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CASWELL FILE

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OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MAR 23 1990

MEMORANDUM

SUBJECT: DEET: Review of a two-generation reproduction in rats and
a 90-day dose-range finding study in hamsters

Caswell No. 346 HED Project NO. 0-0837
MRID No. 413441-01 (90-day Hamster study)
409790-01 (2-generation reproduction in rats)
EPA Record No. 260700

TO: Donna Williams, PM Team (17)
Special Review and Re-registration Division (H5705C)

FROM: Whang Phang, Ph.D. *Whang Phang 3/16/90*
Pharmacologist
HFAS/Tox. Branch II/ HED (H5709C)

THROUGH: K. Clark Swentzel, Section Head *K. Clark Swentzel 3/16/90*
and
Marcia van Gemert, Ph.D. *M. van Gemert 3/19/90*
Branch Chief
HFAS/Tox. Branch II/ HED (H5709C)

Toxicology Branch II has been requested to review a 2-generation reproduction study in rats, a 90-day dose-range finding study in hamsters, a mouse oncogenicity study, and a rat teratology study on Deet by Special Review and Re-registration Division. These studies were listed under the same Data Review Record. 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 dose-range finding study in hamsters are 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 has been reviewed first while the mouse oncogenicity and the rat teratology studies will be reviewed in a later date. The data evaluation reports of the two evaluated studies are attached, and the conclusions are as follows:

- 1). 2-generation reproduction study in rats: 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 classified as core minimum.

- 2). 90-day dose-range finding study in hamsters: 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.

Reviewer: Whang Phang, Ph.D. *Whang* 3/16/90
HFAS/Tox. Branch II (H7509C)

Secondary Reviewer: K. Clark Swentzel, Section Head *K. Clark Swentzel*
HFAS/Tox. Branch II (H7509C) 5/16/90

DATA EVALUATION REPORT

Study Type: 90-Day feeding study in hamster (Dose-range finding study)

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

Caswell No. 346

HED Proj. No. 0-0837

MRID No. 413441-01

EPA Record No. 260700

EPA ID No. CSMA TF

Sponsor: DEET Joint Venture/Chemical Specialties Manufacturers Association

Testing Facility: International Research and Development Corp.
500 N. Main
Mattawan, Michigan 49071

Citation: Goldenthal, E.I. (1989) Evaluation of DEET in a 90-day dose-range finding study in hamsters. International Research and Development Corp.; Lab. Project No. 555-012. Oct. 25, 1989

Conclusion: In this study, 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 the data requirements for a 90-day feeding study in rodent (Guideline No. 82-1) and is classified as core minimum.

Methods and Materials

Test article: Technical DEET (98.3%) was "a mixture consisting of equal parts of four representative production runs" supplied by four manufacturers. The test article was a pale yellow liquid and assigned the ID No. IRDC 8812B at the testing laboratory.

Test animals: Groups of 35 days old Golden Syrian VAF/Plus^(R) hamsters (96 males and 97 females) were obtained from Charles River Lab., Inc. Montreal, Canada. These hamsters were acclimated to the laboratory conditions for 21 days, during when they were given detailed examinations and were observed daily for signs of abnormality.

Study Design

1. Animal assignments: All hamsters were weighed at 10 days and again at 7 days before the initiation of the study. Any hamster whose weight gain during this period or any hamster whose absolute body weight at the second weighing was outside of $\pm 20\%$ of population mean was not included in the test. Seventy-five males (body weight 105-131 gm) and 75 females (body weight 105-131 gm) were selected and randomly assigned to the following treatment groups:

<u>Dosage Levels</u> ppm	<u>Number of Animals</u>	
	<u>Males</u>	<u>Female</u>
(control) 0	15	15
1,000	15	15
5,000	15	15
10,000	15	15
15,000	15	15

The test hamsters were housed individually.

