	3 (20)	1 (7)	2 (13)	4 (27)
Black material around eye	1-14	1 (7)	1 (7)	1 (7)	1 (7)
Eye pale	1-14	0	0	0	1 (7)
Eye protruded	1-14	0	0	1 (7)	0
Surface of eye irregular in shape	1-14	0	0	1 (7)	0
Red congested area, eye	1-14	0	1 (7)	2 (13)	0
Red material, mouth, nasal region	1-14	0	1 (7)	0	0
Black material, nasal region	1-14	0	2 (13)	0	0
Hard, white protrusion, roof of mouth	1-14	0	1 (7)	0	0
Nasal region malaligned	1-14	0	2 (13)	1 (7)	0
Incisors malaligned	1-14	1 (7)	4 (27)	2 (13)	4 (27)
Yellow material, anogenital region	1-14	0	0	0	1 (7)

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[a]Number of animals affected during interval
[b]Percent of animals affected based on survival at start of interval indicated
[c]Includes any body surface except application site

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TABLE 1. Cont.

MALES: Summary of Clinical Findings
Total Incidence[a] (% Affected)[b]

Observation	Study Interval (Weeks)	0 mg/kg (Control)	100 mg/kg	300 mg/kg	1000 mg/kg
Red material, prepuce	1-14	1 (7)	0	0	0
Rales	1-14	0	1 (7)	0	0
Cold to the touch	1-14	0	1 (7)	0	0
Decreased defecation	1-14	0	1 (7)	0	0
Labored breathing	1-14	0	1 (7)	0	0
Reduced motor activity	1-14	0	1 (7)	0	0
Moribund	1-14	0	1 (7)	0	0

[a]Number of animals affected during interval
[b]Percent of animals affected based on survival at start of interval indicated

TABLE 1. Cont.

FEMALES: Summary of Clinical Findings
Total Incidence[a] (% Affected)[b]

Observation	Study Interval (Weeks)	0 mg/kg (Control)	100 mg/kg	300 mg/kg	1000 mg/kg
Red area, application site	1-14	0	11 (73)	13 (87)	14 (93)
Scabbed area, application site	1-14	1 (7)	7 (47)	11 (73)	8 (53)
Scabbed areas[c]	1-14	2 (13)	0	0	0
Hair loss	1-14	1 (7)	0	5 (33)	4 (27)
Area around eye red	1-14	0	0	2 (13)	0
Black material around eye	1-14	0	0	2 (13)	0
Eye pale	1-14	0	0	1 (7)	0
Surface of eye irregular in shape	1-14	1 (7)	0	1 (7)	0
Pupils dilated, did not respond to light	1-14	1 (7)	0	0	0
White area, internal eye	1-14	1 (7)	0	0	0
Eye dark	1-14	1 (7)	0	1 (7)	0
Raised white area, eyelid	1-14	0	0	1 (7)	0
Abraded area, eyelid	1-14	0	0	1 (7)	0
Brown material around eye	1-14	0	0	1 (7)	0
Brown material around mouth, nasal region	1-14	0	0	0	1 (7)
Yellow material, anogenital region	1-14	0	0	0	2 (13)
Incisors malaligned	1-14	0	0	2 (13)	0
Labored breathing	1-14	0	0	2 (13)	0

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[a]Number of animals affected during interval
[b]Percent of animals affected based on survival at start of interval indicated
[c]Includes any body surface except application site

4. Statistics - The statistical methods used in this study are presented in Appendix 2.

5. Quality assurance was performed.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of dermal toxicity and "pharmacotoxicity".

Mortality: Only one male in 100 mg/kg group died prior to the termination of the study. The cause of death was not compound related.

"Pharmacotoxic" signs: The summary of clinical observations are presented in Table 1. Increased incidences of red and scabbed areas on the application site were observed in the treated rats of both sexes relative to the controls. No neurotoxic signs were reported in any test animals.

2. Body weight

Animals were weighed weekly. The summary of mean body weights at week 13 and mean body weight changes is presented in Table 2. Both high dose males and females showed weight loss relative to the control, and the loss in high dose males was statistically significant (Table 3).

TABLE 2

Mean Body Weight and Mean Body Weight Change

Dose Levels mg/kg	Male		Female	
	Week 13 Mean Body Wt.; gm	Week -1 to 13 Mean Body Wt. Change; gm	Week 13 Mean Body Wt.; gm	Week -1 to 13 Mean Body Wt. Change; gm
0(cont)	534	244	312	99
100	509 (-4.7)	221 (-9.4)	310 (-0.6)	98 (-1.0)
300	509 (-4.7)	225 (-7.8)	311 (-0.3)	96 (-3.0)
1000	484 (-9.4)	201 (-17.6)	304 (-2.6)	87 (-12.1)

( ): Percent difference from control.

TABLE 3 (Data TAKEN from Submission)

Males: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1000 MG/KG MEAN	S.D.	N
Body Weight	-2	272	14.1	15	271	14.0	15	269	13.6	15	266	13.7	15
grams	-1	290	14.2	15	288	15.3	15	284	13.8	15	283	14.9	15
	1	330	17.3	15	325	18.8	15	320	16.0	15	313	18.6	15
	2	364	17.4	15	356	19.1	15	348	19.9	15	342[1]	20.8	15
	3	392	19.7	15	370	49.8	15	377	21.4	15	369[2]	22.4	15
	4	421	23.4	15	406	25.7	14	402	25.2	15	393[1]	24.5	15
	5	439	27.5	15	425	31.8	14	422	28.4	15	412	27.5	15
	6	460	26.5	15	442	32.1	14	443	27.8	15	429[1]	26.3	15
	7	479	29.3	15	461	33.1	14	459	30.5	15	443[2]	31.4	15
	8	491	30.2	15	476	34.8	14	472	30.8	15	452[2]	40.9	15
	9	508	31.3	15	489	31.8	14	485	33.8	15	470[2]	33.4	15
	10	519	33.1	15	501	32.0	14	495	33.2	15	480[2]	33.5	15
	11	534	34.1	15	515	33.4	14	509	36.1	15	491[2]	35.8	15
	12	541	36.4	15	522	36.9	14	516	37.7	15	501[1]	39.4	15
	13	534	37.6	15	509	33.4	14	509	38.0	15	484[2]	42.6	15

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S.D. - Standard Deviation

N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

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TABLE 3 (Cont'd) (Data TAKEN FROM Submission)

Females: Summary of Body Weight Values*

Parameters Measured	WEEK OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1000 MG/KG MEAN	S.D.	N
Body Weight	-2	201	9.4	15	202	10.2	15	205	9.6	15	205	9.3	15
grams	-1	213	9.8	15	212	12.7	15	215	11.0	15	217	8.7	15
	1	230	12.5	15	230	15.2	15	234	9.4	15	228	10.9	15
	2	247	14.6	15	249	16.3	15	249	16.0	15	248	17.8	15
	3	258	16.1	15	258	17.8	15	258	12.7	15	259	16.2	15
	4	270	17.7	15	270	19.9	15	271	14.1	15	270	18.5	15
	5	275	19.5	15	274	19.7	15	278	17.3	15	275	17.1	15
	6	286	22.2	15	285	21.9	15	286	17.7	15	284	21.4	15
	7	298	20.4	15	295	22.7	15	294	14.4	15	293	20.1	15
	8	303	22.3	15	299	22.0	15	301	15.4	15	299	21.6	15
	9	305	21.8	15	306	23.8	15	309	16.0	15	303	21.4	15
	10	309	22.9	15	309	25.0	15	307	20.0	15	305	21.8	15
	11	317	20.8	15	313	23.8	15	312	15.8	15	310	25.3	15
	12	320	21.3	15	317	24.0	15	314	16.2	15	311	21.9	15
	13	312	23.6	15	310	24.6	15	311	18.8	15	304	23.3	15

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S.D. - Standard Deviation

N - Number of Animals

*No statistical significance observed

IRDC

3. Food consumption

Food consumption was determined, and the results calculated as gm/kg/day were presented in Table 4. Both high dose males and females showed significant increase in food consumption relative to the controls from approximately week 8 to the termination of the study.

4. Ophthalmelogical examinations

Ophthalmalogical examinations were conducted at pretest period and at week 13 on all rats; no compound-related effects were reported.

5. Blood was collected before treatment from 10 animals/sex and at week 13 from all the animal on study for hematology and clinical analysis. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpuscular volume (MCV)
x	Platelet count*	x	Reticulocyte count
	Blood Clotting Measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

Although there were changes in MCHC in high dose females and in MCH in low dose males relative to the controls, these changes were not marked as indicated below and were not considered biologically significant.

	Controls	High Dose Females
MCHC (g/dl)	32.6±0.44	32.2±0.36*
	Controls	**Low Dose Males**
MCV (microns^3)	62 ± 2.4	64 ± 1.8*

* Statistically significant at $p < 0.05$

TABLE 4 (DATA TAKEN From submission)

Summary of Food Consumption Values

Parameters Measured	WEEK OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1000 MG/KG MEAN	S.D.	N
	Males:												
Food Consumption	1	87.1	3.58	15	86.5	3.79	15	87.6	2.79	15	85.7	3.55	15
g/kg/day	2	80.4	2.80	15	79.6	4.60	15	80.9	3.09	15	81.3	3.50	15
	3	77.1	3.50	15	72.6	14.47	15	77.0	3.27	15	78.0	4.03	15
	4	74.1	3.48	14	73.3	3.17	14	73.5	2.61	15	75.1	3.17	15
	5	66.1	3.40	15	67.3	2.96	14	67.6	3.07	15	67.9	2.32	15
	6	64.4	3.78	14	67.2	3.34	13	68.2[1]	3.64	15	69.8[2]	2.93	15
	7	63.3	3.99	15	65.2	3.48	14	65.2	3.13	15	66.2	4.62	14
	8	61.5	3.56	15	63.5	4.82	14	65.3[1]	3.76	15	65.8[1]	4.76	15
	9	60.2	3.42	15	61.2	7.71	14	61.4	3.60	15	65.5[2]	5.06	15
	10	57.6	3.76	15	59.2	3.90	14	59.8	4.25	15	61.9[2]	3.26	15
	11	53.6	3.72	15	54.5	3.04	14	55.5	3.45	15	57.3[2]	2.58	15
	12	52.0	2.76	15	54.3	3.36	14	54.7	3.47	15	56.8[2]	3.19	15
	13	47.6	3.35	15	48.3	3.75	14	49.8	3.66	15	51.3[1]	3.28	15
	Females:												
Food Consumption	1	94.2	4.25	15	97.0	7.21	15	92.9	5.02	15	95.4	6.75	15
g/kg/day	2	90.7	4.42	15	92.9	6.93	15	91.2	4.87	15	95.8	5.68	15
	3	89.4	4.92	15	89.2	7.26	15	89.1	4.75	15	92.0	4.14	15
	4	85.7	5.88	15	86.5	6.23	15	85.6	3.69	15	87.9	4.34	15
	5	79.4	3.84	15	82.7	6.68	15	79.2	4.24	15	83.4	7.27	15
	6	80.5	5.25	15	81.8	6.71	15	80.0	4.11	15	85.8[1]	4.05	15
	7	77.7	4.98	15	80.0	6.12	15	79.9	3.80	15	82.7	5.15	15
	8	76.3	4.23	15	77.9	5.01	15	76.4	3.03	15	80.9[1]	4.63	15
	9	74.6	4.55	15	75.8	4.61	15	76.2	5.76	15	81.1[2]	4.46	15
	10	72.2	3.98	15	74.0	6.12	15	70.7	3.35	15	77.3[2]	3.50	15
	11	64.8	4.08	15	67.9	5.66	15	67.6	3.29	15	73.8[2]	4.63	15
	12	64.2	4.61	15	66.8	6.01	15	66.0	3.29	15	72.0[2]	5.63	15
	13	58.5	4.19	15	62.9	5.51	15	62.8	6.52	14	66.9[2]	4.67	15

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S.D. - Standard Deviation

N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

b. Clinical Chemistry

X	Electrolytes:	X	Other:
|x|	Calcium*	|x|	Albumin*
|x|	Chloride*	|x|	Blood creatinine*
| |	Magnesium*	|x|	Blood urea nitrogen*
|x|	Phosphorous*	| |	Cholesterol*
|x|	Potassium*	|x|	Globulins
|x|	Sodium*	|x|	Glucose*
	Enzymes	|x|	Total Bilirubin*
| |	Alkaline phosphatase	|x|	Total Serum Protein*
| |	Cholinesterase#	| |	Triglycerides
| |	Creatinine phosphokinase*°	| |	Serum protein electrophoresis
| |	Lactic acid dehydrogenase		
|x|	Serum alanine aminotransferase (also SGPT)*		
|x|	Serum aspartate aminotransferase (also SGOT)*		
| |	gamma glutamyl transferase		
| |	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

Marginal increases in blood urea nitrogen (mg/dl) was observed in mid and high dose males relative to the controls (control, 14.3±2.09; mid dose, 16.3±2.51; high dose, 16.3±1.56). These increases in mid and high dose males were statistically significant ($p < 0.05$). There were also significant decreases in glucose in high dose males and in alanine aminotransferase in high dose females; these decreases were not biologically significant.

