OH 335

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

NOV 29 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **NAPTALAM (Alanap):** Review of a subchronic feeding study in the rat, a subchronic feeding study in the dog, rereview of a rat teratology study, rereview of an eye irritation study in rabbits, review of a skin irritation study in rabbits and review of a data waiver request for guideline studies §81-2, -4, and -5.
EPA DP Barcodes: D205250, D207628, D208720; EPA Submission No.s S469508, S473779, S475685; MRID#'s 00106276, 00106277, 00106230, 00078530, and 00060408; EPA Pesticide Chemical Code 030703, Toxicology Chemical No. 780A (Na salt); 592 (acid).

TO: Linda Propst/Susanne Cerrelli, PM 73
Special Review and Reregiscration Division (7508W)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 11/22/94
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M Ioannou 11/22/94
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia van Gemert 11/25/94
Chief, Toxicology Branch II
Health Effects Division (7509C)

Registrant: Uniroyal Chemical Company, Inc.

Action Requested: Review a subchronic feeding study in the rat, in addition review a subchronic feeding study in the dog, rereview a rat teratology study with Naptalam, rereview an eye irritation study in rabbits, and review a skin irritation study in rabbits. Also review of a data waiver request for guideline studies §81-3, -4, and -5.

Recommendations:

1. TBII has determined that the data waiver request for the acute inhalation , primary eye irritation and dermal sensitization studies with Naptalam cannot be supported. The registrant is required to provide the aforementioned studies using the "technical" Naptalam used in the chronic toxicity studies.

2. TBII has reviewed the above listed studies and the results are summarized as follows.

1 9
72

011335

1. Review of Toxicity Studies:

MRID# 00106276: *SUBCHRONIC DIETARY ADMINISTRATION - RATS ALANAP S FINAL REPORT* (Hazleton Laboratories, Incorporated for Uniroyal Inc., Project No. 798-137, May 10, 1968), the following is the Executive Summary from the review:

In a 13 week subchronic feeding study (MRID# 00106276), male and female albino Charles River Caesarean-derived strain rats received either 0, 500, 1000, or 5000 ppm Alanap S (assumed 100% a.i., Lot No. C 465) admixed to the diet.

Systemic toxicity was noted in the high dose group as reduced body weight gains in the females (85% of control) and reduced food efficiency in both males and females. High dose females also had decreased absolute and relative heart and spleen weights. **The Systemic Toxicity LOEL is 5000 ppm with a Systemic Toxicity NOEL of 1000 ppm based on reduced body weight gain, reduced food efficiency and decreased organ weights.**

The study is classified as Core-Supplementary Data and does not satisfy the guideline requirement (§83-1a) for a subchronic toxicity study in rats due to several study design problems.

MRID# 00106277: *FINAL REPORT 13-WEEK Dietary Feeding - Dogs* (Hazleton Laboratories, Incorporated for Uniroyal Inc., Project No. 798-140, March 1, 1968), the following is the Executive Summary from the review:

In a 13 week subchronic feeding study (MRID# 00106277), male and female adult beagle dogs (unknown source) received either 0, 300, 1000, or 3000-5000 ppm of Alanap S (Lot # - C-465, assumed 100% a.i.; equal to 11.4, 29.7, and 124.7 mg/kg/day in males and 9.7, 29.9, and 123.6 mg/kg/day in females).

Systemic toxicity was noted at the high dose (3000-5000 ppm) in the form of reduced body weight gains, reduced food efficiency and increased absolute and relative liver weights. **The LOEL for Systemic Toxicity is 3000 ppm and the NOEL for Systemic Toxicity is 1000 ppm based on reduced body weight gains, reduced food efficiency and increase absolute and relative liver weights.**

The study is classified as Core-Supplementary Data and does not satisfy the guideline requirements (§82-1b) for a subchronic oral toxicity study in non-rodents. This study cannot be upgraded due to numerous reporting and study deficiencies.

MRID# 00106320: *Teratologic Evaluation of Alanap S Technical in Sprague-Dawley Rats* (Food and Drug Research Laboratories, Inc for Uniroyal Inc., Study No. 5888a, December 22, 1978), the following is the Executive Summary from the review:

In a developmental toxicity (teratology) study (MRID# 00106320), sexually mature Sprague-Dawley rats of the BLU: (SD) BR strain from Blue Spruce Farms, Inc., Altamont, NY received either 0, 15, 115, or 500 mg/kg/day Alanap S Technical (Na Salt; unknown purity; Batch No. B19062, CC4035) by oral gavage in corn oil. The study originally had a high dose of 900 mg/kg/day of which all animals died after the first few doses; a new group was substituted using 500 mg/kg/day.

