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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

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DATA EVALUATION RECORD

Study Type: Multigeneration Reproduction
Species: rat Guideline: §83-4

EPA ID #(s).: EPA MRID No. 00031684
EPA Pesticide Chemical Code 030703
Toxicology Chemical No. 780A

Test Material: Alanap Technical

Synonyms: Sodium N-1-naphthylphthalamate, naptalam

Sponsor: Uniroyal Chemical Co., Research and Development, Bethany CT 06525

Testing Facility: Food and Drug Research Laboratories, Inc.

Title of Report: Multigeneration Evaluation of Alanap Technical in the Sprague-Dawley Rat

Study Number(s): 5847

Author(s): Larry Gephart, Francis J. Foschier, Richard A. Parent

Report Issued: January 11, 1980

Conclusions: Albino rats of the Sprague-Dawley BLU:(SD) strain from Blue Spruce Farms, Inc. (Alamont, NY 12009) received either 0, 120, 600, or 3000 ppm of Alanap Technical in the diet. No specific treatment related effects were noted on maternal/paternal parameters measured, although there was a slight effect on body weight gains in the high dose group. The reproductive parameters were unaffected by treatment. Possible systemic toxicity was noted in the offspring in the form of statistically significantly reduced mean pup body weights in the high dose group.

PARENTAL/SYSTEMIC TOXICITY NOEL = 600 ppm
PARENTAL/SYSTEMIC TOXICITY LOEL = 3000 ppm

REPRODUCTIVE TOXICITY NOEL ≥ 3000 ppm
REPRODUCTIVE TOXICITY LOEL > 3000 ppm

Core Classification: Core Minimum Data

This study satisfies the 1984 Pesticide Assessment Guideline (40 CFR §158.340, §83-4) for a multigeneration reproduction study in rats.

I. Materials and Methods: A copy of the "materials and methods" section from the investigators report is appended.

Test Compound:
Alanap s Technical
Purity: 91 %
Density: not provided
Description: not provided
Lot No.: BL 9328 CC0005, BL 9351 CC0002
Receipt date: 4/4/78, 11/27/78, 12/18/78
Contaminants: not provided

Vehicle(s): test compound added to the diet

Test Animal(s):
Species: Albino rat
Strain: Sprague-Dawley BLU:(SD)
Source: Blue Spruce Farms, Inc., Alamont, NY 12009
Age: unknown - "weanling"
Body Weight: 93.6-98.2 g - males; 89.4-93.9 g - females at start of study
INFO on males: same as above

The rats were acclimated for a period of 5 days before they were placed into the study.

Animal Husbandry:

Animals were kept under standard animal care conditions and received Agway Charles River RHM 3200 commercial laboratory chow (Agway, Waverly, NY) and tap water *ad libitum*.

Mating Procedure:

One male was caged with 1 female from the same test group for 6 days or until a sperm plug was noted in the cage pan. This was considered as Gestation Day 0. If a sperm plug was not found after 6 days observation, the first male was removed and replaced by another male, this was repeated again if necessary. Brother-sister matings were avoided.

After successful mating, each pregnant female was individually placed into a cage with a solid bottom and bedding where they were kept through gestation and lactation.

The F_0 parental animals were given test diets for 10 weeks before they were mated. Selection of parents for the F_1 generation was made when the pups were 21 days of age, and the mated animals in the study were approximately 100 days of age at mating.

Group Arrangement:

F_0 animals were randomly assigned to test groups as follows:

Test groups No.	Designation	Dose (ppm)*	Animals per group** Males	Females
1	Control	0	20	20
2	Low (LDT)	120	20	20
3	Mid (MDT)	600	20	20
4	High (HDT)	3000	20	20

* Diets were administered from the beginning of the study until the animals were sacrificed.
** 25 animals were picked from the F_{1a} litters as parents for the F_1 and F_2 generations.