6. Sacrifice and Pathology
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X	Digestive system	X	Cardiovasc./Hemat.	X	Neurologic
	Tongue	x	Aorta*	xx	Brain*†
x	Salivary glands*	x	Heart*	x	Periph. nerve*#
x	Esophagus*	x	Bone marrow*	x	Spinal cord (3 levels)*#
x	Stomach*	x	Lymph nodes*	x	Pituitary*
x	Duodenum*	x	Spleen*	x	Eyes (optic n.)*#
x	Jejunum*	x	Thymus*		Glandular
x	Ileum*		Urogenital	xx	Adrenals*
x	Cecum*	xx	Kidneys*†		Lacrimal gland#
x	Colon*	x	Urinary bladder*	x	Mammary gland*#
x	Rectum*	xx	Testes*†	x	Parathyroids*††
xx	Liver*†	x	Epididymides	x	Thyroids*††
	Gall bladder*#	x	Prostate		Other
x	Pancreas*		Seminal vesicle	x	Bone*#
	Respiratory	xx	Ovaries*†	x	Skeletal muscle*#
x	Trachea*	x	Uterus*	x	Skin*#
x	Lung*			x	All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
\# In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ weight

The summary data of organ weights are presented in Table 5. Absolute and relative kidney weights (kidney/body weight and kidney/brain weight) were increased in both high dose males and females. These increases were statistically significant except the absolute kidney weight of high dose females. Although absolute and relative kidney weights were increased in mid dose males, only the increase in kidney/body weight ratios showed statistical significance.

Absolute and relative liver weights (liver/body weight & liver/brain weight) were increased in all treated females, but statistical significance was seen only in mid and high dose females. Similarily, absolute and relative liver weights of high dose males were also significantly increased.

b. Gross pathology

The findings of gross pathology are presented in Table 6.

TABLE 5

(Data taken from the submission)

Males: Summary of Organ Weight Values

Parameters Measured	DAY OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1000 MG/KG MEAN	S.D.	N
Body Weight g	90	533	37.0	15	512	33.4	14	494[1]	48.1	15	488[1]	48.0	15
Brain g	90	2.04	0.104	15	2.02	0.089	14	2.01	0.088	15	2.00	0.104	15
Brain/Body Weight %x10	90	3.86	0.365	15	3.97	0.284	14	4.11	0.530	15	4.14	0.404	15
Adrenal mg	90	66	10.2	15	71	10.1	14	68	5.1	15	69	9.8	15
Adrenal/Body Weight $\%x10^{3}$	90	12.5	2.01	15	13.8	2.15	14	13.9	1.89	15	14.3	2.19	15
Adrenal/Brain Weight %	90	3.25	0.518	15	3.49	0.486	14	3.38	0.279	15	3.46	0.519	15
Kidney g	90	4.27	0.457	15	4.49	0.633	14	4.65	0.477	15	4.89[2]	0.512	15
Kidney/Body Weight %x10	90	8.03	0.855	15	8.76	0.997	14	9.48[2]	1.356	15	10.08[2]	1.087	15
Kidney/Brain Weight $\%x10^{-2}$	90	2.09	0.256	15	2.22	0.325	14	2.31	0.233	15	2.44[2]	0.246	15
Liver g	90	21.92	2.921	15	21.29	2.444	14	23.23	2.430	15	25.99[2]	3.787	15
Liver/Body Weight %	90	4.12	0.544	15	4.16	0.387	14	4.74[2]	0.707	15	5.32[2]	0.525	15
Liver/Brain Weight $\%x10^{-2}$	90	10.74	1.459	15	10.54	1.262	14	11.56	1.238	15	12.99[2]	1.993	15
Testis g	90	3.55	0.415	15	3.59	0.301	14	3.47	0.211	15	3.63	0.339	15
Testis/Body Weight %x10	90	6.68	0.893	15	7.03	0.510	14	7.10	0.929	15	7.49	0.904	15
Testis/Brain Weight $\%x10^{-2}$	90	1.74	0.206	15	1.78	0.147	14	1.73	0.138	15	1.81	0.165	15

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S.D. - Standard Deviation

N - Number of Animals

[2]Significantly different from the Control group; $p<0.01$

TABLE 5 Cont'd (Data taken from submission)

Females: Summary of Organ Weight Values

Parameters Measured	DAY OF STUDY	0 MG/KG (CONTROL) MEAN	S.D.	N	100 MG/KG MEAN	S.D.	N	300 MG/KG MEAN	S.D.	N	1000 MG/KG MEAN	S.D.	N
Body Weight g	90	314	28.3	15	307	23.8	15	310	26.2	15	305	25.4	15
Brain g	90	1.93	0.091	15	2.00	0.150	15	2.00	0.128	15	1.91	0.096	15
Brain/Body Weight %x10	90	6.18	0.503	15	6.54	0.657	15	6.49	0.627	15	6.31	0.517	15
Adrenal mg	90	84	9.1	15	89	17.0	15	86	12.2	15	90	13.7	15
Adrenal/Body Weight $\%x10^3$	90	27.0	3.40	15	29.1	6.13	15	28.0	4.35	15	29.6	5.02	15
Adrenal/Brain Weight %	90	4.38	0.483	15	4.43	0.717	15	4.34	0.676	15	4.70	0.725	15
Kidney g	90	2.70	0.269	15	2.86	0.279	15	2.87	0.389	15	3.02	0.312	15
Kidney/Body Weight %x10	90	8.64	0.983	15	9.34	0.890	15	9.30	1.301	15	9.92[2]	0.826	15
Kidney/Brain Weight $\%x10^{-2}$	90	1.40	0.132	15	1.43	0.136	15	1.44	0.170	15	1.58[2]	0.179	15
Liver g	90	12.62	1.725	15	14.14	1.750	15	14.45[1]	1.793	15	17.14[2]	2.693	15
Liver/Body Weight %	90	4.04	0.542	15	4.60[1]	0.366	15	4.67[2]	0.494	15	5.61[2]	0.622	15
Liver/Brain Weight $\%x10^{-2}$	90	6.54	0.821	15	7.11	0.900	15	7.22[1]	0.779	15	8.99[2]	1.511	15
Ovary mg	90	151	25.7	15	159	26.9	15	155	20.7	15	157	16.1	15
Ovary/Body Weight $\%x10^2$	90	4.83	0.797	15	5.21	0.881	15	5.05	0.894	15	5.19	0.643	15
Ovary/Brain Weight %	90	7.85	1.426	15	8.01	1.313	15	7.76	1.089	15	8.26	1.012	15

555-003

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

TABLE 6

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination, Terminal Sacrifice

SITE – Observation		0 mg/kg (Control)		100 mg/kg		300 mg/kg		1000 mg/kg	
		DOS	TS	DOS	TS	DOS	TS	DOS	TS
NUMBER OF ANIMALS EXAMINED		0	15	1	14	0	15	0	15
NUMBER WITHIN NORMAL LIMITS		0	13	0	7	0	1	0	0
MALES									
KIDNEY									
– Mottled, bilateral, mild			1		1				2
– Focus, depressed, mild							1		
– Hydronephrosis, unilateral,	– mild				1				
	– moderate								1
– Enlarged, bilateral, mild					2		4		6
– Granular, bilateral,	– trace						1		
	– mild								1
– Pale, bilateral, mild							1		1
LIVER									
– Enlarged, generalized, mild									2
SKIN, EYELID									
– Hair thinned, unilateral, mild							1		
SKIN, TREATED									
– Within normal limits			15	1	10		4		
– Thick,	– trace						1		
	– mild						1		
– Subcutis, white streaks, mild							2		
– Scale, diffuse/focal,	– trace						2		
	– mild				4		9		15
FEMALES									
NUMBER OF ANIMALS EXAMINED			15		15		15		15
NUMBER WITHIN NORMAL LIMITS			13		10		2		2
EYE									
– Lens, cloudy, unilateral, severe			1						
– Rupture, unilateral, png			1						
– Cornea, cloudy, unilateral, mild							1		
							1		
KIDNEY									
– Mottled, bilateral, mild									1
SKIN, EYELID									
– Abrasion, mild							1		
SKIN, TREATED									
– Within normal limits			15		11		2		2
– Scale, diffuse, focal, mild					4		10		13
– Crust, multifocal, mild							2		1

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DOS – Deaths and Unscheduled Sacrifices
TS – Terminal Sacrifice

pmg – Present, no grade
NOS – Not otherwise specified

IRDC

(DATA TAKEN FROM Submission)
90-Day Dermal Toxicity Study-RATS

In all treated males there was an increased incidence of enlarged kidney relative to the controls, and it was dose- and compound-related. Pale and granular kidneys were also observed in mid and high dose males.

In the compound-treated skin of all test males and females, increased incidence of dermal scaling was observed and was dose- and compound-related. Other findings were not considered to be treatment-related.

c. Microscopic pathology

The increased incidence of microscopic findings relative to the controls are presented in Table 7.

In all dosed males, increased incidence of histopathology findings in the kidneys, liver, and treated skin were observed, and these findings were graded trace to mild. The kidney lesions included granular casts, inflammation, regeneration, and hyaline droplets which are summarized in Table 8.

Table 8

Summary of Significant Microscopic Renal Findings in Deet Treated Rats

Dose (mg/kg)	0	100	300	1000
Males				
Granular casts	0/15	8/15	9/15	10/15
Inflammaton	6/15	14/15	15/15	15/15
Regeneration	3/15	14/15	15/15	15/15
Hyaline droplets	0/15	11/15	13/15	14/15
Females				
Hyaline cast	0/15	1/15	0/15	3/15
Inflammation	0/15	1/15	0/15	4/15

The increased incidences of renal cast and inflammation in high dose females were less in number and in severity than those seen in males; nevertheless, the incidence was more than that seen in the concurrent controls. It should be emphaisized that the presence of hyaline in renal tubules was observed in both sexes of the treated animals.

In all treated male rats a slight increase in the incidence of liver change which was characterized by vacuolar change was

TABLE 7.