Maternal toxicity was noted at 115 mg/kg/day and above in the form of reduced body weight gain during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20), for the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period (except 115 mg/kg/day). The 900 mg/kg/day dose group had complete deaths and there was increased maternal wastage at 500 mg/kg/day. **The Maternal Toxicity LOEL is 115 mg/kg/day and the Maternal Toxicity NOEL is 15 mg/kg/day based on reduced body weight gain.**

Developmental toxicity was noted in the 500 mg/kg/day dose group as lower mean fetal weight compared to the control group and there was an increased incidence of unspecified missing sternebrae, incomplete ossification of unspecified vertebrae, unspecified skull bones, unspecified extremities and increased missing or reduced hyoid bone in the 500 mg/kg/day dose group. **The Developmental Toxicity LOEL is 500 mg/kg/day and the Developmental Toxicity NOEL is 115 mg/kg/day based on reduced mean fetal weight and increased skeletal observations.**

The study is classified as Core Supplementary Data and does not satisfy the guideline requirement for a developmental toxicity (teratology) study (§83-3a) in the rat. The study may be upgraded if the deficiencies listed below are addressed to the Agency's satisfaction.

Study Deficiencies: The percent active ingredient of the test compound was not provided. No analysis of dosing solutions was performed (however, toxicity was noted so the animals did receive compound). Bones that were affected in the fetuses were not identified. Limited data were provided for maternal effects; however, this study was conducted prior to the 1984 Guidelines.

011335

MRID# 00060408: *Primary Skin Irritation in Rabbits - Alanap* (Product Safety Laboratories for UNIROYAL CHEMICAL COMPANY, INC., Laboratory Project ID T-210, July 18, 1977), the following is the Executive Summary from the review:

In a primary skin irritation study (MRID# 00060408), New Zealand White Albino Rabbits were exposed to 0.5 ml Alanap (25.34% a.i., Lot No.: B1 #8554 and 074053) on unabraded and abraded skin areas.

Alanap produced a primary irritation score of 0.3, which is considered to be in the non-primary irritant category. There was slight irritation (erythema) present at 72 hours in both intact and abraded skin. **TOXICITY CATEGORY IV**

This study is classified as Acceptable and satisfies the guideline requirement (§81-5) for a primary skin irritation study in rabbits.

TB II has rereviewed the study, MRID# 00078530: Acute Eye Irritation Study in Rabbits - Alanap (Hazleton Laboratories America, Inc. for UNIROYAL CHEMICAL COMPANY, INC., Laboratory Project ID 798-182, April 24, 1978), the following is the Executive Summary from the review:

In a primary eye irritation study (MRID# 00078530), New Zealand White Rabbits were exposed to 0.1 ml Alanap (24.54% a.i., Lot# BL8881 - CC0005 and 0036121) instilled into 1 eye with the other serving as a control. A comparison was made between unwashed and washed eyes.

Alanap produced primary eye irritation which included corneal opacities and eye irritation which were reversible in less than 7 days. TOXICITY CATEGORY III

This study is classified as Acceptable and satisfies the guideline requirement (§81-4) for a primary eye irritation study in rabbits.

II. BACKGROUND:

The registrant has previously requested a Low Volume/Minor Use Waiver for the Chronic Toxicity Study in the Rat (§83-1a), Carcinogenicity in the rat (§83-2a) and General Metabolism (§85-1). With this submission, the registrant has requested that the §81-3 (acute inhalation study), §81-4 (primary eye irritation study) and §81-5 (primary dermal irritation study) be conducted with Alanap-L rather than the *technical* since the *technical* is a *dried down version* of the chemical and it *is never used in the manufacturing process, or elsewhere.* The *highly concentrated*

011335

Alanap technical does not exist. It is noted, however, that the chronic toxicity studies were conducted with the concentrated material; therefore the acute toxicity studies should be conducted with the same material and the data waiver request for guideline studies §81-3 (acute inhalation study), §81-4 (primary eye irritation study) and §81-5 (primary dermal irritation study) should not be granted.

III. DISCUSSION:

A. Recommendations made by the HED RfD/QA Peer Review Committee

Naptalam and Na-naptalam was presented to the RfD/Peer Review Committee on August 25, 1994 in order to determine if the available data and the additional information on the cancer risk provided by the registrant are adequate to satisfy the chronic toxicity and carcinogenicity guideline requirements. The following are the conclusions of the committee for the chronic/carcinogenicity studies:

The Committee considered the chronic toxicity studies in rats (MRID No. 00077053, 41838801, 42784001) and dogs (MRID No. 41057501) to be acceptable and the data evaluation records (HED Doc. 009801, 010741; 009301) to be adequate.