Dose Administration:

Test diets were analyzed for homogeneity of mixtures and chemical stability in dietary mixtures .

Observations:

Parental animals:

Observations and the schedule for those observations is summarized from the report as follows:

Type of observation	Number of animals per sex per group	Frequency
Mortality and signs of toxicity	All	Daily
Detailed clinical observations	All	Daily
Body weight	All	Weekly from initiation to mating
	Maternal animals	Gestation Days 1, 8, 15, 28, 35 & 42
	Paternal animals	not stated
Food consumption	All	as for body weight

Reproductive performance:

Parental reproductive performance was assessed from breeding and parturition records of animals in the study. A mating was considered successful if a sperm plug was found on the cage pan.

The *fertility index* (# pregnancies/# matings) and *gestation index* (# litters cast alive/# pregnancies) were calculated.

Litter observations:

According to the report, the following litter observations were made:

	Time of observation (lactation day)		
Observation	**Birth**	**Day 4**	**Day 21**
Number of live pups	X	X	X
Pup weight	X	X	X
External alterations	not stated		
Number of dead pups	assumed all time points		
Sex of each pup		X	X

It is assumed that dead pups were examined grossly for external and internal abnormalities, and a possible cause of death was determined for pups born or found dead.

The *viability index* (# pups alive at 4 days/# pup cast alive) and *lactation index* (# pups alive at 21 days/# pups culled to at 4 day or percent of dams able to maintain all pups after culling until weaning at 21 day) were calculated.

Necropsy

Parental animals:

It was assumed that all surviving parental males were sacrificed and all maternal animals were sacrificed after the last litter of each generation was weaned and subjected to post mortem examinations.

Offspring:

The F_1, and F_3 offspring were sacrificed at 21 days of age. These animals were subjected to post mortem examinations. The F2 weanlings were ...*inadvertently discarded* (this was discussed with the Agency, letter which describes phone conversation with R.Engler and T.A.Re was included).

Necropsy observations:

Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera. The following tissues were prepared for microscopic examination: brain, pituitary gland, eyes, thyroid glands, parathyroid glands, lungs, heart, liver, spleen, kidneys, adrenal glands, stomach, pancreas, large intestine, small intestine, testes or ovaries, epididymides, prostate and seminal vesicles or uterus and vagina, mammary glands (2), *altered tissues*, and tissue masses.

Statistical analysis:

The following statistical methodology was used (from the investigators report):

Weekly body weights, weekly food consumption, and continuous reproductive data were evaluated using an Analysis of Variance with one-way classification[1]. Treatment differences were declared significant when the probability of committing a Type I error was less than or equal to 5% ($p \leq 0.05$) (Least Significant Difference Test).

Discrete data were evaluated using binomial comparison [illegible]. Each treatment rate was compared with that of the control. Differences were declared significant at the

[illegible] Schork, M.A., Statistics With Applications to the Biological and Health Sciences, Prentice-Hall, Inc., Englewood Cliffs, NJ (1977).

[illegible] Snedecor, G.W. and Cochran, W.G., 95% confidence interval percent for binomial distribution in statistical methods, 6th ed., p. 5, Iowa State University press, Ames, Iowa [illegible]

Historical control data **were not** provided to allow comparison with concurrent controls.

Compliance:

A signed statement of confidentiality claims **was not** provided.

A signed statement of compliance with EPA GLP's FR 40 Part 160 **was not** provided (partially under FDA GLP's).

A signed quality assurance statement **was** provided.

A signed Flagging Statement for Potential Adverse Effects under 40 CFR 158.34 **was not** provided.

II. Results:

A. Analysis of test diets:

Provided information was difficult to interpret.

B. Parental animals

1. Mortality and clinical signs:

There was no indication if any animals died on study. The investigators reported that there were no *daily observations* that were related to treatment with the test compound; however, no data were provided.