Incidence of Microscopic Observations
0 to Termination: Rats

(DATA TAKEN from Submission; MRID No. 402417 02)

TISSUE / OBSERVATION		0 mg/kg (Control)	100 mg/kg	300 mg/kg	1000 mg/kg
Male					
Kidney		(15)	(15)	(15)	(15)
Cast, granular		0	8	9	10
	-trace	8	4	6	4
	-mild	0	4	3	6
Hydronephrosis, mild		0	1	1	0
Inflammation,		6	14	15	15
	-trace	6	2	6	1
	-mild	0	12	9	14
Mineralization, trace		0	0	0	1
Within normal limits		9	1	0	0
Regeneration,		3	14	15	15
	-trace	3	3	5	1
	-mild	0	11	10	14
Hyaline droplets*		0	11	13	14
Liver		(15)	(15)	(15)	(15)
Hypertrophy, mild		0	0	0	1
Within normal limits		15	13	11	13
Vacuolar change, trace		0	2	4	2
Skin, Eyelid		(0)	(0)	(1)	(0)
Inflammation, mild		0	0	1	0
Skin, Treated		(15)	(15)	(15)	(15)
Acanthosis,		0	12	15	15
	-trace	0	5	0	2
	-mild	0	7	15	13
Hyperkeratosis,		0	3	0	4
	-trace	0	2	0	0
	-mild	0	1	0	4
Within normal limits		15	1	0	0
Skin, Untreated		(15)	(15)	(15)	(15)
Acanthosis, mild		0	0	0	2
Erosion, trace		0	0	0	1
Within normal limits		15	15	15	13
Parakeratosis, trace		0	0	0	1
Female					
Kidney		(15)	(15)	(15)	(15)
Cast, hyaline,		0	1	0	3
	-trace	0	1	0	2
	-mild	0	0	0	1
Inflammation, trace		0	1	0	4
Mineralization, trace		0	0	1	1
Within normal limits		15	13	14	7
Liver		(15)	(15)	(15)	(15)
Within normal limits		15	15	15	15
Skin, Treated		(15)	(15)	(15)	(15)
Acanthosis,		0	13	15	15
	-trace	0	6	2	1
	-mild	0	7	13	14
Erosion,		0	0	1	1
	-trace	0	0	1	0
	-mild	0	0	0	1
Exudate,		0	0	3	2
	-trace	0	0	2	0
	-mild	0	0	1	2
Hyperkeratosis,		0	4	0	5
	-trace	0	3	0	1
	-mild	0	1	0	4
Inflammation, trace		0	0	1	0
Within normal limits		15	1	0	0
Skin, Untreated		(15)	(15)	(15)	(15)
Acanthosis, mild		0	0	0	1
Within normal limits		15	15	15	14

555-003 CODE: () = NUMBER OF ANIMALS EXAMINED

90-Day DERMAL Toxicity Study.

found (Table 7), but this change was not observed in females.

In the treated skin of both male and females of all dose levels, increased incidences of acanthosis and/or hyperkeratosis were found. Acanthosis of the skin was also observed in the untreated skin site of a male and a female in 1000 mg/kg groups. The dermal findings were compound-related.

There were other sporadic histopathological findings in different tissues, but they were not considered to be compound-related.

DISCUSSION

When groups of rats (15/sex/dose) were dermally applied DEET at dose level of 0, 100, 300, and 1,000 mg/kg; increased incidences of acanthosis and hyperkeratosis were observed on the application sites of all DEET treated animals.

Body weights of all high dose males were significantly decreased relative to the controls, but food consumption was comparable between treated and control animals.

Clinical chemistry revealed marginal increase in blood urea nitrogen in mid and high dose male rats, and this increase was statistically significant. In view of the histopathological findings in the kidneys of these animals, this slight increase was considered as compound-related.

Absolute and relative (kidney/body and kidney/brain) kidney weights were increased in mid and high dose males. In addition, statistically significant increases in relative kidney weights were observed in high dose females.

Absolute and relative liver weights (liver/body & liver/brain) were increased in all treated females and in mid and high dose males. However, liver histopathology findings did not indicate any adverse effects, and the "changes in liver weight were probably an adaptive response".

Both gross and histopathology data indicated kidney lesions in all treated males and marginal renal effects in high dose females. The histopathology findings in the kidneys of the treated males included granular casts, inflammation, regeneration, and hyaline droplets whereas in high dose female hyaline casts and inflammation were observed.

The renal cast observed in males was different from that of females. The author of the report believed that renal lesions in males were caused by alpha 2u-globulin which is produced in the liver of males only under the androgenic control. However, this does not explain the marginal effects on the kidney

observed in high dose females. In addition, no experimental data were reported to prove that the granular cast in male rats consisted of alpha 2u-globulin.

The study was has been well conducted, and the report is well written. However, based upon the findings of renal lesions on all treated males and dermal lesions on the application sites of all treated rats, a NOEL can not be established. According to the Subdivision F Guidelines, this study is classified as Supplementary.

Appendix 1

DEET toxicology review

Page _____ is not included in this copy.

Pages 24 through 26 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) _____

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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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DATA EVALUATION REPORT

STUDY TYPE: 90-Day Oral Dose Range Finding Study in Rats

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

RECORD NUMBER: 206238 CASWELL NO.: 346

MRID No.: 40241703 EPA ID No.: 51147-1

SPONSOR: DEET Joint Venture/Chemical Specialties Manufacturers Association, Washington, DC.

TESTING FACILITY: International Research & Development Corp., Mattawan, Michigan.

CITATION: Johnson, D.E. Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Rats. International Research and Development Corp., Project No.: IRDC 555-001 (June 1, 1987). Submitted by DEET Joint Venture/Chemical Specialties Manufacturers Association. EPA MRID No.: 40241703.

CONCLUSIONS: When groups of rats (15/sex/dose) were fed DEET at dietary concentrations of 0, 100, 500, 1000, 2000, and 4000 mg/kg, the The following effects were observed:

1. Decreased food consumption and body weight and also deaths in 4,000 mg/kg animals. All the animals in this dose level were sacrificed at week 13.

2. Decreased body weight and food consumption in all treated males and females in 500 mg/kg and above.

3. Increased absolute kidney weight in 500 mg/kg males and increased absolute and relative liver weights in all treated groups except 100 mg/kg females.

4. Increased incidence of renal lesions which included granular casts, inflammation, regeneration, and hyaline droplets in all treated males.

The study has been well conducted, and the report is well written However, based on the renal lesions in all treated males and liver weights in all treated rats, a NOEL can not be established. According to the Subdivision F Guidelines, this study is classified as Supplementary.

A. MATERIALS:

1. Test Compound is 98.3% pure technical N, N-diethyl-m-toluamide. The details of the test article are presented in Appendix 1.

2. Test animals: 5-weeks old Charles Rivers CD rats were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan.

B. STUDY DESIGN:

1. Animal assignment

The animals used in this study were selected based on the body weight (male, 269-300 gm; female, 165-191 gm) and acceptable pretest weight gain. The selected animals were randomly assigned to the following treatment groups:

Test Group	Dose in diet (mg/kg)	90-day oral dose range finding study male	female
1 Cont.	0	15	15
2	100	15	15
3	500	15	15
4	1000	15	15
5	2000	15	15
6	4000	15	15

2. Diet Preparation:

The test compound/diet mixture was prepared weekly with the concentrations adjusted based on mean weekly food consumption measurements. The mixtures were store in stainless steel containers at room temperature. Samples of the mixture were taken for chemical analyses.

The mixture was found to be stable for 21 days, and the individual test diet preparation contained an average of 90 to 105% of the targeted concentrations (Table 1)

3. Animals received food and water ad libitum.

4. Statistics: The statistical methods used in this study are presented in Appendix 2.

5. Quality assurance statement was signed.

TABLE 1 (Data taken from submission)

Periodic Analyses; % of Target Concentration Found[1]

Group	Dosage Level (mg/kg/day)	Sex	Study Week 1	2	3	4	8	12	Mean ± S.D.[5]
2	100	Male	94, 100 (97)	93, 92 (93)	90, 89 (90)	97, 96 (97)	104, 104 (104)	91, 93 (92)	96 ± 5.0%
		Female	98, 103 (101)	95, 93 (94)	91, 87 89, 93 (90)[3]	90, 89 (90)	99, 103 (101)	99, 99 (99)	96 ± 5.2%
3	500	Male	101, 99 (100)	95, 98 (97)	96, 96 (96)	92, 98 (95)	101, 104 (103)	97, 96 (97)	98 ± 3.0%
		Female	95, 100 (98)	97, 95 (96)	94, 94 (94)	96, 94 (95)	100, 101 (101)	101, 97 (99)	97 ± 2.6%
4	1000	Male	102, 99 (101)	102, 101 (102)	96, 99 (98)	99, 100 (100)	102, 103 (103)	95, 97 (96)	100 ± 2.6%
		Female	100, 98 (99)	105, 102 (104)	98, 96 (97)	94, 94 (94)	98, 100 (99)	107, 102 (105)	100 ± 4.2%
5	2000	Male	100, 97 (99)	99, 99 (99)	95, 101 (98)	98, 101 (100)	100, 102 (101)	96, 97, 83 (92)[4]	98 ± 3.2%
		Female	93, 97 (95)	99, 99 (99)	103, 95 (99)	96, 96 (96)	97, 100 (99)	92, 85, 95 (91)[4]	97 ± 3.2%
6[2]	4000	Male	102, 102 (102)						
		Female	100, 97 (99)						

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[1] Values in parenthesis are the average of duplicate assays unless otherwise indicated.
[2] Group 6 terminated at study week 2.
[3] Average of 4 replicate assays
[4] Average of 3 replicate assays
[5] Based on average of replicate assays.
S.D. - Standard deviation

IRDC

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice weekly for signs of toxicity and mortality.

On the first day of week 2, 1 male and 2 females in the 4,000 mg/kg group died or sacrificed *in extremis*. The remaining animals in this group were sacrificed during week 3. The animals, which died or sacrificed *in extremis*, showed signs of reduced defecation, hunched posture, labored breathing, and reduced motor activity prior to death. One female in 500 mg/kg group and 4 females in the 2,000 mg/kg group died prior to termination of the study.

2. Body weight

Animals were weighed weekly during the test and weighed twice prior to the administration of the test materials.

In both males and females decreases in mean body weights were observed in 500; 1,000; 2,000; and 4,000 mg/kg groups (Table 2a and 2b). These decreases were statistically significant at dose levels of 1,000 mg/kg or above in males and of 500 mg/kg or above in females. In 4,000 mg/kg animals, severe weight loss was observed in week 1 of the compound administration; these animals were sacrificed at week 3.

Table 3 summarized the mean body weight and mean body weight changes. Dose-related decreases in body weight gains were found in all treated animals of 500 mg/kg or above relative to that of the controls. The mean body weights of 100 mg/kg animals were comparable to those of the controls.