The Committee recommended upgrading of the chronic toxicity phase of the rat study from Core-supplementary to a Core-minimum status.

In the dog study, the Committee recommended that the no-observable effect level (NOEL) be based on body weight changes and not the changes in alkaline phosphatase activity. No revisions to the data evaluation records were recommended.

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (MRID No. 00077053, 41838801, 42784001) to be marginally acceptable. The highest dose level tested in rats caused 7-9% reduction of body weight gain. The Committee concluded that the treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions.

The Committee considered the carcinogenicity study in mice (MRID No. 00119003) to be unacceptable because of major deficiencies in the study conduct and reporting. Deficiencies observed in this study included mixing of

011335

dietary concentrations in the first few months of the study, lack of purity information about the technical used, and possible technical problems in the histopathological evaluation (the slides were read by two pathologists raising questions about the uniformity of criteria used in reading of these slides). The data provided a suggestive evidence of positive carcinogenic response in mice, but on the other hand was hard to analyze statistically because of the uncertainty arising from all deficiencies existed in this study. The Committee debated the question of whether a new mouse study would be required. Based on the current use and/or exposure profile, the consensus was that a new study would not be necessary at this time. The chemical is currently registered as a low volume/minor use chemical. Should the exposure or use profile change (expand) in the future, a new mouse study should be requested. **The chemical was classified as a "Group D" based on inadequacy of the data available.** It was also suggested that a surrogate risk analysis based on the worst case scenario may be performed if needed.

The reproductive toxicity study in rats (MRID No. 00031684, 42739702) and the developmental toxicity studies in rabbits (MRID No. 00157186) were considered to be acceptable and the data evaluation records (HED Doc. No. 005873, 009801; 009803, 010741) were considered to be adequate. The Committee generally agreed with the reviewer's evaluation and interpretation of data. Although the developmental toxicity study in the rat (MRID No. 00106320) was classified as Core-supplementary due to missing/inadequate information, the scientific validity of the endpoints was not in question, and it was considered adequate for the evaluation of developmental toxicity in this species. The Committee further noted that body weight changes at the mid-dose in this study were not supported statistically, but were considered biologically relevant because of their magnitude (more than 10% lower than the concurrent controls), and because of the apparent dose related trend observed. The Committee recommended that the classification of the study remains unchanged until all questions raised by the respective branch are addressed. No changes to the data evaluation records were recommended. There was no evidence, based on the data available, to suggest that Naptalam was associated with major developmental or reproductive toxicity.

011335

B. Data Waiver Request

Relating to the acute toxicity studies with the Alanap-L (§81-3, -4, and -5), since the chronic toxicity studies were conducted with a near to 100% active ingredient concentration test substance and the guideline requirements (see §158.340) for acute toxicity testing includes both "technical" and end-use products, the acute toxicity testing with the test substance concentration used in the chronic studies **is required**. Specific guideline requirements for inhalation, dermal and eye irritation can be waived if proof of severe irritation is provided which then would require a Toxicity Category of I to be listed for that guideline requirement.

011335

III. Toxicology Profile for Naptalam and Na-Naptalam (40 CFR §158.340)

Technical: Naptalam and Na-Naptalam
Use Pattern: food use

This compound is a registered active ingredient, a reregistration **List B** chemical; the following data are available for Naptalam and Na-Naptalam. Study requirements have been based on the use pattern for this chemical. **THE FOLLOWING DOES NOT NECESSARILY REFLECT REREGISTRATION REQUIREMENTS.**

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	**NO**
§81-4 Primary eye irritation in rabbits	Yes	**NO**
§81-5 Primary dermal irritation in rabbits	Yes	**NO**
§81-6 Dermal sensitization - guinea pig	Yes	**NO**
§82-1(a)90 day feeding - rat	Yes	NO[1,2]
§82-1(b)90 day feeding - dog	Yes	NO[1,2]
§83-1(a)2-year feeding - rodent	Yes	Yes[3]
§83-1(b)1 year feeding - nonrodent	Yes	Yes
§83-2(a)Carcinogenicity - rat	Yes	Yes[3]
§83-2(b)Carcinogenicity - mouse	Yes	**NO**[2]
§83-3(a)Teratology - rat	Yes	**NO**[1,3]
§83-3(b)Teratology - rabbit	Yes	Yes[3]
§83-4 Multigeneration reproduction-rat	Yes	Yes[3]
§84-2(a)Mutagenicity-Gene Mutation	Yes	Yes
§84-2(b)Mutagenicity-Struct. Chromosome Aberr.	Yes	Yes
§84-4 Mutagenicity-Other Genotoxic Effects	Yes	Yes
§85-1 General metabolism - rat	Yes	**NO**

[1] = study reviewed in this document.
[2] = satisfied by an acceptable chronic toxicity study.
[3] = see discussion in this document.