2. Test article administration: The animals received the test chemical in the diet. Although the main route of human exposure to DEET is by dermal route, there are two reasons for selecting oral administration of DEET: (1) the existing toxicity indicate that oral route exposure is just as toxic as that with dermal exposure and (2) a practical consideration.

The test diet was prepared by first preparing a premix for each concentration with a portion of the required amount of ground diet. The premix was then blended with the additional required amount of the diet to yield the intended concentrations of 1,000, 5,000, 10,000, and 15,000 ppm of the test article. The test diet

was prepared weekly. Samples were taken and tested for homogeneity and stability. The test chemical concentration in the diet was determined with samples taken on weeks 2 through 4, 8 and 12. The prepared test diets were stored at room temperature in stainless steel containers.

3. Observations: The test animals were observed for any clinical signs of toxicity twice daily. External physical examination which included gentle palpation of internal organs and assessment for abnormal behavior were conducted weekly.
4. Body weight and food consumption: Individual body weight measurements were determined at pretest and weekly during the study. Individual food and compound consumptions were also determined weekly throughout the study period.
5. Hematology and biochemical analyses: At the 13th week of the study, blood samples were collected from 10 hamsters/sex/dose. These animals were fasted overnight (for approximately 16 hrs) prior to sample collection.

Hematology: The following hematological parameters were measured:

erythrocyte count	hemoglobin
leukocyte count	differential leukocyte count
hematocrit	platelet
reticulocyte count	Mean corpuscular volume (MCV)
Mean corpuscular hemoglobin (MCH)	Mean corpuscular hemoglobin concentration (MCHC)

Clinical chemistry: The following biochemistry parameters were determined:

sodium	potassium
chloride	calcium
phosphorus	total bilirubin
aspartate aminotransferase (AST) (SGOT)	alanine aminotransferase (ALT) (SGPT)
urea nitrogen	creatinine
total protein	albumin
globulin	glucose

6. Pathology: At the end of 13 weeks, all animals were weighed and sacrificed.
 - a. Necropsy: A thorough external examination was conducted on each animal. The contents of the abdominal, thoracic, and cranial cavities were examined.

- b. Organ weights: The following organs were removed, trimmed free of fat, and weighed:

adrenals	liver
brain	ovaries
kidneys	testis

- c. Histopathology examination: A full complement of organs and tissues of 10 hamsters/sex were processed and microscopically examined. The animals were randomly selected from the controls and the high dosage groups. In Addition, epididymides of all males in all dose groups, and liver, kidney, and testis from 1000, 5000, and 10000 ppm groups were examined. Mallory-Heidenhain stain (for hyaline droplets) was also applied for microscopic examination for kidneys from 10 selected animals in each dose group.

A full complement of organs and tissues consisted of the following:

adrenals	lung with mainstem and bronchi
bone marrow	lymph nodes (mediastinal and mesenteric)
brain	pancreas
ovary	pituitary
testis with epididymis	spleen
heart	thymic region
spinal cord (entire)	thyroid/parathyroid
kidneys	
liver	

7. Statistics: Analysis of variance (one way classification) and bartlett's test were use to analyze values of the body weights, food consumption, hematology, clinical chemistry, and absolute and relative organ weights.

T-Statistic (for equal or unequal variance) as described by Torrie and Ostle was used to compared the values of the treatment to those of the controls. The significance of difference was determined using Dunnett's multiple comparison tables.

All statistical tests were two-tails, and the level of significance was set at $p < 0.05$ and $p < 0.01$.

8. Quality assurance: A quality assurance statement was signed and included in the report.

Results

1. Clinical observation: Clinical signs such as labored breathing, decreased defecation, decreased activity, and pale skin were reported to be seen frequently in the 15,000 ppm animals which died during the test. Other findings were comparable between treated and control animals.
2. Survival rates: The survival rates were comparable among the animals in 10,000 ppm or less groups and controls. There were 3 and 4 deaths in 15,000 ppm males and females, respectively (Table 1).