2. Body weight and food consumption:

Reported body weight and selected food consumption results are summarized as follows:

Observation & study week	Dose group Control	Low	Mid	High
F_0 Generation Males - Pre-mating				
Mean body weight (g)				
0	97.3	93.6	98.2	96.7
10	404.8	395.3	406.1	401.0
Mean weight gain (g)				
0 - 10	307.5	301.7	307.9	304.3
Mean food consumption (g/rat/week)				
1	128.7	122.9	125.3	123.3
2	155.4	153.6	153.8	148.6
10	167.6	169.5	168.0	167.8
F_0 Generation Females - Pre-mating				
Mean body weight (g)				
0	90.9	93.9	90.0	89.4
10	238.9	239.2	242.6	232.2
Mean weight gain (g)				
0 - 10	148.0	145.3	152.6	142.8
Mean food consumption (g/rat/week)				
1	110.0	112.4	111.4	108.3
2	121.2	124.9	126.5	121.7
5	133.1	131.8	131.3	127.5
7	128.6	126.3	125.5	123.7
10	123.4	121.6	120.8	120.6

continued

Observation & study week	Control	Dose group Low	Mid	High
F_1 Generation Males - Pre-mating				
Mean body weight (g)				
0	195.2	192.0	193.4	182.5
8	407.7	401.7	418.9	387.6
Mean weight gain (g)				
0 - 8	212.5	209.7	225.5	205.1
Mean food consumption (g/rat/week)				
1	169.1	165.0	170.0	159.6
2	188.3	177.7	176.3	181.2
4	192.6	185.9	193.2	184.3
8	178.4	178.3	178.6	174.4
F_1 Generation Females - Pre-mating				
Mean body weight (g)				
0	140.0	141.6	141.0	133.4
8	237.6	235.7	247.9	227.6
Mean weight gain (g)				
0 - 8	97.6	94.1	106.9	94.2
Mean food consumption (g/rat/week)				
1	128.3	128.2	139.4	119.6
2	140.6	137.4	145.1	131.2
4	148.9	148.7	161.0*	140.6
8	143.4	138.8	145.3	136.8
F_2 Generation Males - Pre-mating				
Mean body weight (g)				
0	144.8	145.0	162.1*	146.3
8	370.4	367.8	389.2	359.2
Mean weight gain (g)				
0 - 8	225.6	222.8	227.1	212.9
Mean food consumption (g/rat/week)				
1	160.3	158.6	171.6*	167.3
2	180.5	177.4	186.8	181.3
4	185.7	183.0	190.6	186.2
8	179.1	182.8	189.1	183.2
F_2 Generation Females - Pre-mating				
Mean body weight (g)				
0	114.5	110.8	126.2*	118.6
8	227.8	224.4	231.4	220.1
Mean weight gain (g)				
0 - 8	113.3	113.6	105.2	101.5
Mean food consumption (g/rat/week)				
1	130.8	130.2	135.6	135.0
2	140.2	139.4	138.6	143.1
4	147.3	140.2	142.0	133.6*
8	142.7	142.4	155.2	140.8

*** = P < 0.05 as compared to control; gains calculated by reviewer**

Data extracted from Laboratory Report No. 5847, Tables 11 through 22

Selected group mean body weight values for pregnant or nursing dams were summarized in the report as follows:

Observation	Dose group Control	Low	Mid	High
	F_0 Generation - Litter A			
Mean body weight (g) - days after plug				
0	238.4	242.7	246.8	231.9
8	261.1	268.0	271.1	260.6
15	287.9	300.4	304.2	289.5
19	329.9	342.7	343.2	326.9
28	285.5	291.4	291.4	278.2
35	298.4	309.8	309.2	290.1
42	294.4	299.1	310.2	293.8
	F_1 Generation - Litter A			
Mean body weight (g) - days after plug				
0	247.1	248.1	257.0	234.6*
8	273.1	274.5	287.9*	262.3
15	303.8	307.0	322.4*	294.2
19	346.0	349.2	368.0*	335.8
28	298.6	297.8	313.1	281.5*
35	309.2	310.1	319.4	287.6*
42	311.3	308.2	322.8	291.9*
	F_2 Generation - Litter A			
Mean body weight (g) - days after plug				
0	229.6	231.1	236.8	224.0
8	259.7	263.8	266.9	253.7
15	290.0	293.8	299.8	285.7
19	334.2	335.8	340.4	323.2
28	285.2	290.8	294.0	277.0
35	289.8	299.8	306.0	288.8
42	284.6	294.0	300.0	286.4