TABLE 3*

Mean Body Weight and Mean Body Weight Change
(percent difference from control)

	Male		Female	
Dosage Level (mg/kg/day)	Mean Body Weight, g	Mean Body Weight Change, g	Mean Body Weight, g	Mean Body Weight Change, g
0 (Control)	530	232	274	86
100	525(-0.9)	226(-2.6)	268(-2.2)	82(-4.7)
500	506(-4.5)	209(-9.9)	246(-10.2)	62(-27.9)
1000	455(-14.2)	155(-33.2)	231(-15.7)	44(-48.8)
2000	317(-40.2)	17(-92.7)	200(-27.0)	14(-83.7)

* (Data taken from Submission)

TABLE 2a

Males: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	500 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	-2	283	8.6	15	283	8.5	15	282	8.6	15
	-1	298	10.5	15	299	10.1	15	297	10.3	15
	1	340	13.0	15	342	14.1	15	333	13.1	15
	2	371	14.9	15	371	18.0	15	360	17.4	15
	3	398	17.9	15	398	21.2	15	384	18.9	15
	4	422	19.1	15	423	23.4	15	405	21.1	15
	5	442	20.8	15	441	25.7	15	424	25.0	15
	6	460	22.1	15	460	27.9	15	443	24.3	15
	7	482	22.6	15	477	30.7	15	460	26.5	15
	8	496	23.1	15	490	32.1	15	470[1]	24.7	15
	9	509	24.8	15	504	33.4	15	487	24.6	15
	10	517	24.3	15	513	34.3	15	497	27.4	15
	11	526	24.7	15	519	32.3	15	504	30.4	15
	12	536	24.7	15	525	32.7	15	513	32.4	15
	13	530	29.8	15	525	29.6	15	506	34.8	15

Parameters Measured	WEEK OF STUDY	1000 MG/KG/DAY MEAN	S.D.	N	2000 MG/KG/DAY MEAN	S.D.	N	4000 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	-2	286	8.3	15	284	8.7	15	282	8.7	15
	-1	303	10.3	15	300	9.1	15	297	7.0	15
	1	327[2]	12.5	15	295[2]	12.1	15	221[2]	29.2	15
	2	353[1]	16.0	15	292[2]	9.9	15	319[2,a]	18.2	14
	3	376[2]	16.9	15	316[2]	12.0	15			
	4	392[2]	18.3	15	329[2]	17.1	15			
	5	410[2]	18.0	15	336[2]	20.5	15			
	6	420[2]	19.9	15	332[2]	22.4	15			
	7	431[2]	19.4	15	327[2]	27.5	15			
	8	440[2]	25.7	15	326[2]	31.0	15			
	9	453[2]	24.8	15	329[2]	33.5	15			
	10	454[2]	30.0	15	331[2]	37.6	15			
	11	458[2]	31.3	15	328[2]	38.6	15			
	12	462[2]	32.8	15	326[2]	39.1	15			
	13	455[2]	36.9	15	317[2]	38.4	15			

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S.D. - Standard Deviation

N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

[a]Animals removed from treatment

(DATA TAKEN From Submission)

TABLE 26

Females: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	500 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	-2	180	7.5	15	178	7.4	15	177	7.4	15
	-1	188	7.9	15	186	7.5	15	184	7.6	15
	1	202	12.3	15	204	8.7	15	194	9.8	15
	2	217	12.7	15	213	13.0	15	205[1]	11.8	15
	3	232	14.5	15	224	13.1	15	215[2]	11.5	15
	4	241	17.5	15	233	11.9	15	221[2]	13.3	15
	5	248	18.5	15	241	12.2	15	227[2]	14.5	15
	6	257	20.5	15	246	16.8	15	231[2]	15.2	15
	7	266	20.8	15	255	17.0	15	238[2]	14.5	15
	8	268	21.2	15	258	16.2	15	238[2]	14.6	15
	9	272	26.2	15	262	16.9	15	245[2]	16.0	15
	10	276	23.2	15	266	20.3	15	245[2]	19.1	15
	11	277	25.0	15	269	19.2	15	248[2]	18.0	14
	12	278	24.1	15	271	17.4	15	249[2]	17.5	14
	13	274	23.6	15	268	17.5	15	246[2]	17.3	14

Parameters Measured	WEEK OF STUDY	1000 MG/KG/DAY MEAN	S.D.	N	2000 MG/KG/DAY MEAN	S.D.	N	4000 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	-2	180	7.3	15	178	7.4	15	181	6.9	15
	-1	187	8.0	15	186	7.3	15	189	8.5	15
	1	182[2]	8.5	15	162[2]	8.5	15	136[2]	9.3	13
	2	188[2]	10.9	15	139[2]	9.7	13	200[2,4]	9.7	13
	3	200[2]	10.0	15	167[2]	11.8	13			
	4	211[2]	10.7	15	179[2]	13.1	13			
	5	217[2]	11.2	15	184[2]	15.0	13			
	6	219[2]	10.6	15	181[2]	17.7	13			
	7	225[2]	10.9	15	181[2]	19.2	13			
	8	229[2]	10.6	15	182[2]	20.0	13			
	9	234[2]	10.7	15	188[2]	24.1	13			
	10	235[2]	10.5	15	189[2]	26.4	13			
	11	233[2]	11.9	15	189[2]	30.1	13			
	12	235[2]	11.5	15	189[2]	33.3	13			
	13	231[2]	12.1	15	200[2]	14.3	11			

SSS 001

S.D. - Standard Deviation
N - Number of Animals
[2]Significantly different from the Control group; $p<0.01$
[4]Animals removed from treatment

(DATA TAKEN FROM Submission)

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Compound intake was calculated from the consumption. These data are presented in Table 4a and 4b.

Dose-related decreases in food consumption were observed in treated animals of 500 mg/kg or above. When food consumption values were expressed as mg/animal/day, statistically significant decreases were seen in animals treated with 500 mg/kg or above. The food consumption of 100 mg/kg animals was comparable to that of the controls.

5. Blood was collected before treatment (5 animals/sex/dose) and at week 13 (10 animals/sex/dose) for hematology and clinical analyses. The CHECKED (X) parameters were examined.

a. Hematology

X		X	
x	Hematocrit (HCT)*	x	Leukocyte differential count*
x	Hemoglobin (HGB)*	x	Mean corpuscular HGB (MCH)
x	Leukocyte count (WBC)*	x	Mean corpuscular HGB conc.(MCHC)
x	Erythrocyte count (RBC)*	x	Mean corpuscular volume (MCV)
x	Platelet count*	x	Reticulocyte count
	Blood Clotting Measurements		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Required for subchronic and chronic studies

In males, there was a decrease in lymphocytes in 1,000 and 2,000 mg/kg groups as indicated below:

	Control	1000 mg/kg	2000 mg/kg
Lymphocytes ($\times 10^3$/cmm)	10.3 ± 2.11	8.4 ± 0.95	8.1 ± 1.86

In females, there were slight increases in hematocrit and erythrocyte values and decreases in MCV and MCH values of 2000 mg/kg animals; as indicated below these changes were significantly different from those of the controls.

	Hematocrit %	erythrocyte $\times 10^6$/cmm	MCV microns	MCH (pg)
Control	49 ± 1.9	7.4 ± 0.24	66 ± 1.2	21.4 ± 0.47
2000 mg/kg	52 ± 4.3*	8.4 ± 0.88†	63 ± 2.5†	20.2 ± 0.50†

* significanty at $p<0.05$ † significant at $p<0.01$

TABLE 4a

MALE ANIMALS: MEAN FOOD AND COMPOUND CONSUMPTION

OBSERV. PERIODS	0 MG/KG/DAY (CONTROL) FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	100 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	500 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	1000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	26.6	1.26	78.3	0.000	26.5	1.78	77.5	96.1	25.0*	1.04	75.3*	467	22.8*	1.98	69.4*	860
2	27.4	1.35	73.7	0.000	27.0	1.96	72.8	90.3	26.0	1.37	72.5	449	25.0*	2.26	70.9	878
3	27.5	1.42	69.2	0.000	27.1	1.97	68.2	103	25.6*	1.06	66.8	506	24.9*	1.93	66.1*	1026
4	26.8	1.35	63.4	0.000	26.7	1.66	63.1	101	25.7	1.08	63.6	523	24.1*	1.62	61.3	1020
5	25.9	1.06	58.6	0.000	25.8	1.69	58.5	101	25.2	1.34	59.6	515	24.4*	2.45	59.7	1070
6	25.6	1.52	55.5	0.000	25.3	1.65	55.0	103	24.5	1.34	55.3	510	23.4*	1.87	55.6	1024
7	27.9	1.03	58.1	0.000	26.9	1.74	56.4	106	25.7*	1.33	55.9*	515	24.4*	2.47	56.1	1033
8	28.4	1.14	57.4	0.000	27.4	1.93	55.9	105	26.1*	1.35	55.8	515	24.5*	2.31	55.5	1023
9	27.7	1.38	54.8	0.000	27.4	1.85	54.4	102	27.3	1.54	56.1	517	24.6*	2.36	53.9	993
10	26.8	1.56	51.9	0.000	26.8	1.21	52.4	98.6	26.1	1.49	52.5	484	24.3*	2.45	52.5	968
11	26.8	1.20	51.0	0.000	26.2	1.11	50.6	95.2	26.0	1.44	52.2	481	23.2*	2.60	50.5	930
12	26.1	1.05	48.8	0.000	25.8	1.40	49.3	107	25.9	1.61	50.6+	533	23.2*	2.35	50.4	1095
13	24.0	2.39	45.2	0.000	23.8	2.94	45.4	101	23.2	2.47	45.9	499	19.8*	3.27	44.0	962

OBSERV. PERIODS	2000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	4000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	15.9*	3.79	53.9*	1335	4.8*	3.04	20.9*	1036
2	19.6*	1.48	66.8*	1655	30.7*	2.29	96.3*	0[a]
3	22.8*	1.52	72.1	2158				
4	21.8*	1.75	66.5*	2030				
5	20.2*	1.22	60.8*	2010				
6	19.1*	2.23	56.3	2037				
7	18.9*	2.55	56.2	2033				
8	18.8*	1.85	57.5	2081				
9	19.4*	2.31	57.2	2069				
10	18.1*	2.71	54.5	1973				
11	17.9*	2.41	55.1	1993				
12	17.6*	2.82	52.0+	2083				
13	16.0*	2.98	48.5	2046				

555-001

OBSERV. - Observation
ANIM - Animal
STD DEV - Standard deviation
CMPD - Compound consumption
[a]Animals received control diet week 2

* Significantly different from controls ($p < 0.01$)
+ Significantly different from control ($p < 0.05$)

(DATA TAKEN FROM Submission)

TABLE 4b

FEMALE ANIMALS: MEAN FOOD AND COMPOUND CONSUMPTION

OBSERV. PERIODS	0 MG/KG/DAY (CONTROL) FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	100 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	500 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	1000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	18.4	1.48	90.9	0.000	18.5	1.48	90.3	101	15.2	1.29	78.5*	442	11.8	1.53	64.8*	730
2	19.1	1.32	86.2	0.000	19.4	1.70	91.1	102	17.8	1.35	86.9	488	14.3	1.63	75.9+	855
3	19.7	1.53	84.7	0.000	19.6	1.97	87.4	95.9	17.9	1.17	83.4	480	16.4	1.15	81.9	1078
4	18.9	2.09	78.5	0.000	18.9	1.46	81.0	92.7	17.0	1.19	76.9	461	16.6	0.80	79.2	966
5	18.6	1.75	75.0	0.000	17.9	1.57	74.4	91.9	16.1	1.09	71.0+	461	15.4	1.43	70.9+	895
6	17.6	1.49	68.6	0.000	17.4	1.68	70.7	95.0	15.4	0.93	66.7	469	14.8	0.90	67.5	951
7	18.4	1.30	69.4	0.000	18.4	1.56	72.3	97.2	16.1	0.92	67.7	476	15.6	1.20	69.6	981
8	18.8	1.35	70.6	0.000	18.4	1.48	71.5	96.1	16.4	2.28	68.8	484	16.3	0.99	71.2	1004
9	18.8	2.57	69.2	0.000	18.4	1.92	69.9	94.0	16.6	1.71	67.6	475	15.4	1.08	65.7	926
10	17.9	1.95	65.2	0.000	18.2	1.92	68.5	92.0	16.0	1.10	65.4	460	14.7	1.28	62.5	882
11	18.4	1.44	66.7	0.000	18.8	1.33	70.0	94.2	15.9	1.32	64.1	451	14.1	1.47	60.2*	849
12	17.2	1.52	61.9	0.000	17.9	1.26	66.1	94.4	15.6	1.18	62.8	489	13.8	0.83	58.9	977
13	15.9	1.58	58.1	0.000	16.3	1.29	60.8	92.2	14.2	1.21	57.7	459	13.0	1.48	56.2	955

OBSERV. PERIODS	2000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	4000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	7.8	1.03	47.8*	1078	3.6	1.65	26.1*	1175
2	7.0	1.16	50.5*	1138	23.5	1.79	117.0*	0a
3	14.5	1.35	86.2	1955				
4	14.1	1.49	78.5	1821				
5	12.6	1.51	67.7*	1724				
6	11.9	1.30	65.7	1942				
7	11.7	1.72	65.0	1919				
8	12.5	1.68	68.2	2014				
9	12.2	1.74	65.3	1929				
10	11.8	2.09	63.1	1863				
11	12.3	1.93	63.6	1878				
12	12.2	2.75	62.7	1974				
13	11.1	1.16	55.5	1755				

555 001

OBSERV. - Observation
ANIM - Animal
STD DEV - Standard deviation
CMPD - Compound consumption
aAnimals received control diet week 2

* Significantly different from controls ($p < 0.01$)

\+ Significantly different from controls ($p < 0.05$)

(DATA TAKEN FROM submission)

b. Clinical Chemistry

X	Electrolytes:	X	Other:
x	Calcium*	x	Albumin*
x	Chloride*	x	Blood creatinine*
	Magnesium*	x	Blood urea nitrogen*
x	Phosphorous*		Cholesterol*
x	Potassium*	x	Globulins
x	Sodium*	x	Glucose*
	Enzymes	x	Total Bilirubin*
	Alkaline phosphatase	x	Total Serum Protein*
	Cholinesterase#		Triglycerides
	Creatinine phosphokinase*°		Serum protein electrophoresis
	Lactic acid dehydrogenase		
x	Serum alanine aminotransferase (also SGPT)*		
x	Serum aspartate aminotransferase (also SGOT)*		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

* Required for subchronic and chronic studies
\# Should be required for OP
° Not required for subchronic studies

Certain changes in clinical chemistry parameters were seen predominantly in 2,000 mg/kg females, and these changes included decreases in total protein, albumin, glucose, and globulin and increases in potassium and phosphorus. In 2,000 mg/kg males a decrease in phosphorus was observed. Although most of these changes showed statistical significance, they were not marked and were related more to nutritional effects than to the direct effects of the compound.