Table 1*
Survival Rates of DEET Treated Hamsters at 13 Weeks

<u>Dose Level (ppm)</u>	<u>Males</u>	<u>Females</u>
(control) 0	15/15	15/15
1,000	15/15	15/15
5,000	14/15	15/15
10,000	15/15	15/15
15,000	12/15	11/15

* Table excerpted from the report (IRDC No. 555-012; page 24).

3. Body weights: The mean body weight values were excerpted from the report and presented in Table 2. The results showed that for males which received 5,000 ppm DEET or more, there was a consistent decrease in body weight relative to the controls throughout the entire test period. The decrease was statistically significant for 15,000 ppm males during the duration of treatment (Table 2). At 13 week the decrease in 5,000, 10,000, and 15,000 ppm males was greater than 10% of the controls.

For females, the animals at 10,000 ppm and 15,000 ppm showed statistically significant drop in body weight during the study (Table 2).

4. Food consumption: The food consumption data indicated that there was a decrease in food intake in males which received 5,000 ppm or more and in females at 10,000 and 15,000 ppm (Table 3). The decrease in food intake in 15,000 ppm males and females was greater than 10%.
5. Test diet analysis: The samples throughout the study showed the prepared test diets "at levels of 1,000, 5,000, 10,000, and 15,000 ppm contained 99, 100, 98, and 99% of the respective target concentrations". The compound in the diet was found to be stable for at least 10 days at room temperature.

6. Compound intake: The average compound intake during 13 week of the study was presented below:

Concentrations in the diet (ppm)	Average compound intake(mg/kg/day)	
	Male	Females
(control) 0	0	0
1,000	61	61
5,000	304	305
10,000	611	636
15,000	940	939

7. Hematology: There sporadic changes in certain parameters, but these changes were not consistent and did not show any dose-relationship. Therefore, there were no treatment related changes in all parameters examined.
8. Clinical chemistry: In 15,000 ppm males and females, there was a statistically significant increase in potassium level. Additional compound related changes were not seen. The values for potassium were excerpted from the report and presented below:

Dose level (ppm)	Potassium (mEq/L)	
	Males	Females
(Control) 0	6.7 ± 0.46	7.0 ± 0.55
1,000	7.3 ± 0.86	7.2 ± 0.63
5,000	7.1 ± 0.78	6.9 ± 0.44
10,000	7.3 ± 0.46	7.0 ± 0.20
15,000	7.8 ± 0.60*	7.7 ± 0.56*

* Significantly different from control; $p < 0.05$

9. Pathology

- a. Macroscopic: Small testes and epididymides were seen in both the controls and the treated animals, but the incidence was increased in 10,000 and 15,000 ppm males (Table 4). These findings were compound-related. Other macroscopic findings were not compound-related (Table 4).
- b. Organ weights: The relevant organ weights were excerpted from the report and presented below:

Summary of Selective Organ Weights		
ppm	testis (g)	testis/brain (%)
(Control) 0	2.08 ± 0.966	185.30 ± 88.252
1,000	2.12 ± 0.906	190.88 ± 85.083
5,000	2.22 ± 0.983	201.69 ± 89.406
10,000	1.23 ± 0.783*	110.59 ± 71.265
15,000	1.17 ± 0.859*	108.89 ± 83.047

* Significantly different from the controls; $p < 0.05$

The absolute testis weight of 10,000 and 15,000 ppm males was significantly decreased ($p < 0.05$) from that of the controls. This finding was consistent with the gross pathology observation for small testes. In addition, the ratios of testis weight/brain weight and testes/body weight were decreased for these two treatment groups relative to that of the controls. There were also increases in the ratios of liver/body weight and kidney weight/body weight, but these increases were secondary to the decreases in the body weights of these animals. Other organ weights were comparable to those of the controls.