Formulation: Alanap L

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	**NO**
§81-2 Acute dermal toxicity in rabbits	Yes	**NO**
§81-3 Acute inhalation toxicity in rats	Yes	**NO**
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes

IV. Data Gaps

The following are data gaps for technical Naptalam and Na-Naptalam (see discussion in this document):

§81-3 Acute inhalation toxicity in rats
§81-4 Primary eye irritation in rabbits
§81-5 Primary dermal irritation in rabbits
§81-6 Dermal sensitization - guinea pig
§83-3(a)Teratology - rat (additional data required)
§85-1 General metabolism - rat

Also, the Neurotoxicity Guidelines study requirements are still reserved at this time until more information of the toxicity of this chemical is available.

The following are the data gaps for the formulation Alanap L:

§81-1 Acute oral toxicity in rats
§81-2 Acute dermal toxicity in rabbits
§81-3 Acute inhalation toxicity in rats

V. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

VI. Reference Dose

An RfD of 0.053 mg/kg/day based on a 1 year feeding study in the dog with a NOEL of 5.3 mg/kg/day (body weight changes were observed at the next higher dose of 25.8 mg/kg/day) and an uncertainty factor of 100 has been established.

VII. Pending Regulatory Actions

None.

VIII: Toxicological Issues Pertinent to this Request

A. New toxicology Data on Naptalam and Na-Naptalam

The new study has been discussed above.

B. Carcinogenicity and Mutagenicity

See discussion on carcinogenicity, this memo. There are one positive and one possible positive mutagenicity studies.

011335

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 9/11/94
Senior Pharmacologist, Review Section I, TBII (7509C)

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M.I 8/18/94
Section Head, Review Section I, TBII (7509C)

DATA EVALUATION RECORD

Study Type: Subchronic Oral (Dietary) Toxicity
Species: Rat Guideline: §82-1a

EPA Numbers: EPA MRID# 00106276
EPA Pesticide Chemical Code 030703 (Na Salt)
Toxicology Chemical No. 592 (Na Salt)
EPA DP Barcode D205250
EPA Submission Barcode S469508

Test Material: Alanap S (Lot No. C 465)

Synonyms: Naptalam

Title of Report: SUBCHRONIC DIETARY ADMINISTRATION - RATS
ALANAP S
FINAL REPORT

Sponsor: Uniroyal Inc., Bethany, Connecticut

Testing Facility: Hazleton Laboratories, Incorporated
Falls Church, Virginia

Study Number: Project No. 798-137

Author(s): G. Carl Holsing

Report Issued: May 10, 1968

Executive Summary: In a 13 week subchronic feeding study (MRID# 00106276), male and female albino Charles River Caesarean-derived strain rats received either 0, 500, 1000, or 5000 ppm Alanap S admixed to the diet.

Systemic toxicity was noted in the high dose group as reduced body weight gains in the females (85% of control) and reduced food efficiency in both males and females. High dose females also had decreased absolute and relative heart and spleen weights. **The Systemic Toxicity LOEL is 5000 ppm with a Systemic Toxicity NOEL of 1000 ppm based on reduced body weight gain, reduced food efficiency and decreased organ weights.**

The study is classified as Core-Supplementary Data and does not satisfy the guideline requirement (§83-1a) for a subchronic toxicity study in rats due to several study design problems.

011335

A. Materials and Methods: A copy of the Materials and Methods section from the investigators report is attached.

1. Test compound: Alanap S (Naptalam)
Description - Fine, pale tan powder with a slightly unpleasant odor
Lot # - C 465
Purity - assumed 100%
Received - July 27, 1967
Contaminants - none reported

2. Vehicle(s): None used

3. Test animals: Species: albino male and female rats
Strain: Charles River Caesarean-derived strain
Age: not provided
Weight: males 72-96 gm; females 70-93 gm at study initiation
Source: Charles River

4. Animal assignment

Animals were assigned to the following test groups by *stratified randomization*:

Test Group	Dose in Diet (ppm)	# males	#females
1 Control	None	10	10
2 Low (LDT)	500	10	10
3 Mid (MDT)	1000	10	10
4 High (HDT)	5000	10	10

5. Diet preparation

Diet was prepared weekly, no storage method provided. There was no indication if samples of dietary admix were analyzed for stability and concentration.