6. Sacrifice and Pathology

According to the original protocol, histopathology was to be conducted on 10 randomly selected animals/sex of controls and the high-dose groups. However, the highest dose (4,000 mg/kg) animals were terminated early in the study, and the animals in the next highest dose level showed severe body weight loss; "it was decided that the toxicological potential of the test compound could best be defined by examining a full tissue complement from randomly selected 10 animals/sex from the control and 1,000 mg/kg groups". In addition, limited number of tissue samples from 10 animals/sex from the remaining dosage groups.

The CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		.Aorta*	xx	.Brain*†
	.Salivary glands*	x	.Heart*		Periph. nerve*#
	.Esophagus*	x	.Bone marrow*	x	Spinal cord (3 levels)*#
	.Stomach*	x	.Lymph nodes*	x	.Pituitary*
	.Duodenum*	x	.Spleen*		Eyes (optic n.)*#
	.Jejunum*	x	.Thymus*		Glandular
	.Ileum*		Urogenital	xx	.Adrenals*
	.Cecum*	xx	.Kidneys*†		Lacrimal gland#
	.Colon*		.Urinary bladder*		Mammary gland*#
	.Rectum*	xx	.Testes*†	x	.Parathyroids*††
xx	.Liver*†	x	Epididymides	x	.Thyroids*††
	Gall bladder*#		Prostate		Other
x	.Pancreas*		Seminal vesicle	x	Bone*#
	Respiratory	xx	Ovaries*†	x	Skeletal muscle*#
	.Trachea*		.Uterus*		Skin*#
x	.Lung*				All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ weight

The absolute and relative organ weights are presented in Table 5a and 5b.

Significant decrease in absolute brain weight was observed in 2,000 mg/kg males. Statistically significant increases in relative brain weight (brain/body) were seen in both males and females of 500, 1000, and 2000 mg/kg groups. The increase in relative brain weight was primarily due to marked decreases in body weights of those animals.

Absolute liver weights were significantly increased in 100; 500; and 1,000 mg/kg males and in 500; 1000; and 2000 mg/kg females. Relative liver weights (liver/body & liver/brain) were significantly increased in all treated males and in all females of 500 mg/kg or above.

TABLE 5a

Absolute + Relative Organ Weights of DEET TREATED Male RATS

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	500 MG/KG/DAY MEAN	S.D.	N	1000 MG/KG/DAY MEAN	S.D.	N	2000 MG/KG/DAY MEAN	S.D.	N
Body Weight g	13	528	38.6	15	526	28.9	15	507	31.4	15	452[2]	43.4	14	319[2]	38.9	14
Brain g	13	2.04	0.085	15	2.04	0.155	15	2.10	0.127	15	2.04	0.116	15	1.94[2]	0.068	15
Brain/Body Weight $\bar{x}\times10$	13	3.89	0.312	15	3.90	0.376	15	4.14[1]	0.284	15	4.54[2]	0.466	14	6.17[2]	0.636	14
Adrenal mg	13	66	11.8	15	64	6.7	15	72	9.3	15	71	23.6	15	63	8.8	15
Adrenal/Body Weight $\bar{x}\times10^3$	13	12.7	2.87	15	12.2	1.53	15	14.2	1.96	15	16.2	7.35	14	20.0[2]	1.88	14
Adrenal/Brain Weight $\bar{x}$	13	3.26	0.644	15	3.14	0.404	15	3.44	0.498	15	3.50	1.221	15	3.23	0.422	15
Liver g	13	21.74	2.635	15	23.56[1]	1.867	15	26.79[2]	2.195	15	25.54[2]	4.502	15	21.44	3.817	15
Liver/Body Weight $\bar{x}$	13	4.12	0.336	15	4.48[2]	0.269	15	5.28[2]	0.317	15	5.67[2]	0.538	14	6.86[2]	0.566	14
Liver/Brain Weight $\bar{x}\times10^{-2}$	13	10.65	1.240	15	11.61	1.475	15	12.83[2]	1.308	15	12.53[1]	2.268	15	11.02	1.787	15
Kidney g	13	4.01	0.377	15	4.13	0.440	15	4.47[1]	0.607	15	3.97	0.285	15	3.27[2]	0.477	15
Kidney/Body Weight $\bar{x}\times10$	13	7.62	0.647	15	7.87	0.946	15	8.85[2]	1.295	15	8.81[2]	0.658	14	10.44[2]	0.994	14
Kidney/Brain Weight $\bar{x}\times10^{-2}$	13	1.97	0.191	15	2.04	0.337	15	2.13	0.266	15	1.95	0.178	15	1.68[2]	0.228	15

S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

(DATA TAKEN From Submission)

TABLE 5b

Absolute + Relative ORGAN Weights OF [redacted] TREATED FEMALE RATS

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	100 MG/KG/DAY MEAN	S.D.	N	500 MG/KG/DAY MEAN	S.D.	N	1000 MG/KG/DAY MEAN	S.D.	N	2000 MG/KG/DAY MEAN	S.D.	N
Body Weight g	13	275	23.6	15	270	13.5	15	242[2]	23.0	14	230[2]	9.2	15	200[2]	15.6	11
Brain g	13	1.86	0.092	15	1.87	0.124	15	1.89	0.096	14	1.87	0.072	15	1.77	0.141	11
Brain/Body Weight %x10	13	6.81	0.682	15	6.94	0.509	15	7.80[2]	1.042	14	8.15[2]	0.467	15	8.88[2]	0.716	11
Adrenal mg	13	70	15.8	15	76	11.2	15	72	11.7	14	68	15.9	15	64	14.9	11
Adrenal/Body Weight %x10[3]	13	25.5	6.13	15	28.4	4.90	15	30.0	6.26	14	29.6	6.79	15	32.5	8.98	11
Adrenal/Brain Weight %	13	3.76	0.942	15	4.12	0.751	15	3.82	0.634	14	3.61	0.781	15	3.68	0.998	11
Liver g	13	11.07	1.464	15	11.78	1.068	14	12.69[2]	1.112	14	13.37[2]	1.129	15	13.45[2]	0.919	11
Liver/Body Weight %	13	4.05	0.662	15	4.38	0.410	14	5.27[2]	0.590	14	5.80[2]	0.398	15	6.74[2]	0.446	11
Liver/Brain Weight %x10[-2]	13	5.96	0.884	15	6.29	0.704	14	6.74[1]	0.701	14	7.14[2]	0.606	15	7.63[2]	0.785	11
Kidney g	13	2.30	0.221	15	2.32	0.207	14	2.19	0.159	14	2.12[2]	0.107	15	1.73[2]	0.116	11
Kidney/Body Weight %x10	13	8.43	1.086	15	8.63	0.608	14	9.09	0.939	14	9.21[1]	0.504	15	8.67	0.653	11
Kidney/Brain Weight %x10[-2]	13	1.24	0.127	15	1.24	0.130	14	1.16	0.119	14	1.13[1]	0.076	15	0.98[2]	0.113	11
Ovary mg	13	130	33.4	15	136	17.8	15	134	21.9	14	119	19.5	15	96[2]	19.5	11
Ovary/Body Weight %x10[3]	13	4.72	1.253	15	5.06	0.739	15	5.64	1.397	14	5.20	0.913	15	4.77	0.881	11
Ovary/Brain Weight %	13	7.00	1.854	15	7.32	1.098	15	7.10	0.994	14	6.37	0.992	15	5.41[2]	1.050	11

555-001

S.D. - Standard Deviation
N - Number of Animals

*No statistical significance observed

(DATA TAKEN FROM Submission)

In male rats, the absolute kidney weight was increased in 500 mg/kg group whereas that in 2000 mg/kg group was decreased. The kidney/body weight ratios were consistently increased in male of 500 mg/kg or above. A significant decrease in kidney/brain weight was observed in 2000 mg/kg males. In females, significant decreases in absolute kidney weight and the ratios of kidney/brain weight were found in 1000 and 2000 mg/kg groups. The changes in the ratios of kidney/body weight were variable among various treatment groups.

Absolute ovary weight and ovary/brain weight were significantly decreased in 2000 mg/kg females whereas the relative testes weights (testes/body) were increased in 1000 and 2000 mg/kg males.

b. Gross Pathology

Gross pathology data are presented in Tables 6a and 6b.

Increased incidence of granular kidneys were observed in 500 and 1000 mg/kg males relative to the controls. Increased incidences of rounded edge and tan/white foci of the liver were also observed in 500 and 2000 mg/kg males, respectively.

c. Histopathology

The increases in the incidence of histopathology findings are presented in Tables 7a and 7b. The kidney lesions seen in males are further tabulated on Table 8.

Table 8*

Incidence of Kidney Lesions in Male Rats

Doses (mg/kg)	0	100	500	1000	2000
Granular casts	0/10	1/10	5/10	2/20	3/20
Inflammation	0/10	3/10	10/10	7/10	5/10
Regeneration	3/10	4/10	10/10	8/10	7/10
Hyaline droplets	2/10	9/10	10/10	9/10	5/10

* Data taken from submission

TABLE 6a

(DATA TAKEN FROM Submission)

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination, Terminal Sacrifice - MALES

SITE - Observation		0 mg/kg/day (Control)		100 mg/kg/day		500 mg/kg/day		1000 mg/kg/day		2000 mg/kg/day		4000 mg/kg/day	
		DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS*
NUMBER OF ANIMALS EXAMINED		0	15	0	15	0	15	0	15	0	15	1	0
NUMBER WITHIN NORMAL LIMITS		0	8	0	10	0	5	0	5	0	3	0	0
CAVITY, ABDOMINAL													
- Fluid, clear, moderate									1				
EYE													
- Phthisis bulbi, unilateral, png							1						
KIDNEY													
- Granular, bilateral,	- trace	2					6		4		2		
	- mild	1		1		1			1		1		1
- Exudate, suppurative, bilateral, moderate									1				
- Calculi, intrapapillary, unilateral, trace									1				
- Dilated pelvis, unilateral, mild									1		1		
- Discoloration, tan, bilateral, mild									1		1		
- Cyst, unilateral, mild									1				
LIVER													
- Rounded edge, multilobar, diffuse,	- trace								1				
	- mild			2		5			1		1		
- Enlarged, moderate									1				
- Focus/foci, tan/white, multilobar, mild		1							1		7		
- Accentuated lobulations,	- trace			1									
	- mild										2		
	- moderate										1		
- Focus, red, raised, mild											1		
LUNG													
- Nodule			4		1		2		5				1
- Foci, tan/white,	- trace				1								
	- mild				1								
- Congestion, multifocal, mild													
ORAL TISSUES													
- Teeth broken, png			1										
- Thick gingiva, mild			1										
PROSTATE													
- Abscess, moderate									1				