- d. Histopathology: Increased incidence of tubular degeneration in the testes and of accumulation of cellular luminal debris in the epididymides of 10,000 and 15,000 ppm males were found. Although these observations were also found in the control males, but the degree of injury in these two high-dose groups was more severe (Table 5). The effects seen in testes and epididymides were consistent with the macroscopic findings, and they were compound related. The report described the testicular tubular degeneration as characterized by the presence of degenerating tubular epithelial cells within the seminiferous tubules of the testes. This lesion was bilateral and ranged from trace to moderate in severity. The hamsters with testicular degeneration also had small epididymides with macroscopic examination. This reviewer agreed with the study author that epididymal finding was secondary to the testicular alteration. Other histologic findings were also seen, but these findings were infrequent and did not show any dose-related effects. They were not considered to be compound-related effects.

Discussion

There were two objectives in conducting this 90-day feeding study in hamsters. The primary goal was to determine if a kidney lesion which characterized by hyaline droplets formation in the renal tubules of male rats treated with DEET for 90 day would occur in male or female hamsters. If the kidney lesion was not seen in the DEET treated hamsters, the other objective was to obtain results which could be used for selecting doses for a chronic feeding study on hamsters.

In this study, 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 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 study satisfies the data requirements for a 90-day feeding study in rodent (Guideline No.: 82-1) and is classified as core minimum.

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TABLE 2*

Males: Summary of Body Weight Values

Parameters Measured	WEEK OF STUDY	0 PPM (CONTROL)			1,000 PPM			5,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight grams	ALLOC	119	7.8	15	117	7.6	15	118	7.9	15
	1	123	6.9	15	120	8.7	15	112 ²	7.6	15
	2	128	6.3	15	126	9.9	15	119 ²	9.4	15
	3	129	7.7	15	128	9.5	15	122	9.9	15
	4	140	9.5	15	136	11.8	15	133	11.9	15
	5	148	10.0	15	142	12.3	15	138	13.0	15
	6	150	11.4	15	140	13.5	15	142	13.3	15
	7	156	12.3	15	152	13.2	15	147	14.9	15
	8	161	13.1	15	158	13.8	15	151	16.6	15
	9	165	12.8	15	165	14.9	15	155	19.0	14
	10	172	14.1	15	169	14.8	15	159	20.2	14
	11	175	12.8	15	174	15.1	15	162	22.2	14
	12	178	14.1	15	176	15.7	15	161	24.3	14
13	174	14.9	15	171	15.2	15	156	26.4	14	

Parameters Measured	WEEK OF STUDY	10,000 PPM			15,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N
Body Weight grams	ALLOC	117	8.1	15	119	8.0	15
	1	104 ²	9.2	15	89 ²	10.3	15
	2	114 ²	7.7	15	88 ²	21.3	15
	3	120 ¹	7.8	15	103 ²	13.7	12
	4	131	17.8	15	120 ²	12.4	12
	5	139	15.0	15	128 ²	10.8	12
	6	143	18.4	15	133 ¹	11.9	12
	7	146	20.1	15	135 ²	13.3	12
	8	152	16.2	15	137 ²	15.2	12
	9	157	17.2	15	142 ²	15.7	12
	10	159	16.6	15	141 ²	20.9	12
	11	162	16.2	15	145 ²	19.6	12
	12	159 ¹	15.3	15	151 ²	21.1	12
13	152 ¹	16.8	15	143 ²	23.3	12	

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Females: Summary of Body Weight Values*

Parameters Measured	WEEK OF STUDY	0 PPM (CONTROL)			1,000 PPM			5,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Body Weight grams	ALLOC	120	9.9	15	118	9.9	15	120	9.8	15
	1	131	9.6	15	126	12.4	15	121	15.9	15
	2	139	10.5	15	137	11.9	15	132	14.3	15
	3	144	12.2	15	143	12.1	15	141	10.0	15
	4	153	13.2	15	154	12.2	15	151	12.4	15
	5	162	14.1	15	161	13.8	15	157	13.0	15
	6	169	13.8	15	167	15.9	15	165	9.6	15
	7	173	14.8	15	170	16.5	15	169	10.0	15
	8	179	13.6	15	173	15.8	15	173	10.9	15
	9	183	12.8	15	180	17.4	15	179	12.6	15
	10	183	17.7	15	184	16.2	15	183	13.0	15
	11	185	20.3	15	186	16.0	15	185	13.5	15
	12	191	18.0	15	189	16.8	15	186	15.7	15
13	186	12.7	15	182	15.6	15	180	18.0	15	