*** = P < 0.05 as compared to control**

Data extracted from Laboratory Report No. 5847, Tables 24 through 26.

Very slight effects were noted in the high dose males and females; however, only the F_1 and F_2 females were close to a 10% difference from control.

Food consumption was occasionally reduced in the high dose groups.

3. Test Substance Intake:

Data were not provided by the investigators, direct calculation using a factor of 0.050 to convert ppm into mg/kg/day gives 6, 30, and 150 mg/kg/day for the 120, 600, and 3000 ppm dose groups, respectively.

4. Reproductive performance:

Results for the parental animals and offspring are summarized from the report as follows:

Observation	Dose group: Control	Low	Mid	High
F_0 Generation - Litter A				
Precoital interval (days)	not provided			
Males				
Mated	20	20	20	20
Fertile	not provided			
Females				
Number mated	20	20	20	20
Number fertile	17	20	20	20
Fertility index (%)	85	100*	100*	100*
Gestation interval (days)	not provided			
Number of litters				
Day 1	17	20	20	20
Day 4	17	20	19	20
Day 21	16	18	19	20
Gestation index (%)	100	100	100	100
Mean litter size				
Birth	11.4	12.3	12.9*	11.0
Day 4	11.2	11.9	12.9	10.8
Day 4C	8.0	7.9	8.0	7.7
Day 21	7.9	7.9	8.0	7.7
Number of pups				
Day 1	193	246	258	220
Day 4	191	237*	245*	213*
Day 4C	136	158	152	154
Day 21	135	151*	152	154
Pups born dead	8	7	1*	2*
Pup deaths (Days 1-21)	9	7	1*	2*
Viability Index (%)	99	96*	95*	97*
Pup Lactation Index (%)	99	96*	100	100
Dam Lactation Index (%)	100	90	100	100
Mean litter weight (g)				
Day 1	68.7 (2.9)	77.1 (2.6)	81.7* (3.3)	68.3 (4.2)
Day 4	79.8 (2.2)	76.2 (3.5)	77.8 (2.0)	75.9 (4.2)
Mean pup weight (g) day 21	51.4 (1.2)	52.0 (0.7)	51.4 (1.0)	47.5* (1.5)

continued

Observation	Dose group Control	Low	Mid	High
F_1 Generation - Litter A				
Precoital interval (days)	not provided			
Males				
Mated	25	25	25	25
Fertile	not provided			
Females				
Number mated	25	25	25	25
Number fertile	23	23	24	23
Fertility index (%)	92	92	96	92
Gestation interval (days)	not provided			
Number of litters				
Day 1	23	23	24	23
Day 4	23	23	24	23
Day 21	23	22	24	23
Gestation index (%)	100	100	100	100
Mean litter size				
Birth	13.4	13.2	14.1	13.1
Day 4	13.4	13.1	14.0	13.1
Day 4C	9.7	10.0	10.0	9.8
Day 21	9.7	10.0	10.0	9.8
Number of pups				
Day 1	309	304	338	302
Day 4	309	301	335	301
Day 4C	224	230	241	226
Day 21	224	229	241	226
Pups born dead	1	3	4*	1
Pup deaths (Days 1-21)	1	4	4	1
Viability Index (%)	100	99*	99	100
Pup Lactation Index (%)	100	100	100	100
Dam Lactation Index (%)	100	90	100	100
Mean litter weight (g)				
Day 1	78.4 (3.2)	78.3 (2.0)	83.1 (2.0)	78.1 (2.7)
Day 4	92.1 (2.7)	96.6 (2.2)	95.5 (2.2)	92.2 (2.2)
Mean pup weight (g) day 21	47.4 (1.1)	46.4 (0.6)	46.1 (0.8)	41.6* (1.2)