DOS - Deaths and Unscheduled Sacrifices
TS - Terminal Sacrifice
png - Present, no grade
* - Surviving animals sacrificed and discarded

TABLE 66

INCIDENCE OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination, Terminal Sacrifice - FEMALES

SITE - Observation		0 mg/kg/day (Control)		100 mg/kg/day		500 mg/kg/day		1000 mg/kg/day		2000 mg/kg/day		4000 mg/kg/day	
		DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS*
NUMBER OF ANIMALS EXAMINED		0	15	0	15	1	14	0	15	0	15	2	0
NUMBER WITHIN NORMAL LIMITS		0	9	0	12	0	10	0	10	0	9	0	0
CECUM													
- Lumen, exudate, mucoid, moderate						1							
COLON													
- Lumen, exudate, mucoid, moderate						1							
DUODENUM													
- Lumen, exudate, mucoid, moderate						1							
EYE													
- Cornea, scab, unilateral, moderate								1					
ILEUM													
- Lumen, exudate, mucoid, moderate						1							
JEJUNUM													
- Lumen, exudate, mucoid, moderate						1							
KIDNEY													
- Dilated pelvis/hydronephrosis, unilateral,	- mild		2		1		1		1				
	- moderate				1				1				
	- severe												
- Calculi, intrapelvic, unilateral,	- mild		1				1						
	- moderate				1								
LIVER													
- Foci/focus, tan, diffuse/NOS, mild			1						1				
- Accentuated lobulations,	- trace										1		
	- mild										1		
LUNG													
- Foci, tan, mild			1		1		1		1				
- Nodule			1		1		1						
LYMPH NODE, MEDIASTINAL													
- Enlarged, mild					1								

DOS - Deaths and Unscheduled Sacrifices
TS - Terminal Sacrifice
NOS - Not otherwise specified
* - Surviving animals sacrificed and discarded

555-001

(DATA TAKEN FROM Submission)

IRDC

TABLE 7a

Incidence of Microscopic Observations
0 to Termination: Rats
Male

TISSUE / OBSERVATION		0 mg/kg/day (Control)	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Kidney		(10)	(10)	(10)	(10)	(10)	(0)
Cast, granular		0	1	5	2	3	0
	-trace	0	0	2	1	2	0
Cyst, mild	-mild	0	1	3	1	1	0
Hydronephrosis, mild		0	0	0	1	0	0
Inflammation,		0	0	0	1	0	0
	-trace	0	3	10	7	5	0
	-mild	0	0	4	5	4	0
Necrosis, trace		0	1	6	2	1	0
Within normal limits		7	5	0	0	0	0
Regeneration,		3	4	10	2	2	0
	-trace	3	3	3	8	7	0
	-mild	0	1	6	7	5	0
	-moderate	0	0	1	1	2	0
Hyaline droplets*		2	9	10	0	0	0
Liver		(10)	(10)	(10)	(10)	(10)	(0)
Inflammation, trace		1	0	0	2	0	0
Necrosis, mild		0	0	0	0	1	0
Within normal limits		7	10	10	8	9	0
Vacuolation,		2	0	0	0	0	0
	-trace	1	0	0	0	0	0
	-mild	1	0	0	0	0	0

555-001 CODE: () = NUMBER OF ANIMALS EXAMINED

(DATA TAKEN FROM SUBMISSION)

TABLE 76

Incidence of Microscopic Observations
0 to Termination: Rats
Female

TISSUE OBSERVATION		0 mg/kg/day (Control)	100 mg/kg/day	500 mg/kg/day	1000 mg/kg/day	2000 mg/kg/day	4000 mg/kg/day
Liver		(10)	(10)	(10)	(10)	(10)	(0)
Hematopoiesis, extramedullary, trace		1	0	0	0	0	0
Hypertrophy, trace		0	1	0	1	0	0
Inflammation, moderate		1	0	0	0	0	0
Within normal limits		8	9	10	9	10	0
Kidney		(10)	(10)	(10)	(10)	(10)	(0)
Crystals, mild		0	1	0	0	0	0
Cast, hyaline, trace		1	0	0	0	0	0
Hydronephrosis,		3	0	1	2	1	0
	-trace	1	0	0	0	0	0
	-mild	1	0	1	0	1	0
	-moderate	1	0	0	1	0	0
	-severe	0	0	0	1	0	0
Inflammation,		1	0	0	2	1	0
	-trace	1	0	0	1	1	0
	-mild	0	0	0	1	0	0
Within normal limits		6	9	9	6	8	0
Regeneration, trace		0	0	0	0	1	0

555-001 CODE: () = NUMBER OF ANIMALS EXAMINED

*Examined with Mallory-Heidenhain stain

(DATA TAKEN FROM Submission)

The increased incidence of compound-related histopathology lesions were predominantly found in the kidney of treated males of all dose groups. The kidney histopathology findings included granular casts, inflammation, regeneration, and hyaline droplets. These findings seem to be more marked in 500 mg/kg males (Table 8).

DISCUSSION

When groups of rats (15/sex/dose) were fed DEET at dietary concentrations of 0, 100, 500, 1000, 2000, and 4000 mg/kg, the animals at 4000 mg/kg showed marked decreases in food consumption and in body weight. Death also occurred at week 2 of the study. At week 3, the animals in 4000 mg/kg were terminated from the study.

Decreased defecation, reduced motor activity, haunched posture, and labored breathing were observed in animals which were sacrificed *in extremis*.

Decreases in mean body weight, body weight gain, and food consumption were found in all treated males and females of 500 mg/kg or above. Little changes were observed in body weight, food consumption, and body weight gain in 500 mg/kg animals relative to the controls.

Slight decrease in lymphocytes was observed in 1000 and 2000 mg/kg males. In 2000 mg/kg females, increase in hematocrit and erythrocyte and slight decreases in MCH and MCV were found. However, the changes in the hematological parameters could be related to the poor nutritional state.

At terminal sacrifice, gross pathology findings such as granular kidneys in 500 and 1,000 mg/kg males and livers with tan/white foci and/or round edge in 500 and 2000 mg/kg males were found.

Increases in absolute kidney weights in 500 mg/kg males and in absolute and relative liver weights (liver/body and liver/brain) om all dose groups except 100 mg/kg females were seen, and these changes were considered to be compound-related.

Histopathology findings showed increased incidence of kidney lesions, which included granular casts, inflammation, regeneration, and hyaline droplets, in all treated males. The increase in kidney lesions was more marked in 500 mg/kg males than any other treatment groups.

The study was well conducted, and the report was also well written. However, based upon the kidney lesions and changed in organ weights, a NOEL could not be established. In addition, the study was a dose range-finding study. Therefore, this study is classified as Supplementary.

Appendix 1

DEET toxicology review

Page _____ is not included in this copy.

Pages 47 through 49 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

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Reviewed by: Whang Phang, Ph.D. Whang Phang 2/4/88
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DATA EVALUATION REPORT

STUDY TYPE: 90-Day Oral Dose Range Finding Study in Mice

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

RECORD NUMBER: 206238 CASWELL NO.: 346

MRID No.: 40241704 EPA ID No.: 51147-1

SPONSOR: DEET Joint Venture/Chemical Specialties Manufacturers Association, Washington, DC.

TESTING FACILITY: International Research & Development Corp., Mattawan, Michigan.

CITATION: Johnson, D.E. Evaluation of DEET in a 90-Day Oral Dose Range Finding Study in Mice. International Research and Development Corp., Project No.: IRDC 555-002 (June 2, 1987). Submitted by DEET Joint Venture/Chemical Specialties Manufacturers Association. EPA MRID No.: 40241704.

CONCLUSIONS: When groups of CR CD-1 mice (15/sex/dose) were fed DEET at dietary concentrations of 300, 1000, 3000, 6000, and 10000 mg/kg for 13 weeks, the following effects were observed:

1. Markedly decreased food intake and body weight and death during the first week of the study in 6000 and 10000 mg/kg mice which were removed from the study at at week 3.

2. Decreased body weights in 3000 mg/kg males and females.

3. Increased absolute and relative liver weights in 1000 and 3000 mg/kg mice and relative liver weights in 300 mg/kg females.

4. Increased incidence of liver hypertrophy in 3000 mg/kg males and females and in 1000 mg/kg females.

The study has been well conducted, and the report is well written. However, based on liver weight increase in all treated females, a NOEL can not be established. In addition, this study was a dose range finding study. According to the Subdivision F Guidelines, this study is classified as Supplementary.

A. MATERIALS:

1. Test Compound is 98.3% pure technical N, N-diethyl-m-toluamide. The details of the test article are presented in Appendix 1.

2. Test animals: 5-weeks old Charles Rivers CD-1 mice were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan.

B. STUDY DESIGN:

1. Animal assignment

The mice used in this study were selected based on the body weight of those animals which did not lost any weight during pretest period (21 days). The selected animals (with body weights of 26-32 gm for males; 20-26 gm, females) were randomly assigned to the following test groups:

Test Group	Dose in diet (mg/kg)	90-day oral dose range finding study male	female
1 Cont.	0	15	15
2	300	15	15
3	1000	15	15
4	3000	15	15
5	6000	15	15
6	10000	15	15

2. Diet Preparation:

The test compound/diet mixture was prepared weekly with the concentrations adjusted based on mean weekly food consumption measurements. The mixtures were store in stainless steel containers at room temperature. Samples of the mixture were taken for chemical analyses.

The mixture was found to be stable for 21 days, and the test diet preparations were periodically analyzed at weeks 1, 2, 3, 4, 8, and 12. The results indicated that the mean concentrations of the test diets were 94 to 101% of the targeted concentrations.

3. Animals received food and water ad libitum.

4. Statistics: The statistical methods used in this study are presented in Appendix 2.

5. Quality assurance statement was signed.

C. METHODS AND RESULTS:

1. Observations

Animals were inspected twice daily for signs of toxicity and mortality. Daily inspections included an external physical examination, gentle palpation of internal organs, and assessment for abnormal behavior or clinical signs.

Toxicity/Mortality (survival)

The mice in 6000 and 10000 mg/kg groups rejected the test diet as indicated by a sharp drop in food consumption (Table 3a & 3b). The body weights of these animals were significantly decreased (Table 1a & 1b). These animals showed signs of inanition. During the first week of treatment some deaths occured in 10000 mg/kg groups while in the 6000 mg/kg groups death or sacrifice in extremis occured in week 2. Prior to death, the animals in the 6000 and 10000 mg/kg groups showed signs of decreased defecation, haunched posture, hypothermia, tremors, reduced motor activity, labored breathing, partially closed eyes, and yellow material in the anogenital region. The animals in 6000 and 10000 mg/kg groups were sacrificed at week 3.

The survival rates of the animals in other dose groups were comparable to those of the controls. In the 3000 mg/kg group, decreased defecation was observed in most of the males, and hunched posture was also found in 2 females. For the 1000 and 300 mg/kg animals, there were no treatment related differences in clinical signs were observed relative to the controls.

2. Body weight

Animals were weighed weekly during pretest and treatment periods. The mean body weight of the test animals are presented in Tables 1a and 1b.

The decreases in body weights in 6000 and 10000 mg/kg males and females were discussed above. Statistically significant decreases in body weights of 3000 mg/kg males and females were observed. The mean body weights of 300 and 1000 mg/kg mice were comparable between treated and control mice.

The group mean body weight at week 13 and mean body weight changes from pretest period through week 13 are presented in Table 2. Greater than 10% drop in body weight was observe in 3000 mg/kg male and female mice at week 13 relative to the controls.