Parameters Measured	WEEK OF STUDY	10,000 PPM			15,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N
Body Weight grams	ALLOC	115	9.5	15	123	8.9	15
	1	109 ²	10.7	15	93 ²	13.8	15
	2	122 ²	9.7	15	104 ²	21.0	12
	3	127 ²	9.9	15	120 ²	15.5	11
	4	142	13.9	15	138 ¹	10.9	11
	5	149 ¹	14.5	15	146 ¹	10.2	11
	6	153 ²	14.7	15	152 ²	12.0	11
	7	154 ²	20.6	15	155 ¹	12.6	11
	8	157 ²	26.0	15	156 ²	12.7	11
	9	163 ¹	27.6	15	160 ²	9.3	11
	10	168 ¹	21.9	15	165 ¹	9.0	11
	11	171	19.2	15	168 ¹	10.4	11
	12	173 ¹	19.6	15	170 ²	9.8	11
13	168 ²	17.7	14	158 ²	10.3	11	

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

¹Significantly different from the Control group; p<0.05

²Significantly different from the Control group; p<0.01

* TABLE EXCERPTED FROM THE REPORT (IRDL No. 555-012)

TABLE 3*

Males: Summary of Food Consumption Values

Parameters Measured	WEEK OF STUDY	0 PPM (CONTROL)			1,000 PPM			5,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption g/animal/day	1	9.8	1.21	12	9.2	1.01	12			
	2	8.2	0.71	15	8.1	0.80	14	7.3 ²	1.06	11
	3	8.7	0.74	15	9.3 ¹	0.94	15	7.9	1.27	15
	4	10.2	1.29	15	9.6	1.30	15	9.8 ²	0.67	15
	5	9.8	0.89	15	9.3	1.03	15	9.8	1.20	14
	6	8.5	1.15	15	9.0	0.80	15	9.2	1.08	15
	7	9.5	0.95	15	8.9	0.73	14	8.5	0.87	15
	8	9.3	0.83	15	9.1	1.15	15	8.9	1.16	15
	9	9.2	0.77	15	9.4	0.75	15	8.5	1.44	15
	10	9.6	1.20	15	9.4	0.92	15	8.8	1.74	14
	11	9.4	1.31	15	9.5	1.04	15	8.8	1.51	14
	12	9.3	1.44	15	8.8	1.24	15	9.1	1.92	14
	13	7.6	1.50	15	7.5	1.00	14	8.1	1.78	14
							6.9	1.69	12	

Parameters Measured	WEEK OF STUDY	10,000 PPM			15,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption g/animal/day	1	6.0 ²	3.14	14			
	2	9.0 ¹	0.94	13	4.4 ²	3.17	11
	3	9.8 ²	1.10	15	5.6	3.69	10
	4	10.0	2.37	15	9.2	2.15	12
	5	9.5	1.39	15	10.4	1.45	12
	6	8.3	1.40	15	9.4	1.33	12
	7	8.5 ¹	1.12	15	8.9	1.45	12
	8	8.8 ¹	0.50	15	8.1 ²	1.11	11
	9	9.7	1.19	14	8.3 ¹	1.42	12
	10	8.3 ¹	1.54	15	8.3	2.50	12
	11	8.9	1.33	15	8.0 ¹	1.61	9
	12	7.6 ¹	1.86	16	8.0	2.43	12
	13	6.6	1.15	12	8.9	1.83	12
				6.9	1.64	12	

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Females: Summary of Food Consumption Values