continued

Observation	Dose group Control	Low	Mid	High
F_2 Generation - Litter A				
Precoital interval (days)	not provided			
Males				
Mated	25	25	25	25
Fertile	not provided			
Females				
Number mated	25	25	25	25
Number fertile	24	25	24	24
Fertility index (%)	96	100	96	96
Gestation interval (days)	not provided			
Number of litters				
Day 1	24	25	24	24
Day 4	24	25	24	24
Day 21	24	25	23	23
Gestation index (%)	100	100	100	100
Mean litter size				
Birth	12.5	13.0	12.5	12.8
Day 4	12.4	12.9	12.5	12.7
Day 4C	9.8	10.0	10.0	10.0
Day 21	9.8	9.9	9.9	9.9
Number of pups				
Day 1	301	326	301	308
Day 4	298	322	301	305
Day 4C	236	249	239	239
Day 21	236	247	238	238
Pups born dead	2	2	2	4
Pup deaths (Days 1-21)	2	4	3	5
Viability Index (%)	99	99	100	99
Pup Lactation Index (%)	100	99	100	100
Dam Lactation Index (%)	100	100	96	96
Mean litter weight (g)				
Day 1	74.2 (3.1)	76.1 (2.0)	74.8 (2.0)	75.5 (2.2)
Day 4	97.9 (2.9)	92.0 (2.7)	96.9 (2.8)	92.2 (2.1)
Mean pup weight (g) day 21	48.2 (0.9)	48.4 (1.0)	48.0 (0.9)	42.7* (0.6)

* = p < 0.05 as compared to control

Data extracted from Laboratory Report No. 5847, Tables 1 - 10 and 27 - 29.

The reproductive parameters were unaffected by treatment. The only notable observation in the above data is the statistically significantly reduced mean pup body weights in the high dose group.

5. Necropsy results

a. Organ weights:

Not provided.

b. Pathology

i. Macroscopic examination:

No treatment related effects were noted in the provided data (investigator's summary is attached).

ii. Microscopic examination:

No treatment related effects were noted in the provided data (investigator's summary is attached).

6. Study Deficiencies

This study was conducted prior to the 1984 and 1978 Guidelines; however, the study fulfills the minimum data requirements under the Core Guidelines from 1977 and does have evidence of mimimal systemic toxicity at the high dose.

III. DISCUSSION

No specific treatment related effects were noted on maternal/paternal parameters measured, although there was a slight effect on body weight gains in the high dose group. The reproductive parameters were unaffected by treatment. Possible systemic toxicity was noted in the offspring in the form of statistically significantly reduced mean pup body weights in the high dose group.

PARENTAL/SYSTEMIC TOXICITY NOEL = 600 ppm
PARENTAL/SYSTEMIC TOXICITY LOEL = 3000 ppm

REPRODUCTIVE TOXICITY NOEL ≥ 3000 ppm
REPRODUCTIVE TOXICITY LOEL > 3000 ppm

Core Classification: Core Minimum Data

This study satisfies the 1984 Pesticide Assessment Guideline (40 CFR §158.340, §83-4) for a multigeneration reproduction study in rats.

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Pages __14__ through __20__ 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 quality control procedures.

__ _ __ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

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R058679

Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca**
PC Code:	**030702**
HED File Code	**13000 Tox Reviews**
Memo Date:	**11/18/93 12:00:00 AM**
File ID:	***00000000***
Accession Number:	**412-04-0046**

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