TABLE 1a

Males: Summary of Body Weight Values*

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	300 MG/KG/DAY MEAN	S.D.	N	1000 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	-2	30	1.7	15	30	1.7	15	30	1.7	15
	-1	30	1.7	15	30	1.5	15	29	1.8	15
	1	31	1.7	15	31	1.7	15	31	1.5	15
	2	32	1.9	15	32	1.8	15	32	1.8	15
	3	32	2.0	15	32	1.9	15	32	2.0	15
	4	33	2.0	15	33	2.5	15	32	2.0	15
	5	34	1.7	15	34	2.1	15	33	2.0	15
	6	34	1.9	15	34	1.8	15	33	1.8	15
	7	35	2.1	15	34	1.9	15	34	1.9	15
	8	35	1.8	15	34	2.1	15	34	1.6	15
	9	35	1.8	15	35	1.9	15	34	2.0	15
	10	35	1.9	15	35	2.2	15	34	1.8	15
	11	35	2.3	15	35	1.8	15	35	1.8	15
	12	35	2.1	15	36	2.2	15	35	2.0	15
	13	36	2.0	15	36	2.0	15	35	1.7	15

Parameters Measured	WEEK OF STUDY	3000 MG/KG/DAY MEAN	S.D.	N	6000 MG/KG/DAY MEAN	S.D.	N	10000 MG/KG/DAY MEAN	S.D.	N
Body Weight grams	-2	30	1.6	15	30	1.8	15	30	1.7	15
	-1	29	1.5	15	29	2.0	15	29	1.6	15
	1	29[2]	2.0	15	22[2]	1.2	11	31[a]	1.6	12
	2	28[2]	3.0	15	22[2]	0.7	2	33[a]	1.4	17
	3	29[2]	2.6	15						
	4	29[2]	2.4	15						
	5	30[2]	2.2	15						
	6	30[2]	2.5	15						
	7	31[2]	2.1	15						
	8	31[2]	2.0	15						
	9	32[2]	2.2	15						
	10	31[2]	2.0	15						
	11	32[2]	2.0	15						
	12	32[2]	1.6	15						
	13	32[2]	2.0	15						

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S.D. - Standard Deviation

N - Number of Animals

[2]Significantly different from the Control group; $p<0.01$

[a]Animals received control diet

* DATA TAKEN FROM SUBMISSION

TABLE 16

Females: Summary of Body Weight Values*

Parameters Measured	WEEK OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	300 MG/KG/DAY MEAN	S.D.	N	1000 MG/KG/DAY MEAN	S.D.	N
Body Weight	-2	24	1.2	15	24	1.3	15	24	1.2	15
grams	-1	23	1.4	15	23	1.3	15	24	1.4	15
	1	25	1.3	15	25	1.4	15	26	1.8	15
	2	26	1.4	15	26	1.6	15	26	1.4	15
	3	26	1.6	15	27	1.3	15	27	1.6	15
	4	27	1.5	15	27	1.2	15	27	1.8	15
	5	27	1.6	15	28	1.5	15	28	1.8	15
	6	28	1.7	15	27	1.6	15	27	1.4	15
	7	28	1.7	15	28	1.7	15	28	1.3	15
	8	28	1.7	15	28	1.8	15	28	1.2	15
	9	29	1.4	15	28	1.6	15	29	1.4	15
	10	29	1.9	15	28	1.5	15	28	1.2	15
	11	29	1.8	15	29	1.9	15	29	1.7	15
	12	29	1.7	15	29	1.8	15	29	1.5	15
	13	29	2.1	15	29	1.8	15	29	1.5	15

Parameters Measured	WEEK OF STUDY	3000 MG/KG/DAY MEAN	S.D.	N	6000 MG/KG/DAY MEAN	S.D.	N	10000 MG/KG/DAY MEAN	S.D.	N
Body Weight	-2	24	1.3	15	24	1.2	15	24	1.2	15
grams	-1	23	1.1	15	23	1.4	15	23	1.1	15
	1	23[2]	2.0	15	18[2]	1.9	14	25[a]	2.0	8
	2	23[2]	2.2	15	19[2]	1.3	5	27[a]	1.1	8
	3	24[2]	2.1	15						
	4	25[2]	1.7	15						
	5	25[1]	1.5	15						
	6	26[2]	1.7	15						
	7	26[2]	1.2	14						
	8	25[2]	1.9	14						
	9	26[2]	2.0	14						
	10	26[2]	2.1	14						
	11	26[2]	1.7	14						
	12	26[2]	1.3	14						
	13	26[2]	2.2	14						

555-002

S.D. - Standard Deviation

N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

[a]Animals received control diet

* DATA TAKEN FROM Submission

Table 2*

Mean Body Weight and Mean Body Weight Change
(percent difference from control)

Dosage Level (mg/kg/day)	Male		Female	
	Week 13	Weeks (-)1-13	Week 13	Weeks (-)1-13
	Mean Body Weight, g	Mean Body Weight Change, g	Mean Body Weight, g	Mean Body Weight Change, g
0 (Control)	36	6	29	6
300	36 (0.0)	6 (0.0)	29 (0.0)	6 (0.0)
1000	35 (- 2.8)	6 (0.0)	29 (0.0)	5 (-16.7)
3000	32 (-11.1)	3 (-50.0)	26 (-10.3)	3 (-50.0)

* Data taken from submission

3. Food consumption and compound intake

Consumption was determined and mean daily diet consumption was calculated. Compound intake was calculated from food consumption and body weight gain data. The data on food consumption and compound intake are presented in Tables 3a and 3b.

Food consumption was calculated on the bases of both g/animal/day and g/kg/day. In 3000 mg/kg males, food consumption was significnatly increased at several measuring periods in 3000 mg/kg group when reported as g/kg/day. No consistent changes in food intake were found in treated females relative to that of the controls.

4. Ophthalmological examination results are not reported.

5. Results of clinical chemistry and hematology studies were not reported.

TABLE 3a

MALE ANIMALS: MEAN FOOD AND COMPOUND CONSUMPTION

OBSERV. PERIODS	0 MG/KG/DAY (CONTROL) FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	300 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	1000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	3000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	5.6	0.70	179.9	0.000	5.4	0.65	175.2	269	5.3	0.73	171.8	881	4.7*	0.81	161.6	2485
2	5.6	0.53	175.9	0.000	5.5	0.36	171.7	293	5.5	0.35	173.0	1006	5.2	0.95	187.7	3484
3	5.5	0.48	168.9	0.000	5.9	0.89	183.6	314	5.6	0.67	174.0	1012	5.7	0.84	195.5†	3630
4	5.7	0.40	174.1	0.000	5.8	0.67	174.7	286	5.5	0.71	168.7	970	5.7	0.74	192.9*	2964
5	5.6	0.62	164.2	0.000	5.7	0.45	168.9	290	5.4	0.42	163.6	969	5.5	0.80	181.5	2842
6	5.7	0.63	167.8	0.000	5.8	0.80	171.5	305	5.6	0.63	168.1	1028	5.7	0.86	190.4	3165
7	5.6	0.41	163.0	0.000	5.4	0.53	156.9	275	5.4	0.49	160.2	953	5.7	1.04	181.4	2893
8	5.6	0.67	161.4	0.000	5.4	0.53	157.3	301	5.4	0.54	160.3	1002	5.7	0.81	182.9	2868
9	5.5	0.42	156.0	0.000	5.5	0.50	158.9	318	5.3	0.52	156.5	976	5.7	0.81	176.6*	2925
10	5.6	0.50	160.5	0.000	5.6	0.58	163.4	309	5.4	0.52	159.2	1017	5.8	1.70	186.4	3179
11	5.7	0.53	162.2	0.000	5.5	0.37	155.0	284	5.3	0.56	151.6	953	5.7	0.77	181.3*	2933
12	5.3	0.38	150.1	0.000	5.4	0.29	150.8	292	5.2	0.31	150.2	990	5.9	1.87	184.3	3063
13	5.4	0.35	150.6	0.000	5.5	0.53	154.8	308	5.6	0.50	160.9*	1072	5.7	1.01	175.2*	2862

OBSERV. PERIODS	6000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	10000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	2.3†	0.81	103.1†	3173	3.3†	1.11	107.8†	5526
2	3.9	0.00	175.3	5394	6.1†	0.32	188.7	0.000[a]

555-002

OBSERV. - Observation
ANIM - Animal
STD DEV - Standard deviation
CMPD - Compound consumption

[a]Animals received control diet

*Significant at 0.05; †Significant at 0.01

TABLE 36

FEMALE ANIMALS: MEAN FOOD AND COMPOUND CONSUMPTION

OBSERV. PERIODS	0 MG/KG/DAY (CONTROL) FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	300 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	1000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	3000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	5.5	1.19	220.4	0.000	5.4	0.79	215.3	308	5.1	0.86	198.5	946	4.7	0.76	196.9	2817
2	5.8	2.04	223.4	0.000	5.8	1.09	220.4	307	5.2	0.99	200.0	1007	4.8	0.78	206.0	3138
3	5.7	1.13	215.9	0.000	6.0	1.01	224.3	312	5.9	0.99	220.5	1111	5.3	1.11	220.5	3359
4	6.5	2.25	246.4	0.000	6.9	1.94	254.0	338	5.8	0.96	212.8	964	5.8	1.25	232.1	3141
5	5.8	1.19	216.3	0.000	6.1	0.69	220.4	259	5.5	0.62	201.0	942	5.2	0.89	204.7	2633
6	6.2	1.96	224.5	0.000	6.1	0.97	223.4	304	5.5	0.95	199.5	994	5.1	0.56	197.7	2887
7	5.9	1.54	211.1	0.000	6.1	1.23	216.0	290	5.3	0.69	190.4	953	5.2	0.94	200.4	3035
8	6.3	2.11	226.5	0.000	6.3	1.47	225.7	313	5.7	1.07	205.7	1079	5.1*	0.46	201.6	3012
9	5.7	0.97	196.8	0.000	6.0	0.80	210.4	280	5.5	0.64	192.6	934	5.1	0.57	195.0	2918
10	6.0	1.36	207.9	0.000	6.2	0.91	219.8	313	5.6	1.01	190.8	1033	5.1	0.58	196.6	3023
11	5.9	1.42	202.8	0.000	6.1	0.83	211.3	288	5.5	1.13	193.4	971	5.4	1.01	210.3	3207
12	5.3	0.69	180.4	0.000	5.8	0.83	201.4	285	5.4	0.59	189.0	977	5.0	0.51	193.6	2768
13	5.5	0.65	186.3	0.000	6.4	1.36	220.6*	328	5.7	0.94	196.5	1041	5.8	0.88	231.9*	3594

OBSERV. PERIODS	6000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY	10000 MG/KG/DAY FOOD G/ ANIM/ DAY	STD DEV	G/ KG/ DAY	CMPD MG/ KG/ DAY
1	2.3+	0.85	131.5+	3763	2.8+	1.26	111.1+	5296
2	3.5	1.29	189.6	5424	5.5	0.40	203.6	0.000[a]

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OBSERV. - Observation
ANIM - Animal
STD DEV - Standard deviation
CMPD - Compound consumption
[a]Animals received control diet

* Significant at 0.05 ; + Significant at 0.01

(DATA TAKEN From Submission)

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs in addition were weighed.