Parameters Measured	WEEK OF STUDY	0 PPM (CONTROL)			1,000 PPM			5,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption g/animal/day	1	11.3	1.62	15						
	2	9.8	1.12	15	10.3	1.65	14	8.2 ¹	4.59	12
	3	10.6	1.07	14	10.0	1.48	13	8.5	2.54	14
	4	11.1	1.47	15	12.1 ²	1.16	15	12.2 ²	0.91	15
	5	10.7	1.19	15	11.5	1.24	15	11.1	2.91	15
	6	10.2	0.68	15	10.9	1.21	15	10.1	2.20	15
	7	10.2	0.94	15	9.6	1.23	15	10.3	1.27	15
	8	10.1	0.92	15	9.3	1.61	15	9.9	1.35	15
	9	9.9	0.93	15	9.0 ²	0.87	15	10.0	1.13	15
	10	9.3	2.29	15	9.5	1.59	15	10.1	1.64	15
	11	9.3	2.00	15	9.7	1.22	15	10.1	1.22	15
	12	10.3	0.94	15	9.8	1.22	15	10.3	1.40	15
	13	9.3	2.57	14	9.7	1.37	15	9.8	1.61	15
				7.6 ¹	0.99	13	8.0	1.28	14	

Parameters Measured	WEEK OF STUDY	10,000 PPM			15,000 PPM		
		MEAN	S.D.	N	MEAN	S.D.	N
Food Consumption g/animal/day	1	7.5 ²	2.97	8			
	2	10.0	1.52	15	3.0 ²	2.63	9
	3	11.3	0.92	14	7.4 ¹	2.64	10
	4	10.9	1.70	15	11.4	1.52	11
	5	10.5	1.09	15	12.0	1.26	11
	6	9.1 ¹	1.38	14	11.3	1.14	11
	7	9.1	2.54	15	9.5 ¹	0.71	11
	8	9.1	2.20	15	9.4 ¹	0.60	11
	9	9.5	2.88	15	8.6 ²	1.26	11
	10	9.4	1.07	15	9.2	1.15	11
	11	8.0	3.44	15	9.4	0.68	11
	12	9.4	1.22	15	10.0	0.93	11
	13		8.2	1.09	13	9.3	0.86
				7.3 ¹	1.21	10	

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

¹Significantly different from the Control group; p<0.05

²Significantly different from the Control group; p<0.01

* TABLE EXCERPTED FROM THE REPORT (IRDC No. 555-012)

TABLE 4*

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

SITE	0 ppm (Control)		1,000 ppm		5,000 ppm		10,000 ppm		15,000 ppm	
	DOS	TS	DOS	TS	DOS	TS	DOS	TS	DOS	TS
Observation	0	15	0	15	1	14	0	15	3	12
NUMBER OF ANIMALS EXAMINED	0	11	0	11	1	11	0	8	2	6
NUMBER WITHIN NORMAL LIMITS										
Males										
<u>EPIDIDYMS</u>										
- Small, mild	4		4		3		7		5	
<u>ORAL TISSUES</u>										
- Teeth missing, no grade					1					
<u>PENIS</u>										
- Thick, mild									1	
<u>SPLEEN</u>										
- Enlarged, moderate					1					
<u>STOMACH, GLANDULAR</u>										
- Foci, black, mild									1	
<u>TESTIS</u>										
- Small, mild	4		4		3		7		6	
Females										
<u>NUMBER OF ANIMALS EXAMINED</u>										
NUMBER WITHIN NORMAL LIMITS	0	15	0	15	0	15	0	15	4	11
	0	15	0	14	0	15	0	15	1	11
<u>ORAL TISSUES</u>										
- Teeth missing, no grade					1					
<u>STOMACH, GLANDULAR</u>										
- Erosion, mild									2	
- Foci, dark red, mild									1	

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DOS - Deaths and unscheduled sacrifices
TS - Terminal sacrifice

* DATA EXCERPTED FROM THE REPORT (555-012)