X		X		X	
	Digestive system		Cardiovasc./Hemat.		Neurologic
| |	Tongue	| |	.Aorta*	|xx|	.Brain*†
| |	.Salivary glands*	|x|	.Heart*	| |	Periph. nerve*#
| |	.Esophagus*	|x|	.Bone marrow*	|x|	Spinal cord (3 levels)*#
| |	.Stomach*	|x|	.Lymph nodes*	|x|	.Pituitary*
| |	.Duodenum*	|s|	.Spleen*	| |	Eyes (optic n.)*#
| |	.Jejunum*	|x|	.Thymus*		Glandular
| |	.Ileum*		Urogenital	|x|	.Adrenals*
| |	.Cecum*	|xx|	.Kidneys*†	| |	Lacrimal gland#
| |	.Colon*	| |	.Urinary bladder*	| |	Mammary gland*#
| |	.Rectum*	|xx|	.Testes*†	|x|	.Parathyroids*††
|xx|	.Liver*†	|x|	Epididymides	|x|	.Thyroids*††
| |	Gall bladder*#	| |	Prostate		Other
|x|	.Pancreas*	| |	Seminal vesicle	|x|	Bone*#
	Respiratory	|x|	Ovaries*†	| |	Skeletal muscle*#
| |	.Trachea*	| |	.Uterus*	| |	Skin*#
|x|	.Lung*			|x|	All gross lesions and masses*
	Nose°				
	Pharynx°				
	Larynx°				

* Required for subchronic and chronic studies
° Required for chronic inhalation
In subchronic studies, examined only if indicated by signs of toxicity or target organ involvement
† Organ weights required in subchronic and chronic studies
†† Organ weight required for non-rodent studies

a. Organ Weight

Absolute and relative organ weights (organ/body & organ/brain) are presented in Table 4.

In treated males, a slight decrease in absolute kidney weight was observed in 3000 mg/kg mice. Increases in absolute and relative liver weights were found in all treated males, and those of 1000 and 3000 mg/kg groups were significantly different from that of the controls.

In treated females, significnat decreases in absolute brain and kidney weights were observed in 3000 mg/kg mice. The absolute and relative liver weights of all treated females were significantly increased relative to the controls.

TABLE 4

Summary of Organ Weight Values

Parameters Measured	DAY OF STUDY	0 MG/KG/DAY (CONTROL) MEAN	S.D.	N	300 MG/KG/DAY MEAN	S.D.	N	1000 MG/KG/DAY MEAN	S.D.	N	3000 MG/KG/DAY MEAN	S.D.	N
Males:													
Body Weight g	90	35	3.3	15	35	2.5	15	35	2.2	15	33	2.3	15
Brain g	90	0.49	0.031	15	0.51	0.034	15	0.49	0.043	15	0.49	0.037	15
Brain/Body Weight %x10	90	14.4	1.48	15	14.6	1.59	15	14.1	1.56	15	15.0	1.18	15
Kidney g	90	0.72	0.084	15	0.72	0.086	15	0.68	0.072	15	0.64[1]	0.068	15
Kidney/Body Weight %	90	2.09	0.304	15	2.06	0.209	15	1.98	0.179	15	1.95	0.200	15
Kidney/Brain Weight $\%x10^{-2}$	90	1.5	0.17	15	1.4	0.17	15	1.4	0.26	15	1.3	0.14	15
Liver g	90	1.93	0.218	15	2.10	0.166	15	2.44[2]	0.298	15	2.79[2]	0.237	15
Liver/Body Weight %	90	5.59	0.601	15	5.98	0.340	15	7.05[2]	0.647	15	8.53[2]	0.641	15
Liver/Brain Weight $\%x10^{-2}$	90	3.91	0.456	15	4.14	0.501	15	5.07[2]	0.783	15	5.69[2]	0.385	15
Testis g	90	0.27	0.039	15	0.27	0.050	15	0.26	0.036	15	0.26	0.048	15
Testis/Body Weight %x10	90	7.96	0.994	15	7.70	1.486	15	7.48	1.088	15	8.07	1.616	15
Testis/Brain Weight $\%x10^{-1}$	90	5.55	0.649	15	5.30	1.037	15	5.33	0.677	15	5.37	0.936	15
females:													
Body Weight g	90	30	2.7	15	29	1.8	14	29	1.7	15	27[2]	1.8	14
Brain g	90	0.51	0.043	15	0.50	0.027	15	0.49	0.032	15	0.47[1]	0.038	14
Brain/Body Weight %x10	90	17.4	1.84	15	17.2	1.52	14	17.0	1.57	15	17.8	1.76	14
Kidney g	90	0.49	0.044	15	0.48	0.030	15	0.45	0.051	15	0.42[2]	0.044	14
Kidney/Body Weight %	90	1.65	0.162	15	1.68	0.096	14	1.56	0.165	15	1.56	0.201	14
Kidney/Brain Weight $\%x10^{-2}$	90	1.0	0.12	15	1.0	0.08	15	0.9	0.09	15	0.9	0.13	14
Liver g	90	1.66	0.256	15	1.79	0.145	15	1.95[2]	0.161	15	2.34[2]	0.254	14
Liver/Body Weight %	90	5.59	0.613	15	6.19[2]	0.444	14	6.77[2]	0.525	15	8.74[2]	1.000	14
Liver/Brain Weight $\%x10^{-2}$	90	3.25	0.569	15	3.61[1]	0.304	15	4.00[2]	0.368	15	4.95[2]	0.613	14

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S.D. - Standard Deviation
N - Number of Animals

[1]Significantly different from the Control group; $p<0.05$

[2]Significantly different from the Control group; $p<0.01$

(DATA TAKEN FROM submission)

The increases of absolute liver weight in 1000 and 3000 mg/kg males and females and of relative weights in all treated mice were statistically significantly different from those of the controls.

b. Gross Pathology

Gross pathology findings are presented in Table 5a & 5b. Increased incidence of mottled and accentuated lobulations of the liver was observed in males and females of 6000 mg/kg group.

c. Microscopic Pathology

Relevant histopathology findings are abstracted and presented in Table 6. There was an increased incidence of liver hypertrophy in males of 1000 and 3000 mg/kg groups and in 3000 mg/kg females relative to that of the controls.

DISCUSSION

When groups of CR CD-1 mice (15/sex/dose) were fed DEET at dietary concentrations of 300, 1000, 3000, 6000, and 10000 mg/kg, the animals in 6000 and 10000 mg/kg groups showed marked decreases in food intake and body weight during the first week of the study. Also some mice died during that time. The animals clearly could not tolerate 6000 and 10000 mg/kg dose levels, and these animals were sacrificed and removed from the study at week 3.

Early in the study, animals in 3000 mg/kg group showed signs of decreased defecation. No treatment-related clinical signs were observed in 300 and 1000 mg/kg groups.

Mean body weights of 3000 mg/kg males and females were significantly decreased, and at week 13 the body weights of these animals were 10 to 11% lower than that of the controls. However, the food consumption data showed no consistent difference between treated and control animals.

At terminal sacrifice, gross pathology data showed increased incidence of mottled liver and accentuated lobulations of liver in both males and females of 6000 and 10000 mg/kg groups. These findings were observed in animals which died in early part of the study. It should be noted that the surviving animals of these two dose groups were sacrificed at week 3 and discarded.

Absolute and relative liver weights (liver/body & liver/brain)

TABLE 5a

SUMMARY OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination, Terminal Sacrifice of Males

SITE - Observation		0 mg/kg/day (Control)		300 mg/kg/day		1000 mg/kg/day		3000 mg/kg/day		6000 mg/kg/day		10000 mg/kg/day	
		DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS*	DOS	TS*
NUMBER OF ANIMALS EXAMINED		0	15	0	15	0	15	0	15	13	0	3	0
NUMBER WITHIN NORMAL LIMITS		0	13	0	14	0	13	0	15	0	0	0	0
EAR													
- Notched, unilateral, mild					1								
EYE													
- Cloudy, cornea, unilateral, mild							1						
KIDNEY													
- Pitted, unilateral, mild			1										
LIVER													
- Accentuated lobulation, generalized, mild										4			
- Mottled, diffuse/multilobar,	- mild									2			
	- moderate									2			
LUNG													
- Congestion, generalized, mild												1	
PREPUTIAL GLAND													
- Abscess, unilateral, moderate			1										
SOFT TISSUE, FOOT													
- Amputation, png					1		1						
STOMACH, GLANDULAR													
- Mucosa, erosions, foci, dark/red/black,	- mild									5		1	
	- moderate									2		1	
	- severe											1	

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DOS - Deaths and Unscheduled Sacrifices
TS - Terminal Sacrifice
png - Present, no grade
* - Surviving animals sacrificed and discarded

TABLE 56

SUMMARY OF MACROSCOPIC OBSERVATIONS
Deaths and Unscheduled Sacrifices, 0 to Termination, Terminal Sacrifice of Females

SITE - Observation		0 mg/kg/day (Control)		300 mg/kg/day		1000 mg/kg/day		3000 mg/kg/day		6000 mg/kg/day		10000 mg/kg/day	
		DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS*	DOS	TS*
NUMBER OF ANIMALS EXAMINED		0	15	0	15	0	15	1	14	11	0	7	0
NUMBER WITHIN NORMAL LIMITS		0	15	0	14	0	12	1	12	0	0	0	0
ALL TISSUES													
- Autolysis, mild										1			
EYE													
- Cloudy cornea, unilateral, mild					1								
LIVER													
- Mottled, multilobar/diffuse,	- mild									2			
	- moderate									1			
- Accentuated lobulations, diffuse,	- mild									2			
	- moderate									1			
- Pale, moderate												1	
LUNG													
- Congestion, multifocal, mild										2			
- Nodule							1						
OVARY													
- Cyst, unilateral, mild							2						
SKIN													
- Scab, mild										1			
STOMACH, GLANDULAR													
- Mucosa, erosions, foci, black/dark red,	- mild									5		5	
	- moderate											2	
TAIL													
- Necrotic, png									2				
URINARY BLADDER													
- Hemorrhage, ecchymotic, focal, moderate										1			

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DOS - Deaths and Unscheduled Sacrifices
TS - Terminal Sacrifice
png - Present, no grade
* - Surviving animals sacrificed and discarded

TABLE 6

Incidence of Microscopic Observations
0 to Termination: Mice

(DATA TAKEN From Submission)

TISSUE OBSERVATION		0 mg/kg/day (Control)	100 mg/kg/day	1000 mg/kg/day	3000 mg/kg/day	6000 mg/kg/day	10000 mg/kg/day
Female							
Kidney		(10)	(10)	(10)	(10)	(0)	(0)
Cyst, trace		0	1	0	0	0	0
Cast, hyaline, trace		0	0	0	1	0	0
Inflammation,		4	1	0	1	0	0
	-trace	3	1	0	0	0	0
	-mild	1	0	0	1	0	0
Within normal limits		5	8	10	9	0	0
Regeneration, trace		1	1	0	0	0	0
Liver		(10)	(10)	(10)	(10)	(0)	(0)
Hypertrophy,		0	0	3	10	0	0
	-trace	0	0	1	6	0	0
	-mild	0	0	2	3	0	0
	-moderate	0	0	0	1	0	0
Inflammation, trace		0	0	0	2	0	0
Within normal limits		10	10	7	0	0	0
Vacuolar change, mild		0	0	0	1	0	0
Male							
Kidney		(10)	(10)	(10)	(10)	(0)	(0)
Cyst, trace		1	0	0	0	0	0
Cast, hyaline, trace		1	0	0	0	0	0
Inflammation, trace		5	2	3	1	0	0
Within normal limits		5	8	7	9	0	0
Regeneration, trace		1	0	0	1	0	0
Liver		(10)	(10)	(10)	(10)	(0)	(0)
Hypertrophy,		0	0	0	9	0	0
	-trace	0	0	0	2	0	0
	-mild	0	0	0	7	0	0
Inflammation,		2	0	0	0	0	0
	-trace	1	0	0	0	0	0
	-mild	1	0	0	0	0	0
Necrosis, mild		1	0	0	0	0	0
Within normal limits		8	10	10	1	0	0

555-002 CODE: () = NUMBER OF ANIMALS EXAMINED

were increased in animals of 1000 and 3000 mg/kg groups, and similar increases were also found in 300 mg/kg females. The increased liver weight was considered to be biologically significant.

Increased incidences of liver hypertrophy were observed in 3000 mg/kg males and in 1000 mg/kg and 3000 mg/kg females.

Based on increased liver weight in all treated females, a NOEL can not be established. In addition, this study was a dose range-finding study. According to the Subdivision F Guidelines, this study is classified as Supplementary.

Appendix I

DEET toxicology review

Page _____ is not included in this copy.

Pages 66 through 68 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

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