6. Animal Husbandry

Animals were housed in elevated wire mesh cages and received *appropriate diet* (*basal diet* for controls) and water *ad libitum*. No other information was provided.

7. Clinical Observations

Animals were inspected daily for *general appearance, behavior, signs of pharmacologic effect and mortality*. They were weighed weekly and food consumption was determined weekly.

8. Ophthalmological examination

Ophthalmological examination were not performed as they are not required in subchronic studies.

9. Hematology and Clinical Chemistry

Blood was collected before at 1 and 3 months for hematology and clinical analysis from 5 rats per sex.

a. Hematology

The following parameters were measured:

Erythrocyte count (RBC)*
Leukocyte count (WBC)*
Leukocyte differential count*
Hematocrit (HCT)*
Hemoglobin (HGB)*
* Required for subchronic studies

The following parameters required for subchronic studies were not determined:

Platelet count*

b. Clinical Chemistry

The following parameters were measured:

Blood sugar (Glucose)*
Blood urea nitrogen*
Serum glutamic-pyruvic transaminase (Serum alanine aminotransferase, SGPT)*
* Required for subchronic studies

The following parameters required in subchronic studies were not determined:

Calcium*, Blood creatinine*, Phosphorous*, Cholesterol*, Serum glutamic-oxaloacetic transaminase (Serum aspartate aminotransferase, SGOT)*, Sodium*, Potassium*, Chloride*, Total serum Protein (TP)*, Albumin*

10. Urinalysis^

Urine was collected prior to study initiation and at 1 and 3 months; there was no indication if animals were fasted. The following parameters were examined:

Appearance
pH
Specific gravity
Sugar (Glucose)
Acetone (Ketones)
Protein
Bilirubin
Occult Blood
Sediment (microscopic)
Volume
^Not required for subchronic studies

011335

11. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the following tissues were collected for histological examination (performed on 5 animals per sex in the control and high dose groups, only), the bolded organs, in addition, were weighed:

Brain*+
Pituitary*
Eyes (optic nerve?)*#
Thyroids*++
Lung*
Heart*
Liver*+
Spleen
Kidneys*+
Adrenal gland*
Stomach*
Pancreas*
Duodenum*, Jejunum*, Ileum*, Colon*
Urinary bladder*
Ovaries*+
Bone*# (femur)
Bone marrow* (sternum)
Testes*+

The following required for subchronic studies were not examined:

Aorta*, Salivary glands*, Periph. nerve*#, Esophagus*, Spinal cord (3 levels)*#, Lymph nodes*, Thymus*, Cecum*, Lacrimal gland#, Mammary gland*#, Rectum*, Parathyroids*++ (possibly determined with thyroids), Skeletal muscle*#, Trachea*, Uterus*, Skin*#,All gross lesions and masses*

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

011335

12. Statistics

The following statistical procedures were utilized (from the investigators report):

Criteria: Growth rate, total food consumption, terminal body weights, organ weights, and organ/body weight ratios.

Method: All criteria examined by the analysis of variance, or F-test, at the 5% probability level; preliminary tests (where applicable) conducted by the methods of Rao, Bartlett, Scheffe, Sachs, and Fisher-Behrens (modified t-test).

References: More detailed descriptions of these methods are to be found in Ostle, B., Statistics in Research, Iowa State College Press, Ames, Iowa, 1956; Rao, C. R., Biometrics 14, 1, 1958; Snedecor, G. W., Statistical Methods, Iowa State College Press, Ames, Iowa, 1956; Sachs, R., Tox. Appl. Pharm. 1, 203, 1959; Sachs, R., J. Assoc. Offic. Agr. Chemists 42, 741, 1959.

13. Compliance

No statements of data confidentiality claims, compliance with GLP's quality assurance or flagging criteria were provided.

B. RESULTS:

1. Clinical Observations

a. Clinical signs of toxicity/mortality

No clinical signs of toxicity were reported. No animals were reported to have died.

b. Body weight

The investigators provided group mean, group range and graphical depiction data only, no individual animal data were provided. The following table presents the body weight gains (g) calculated by the reviewer from the group mean data provided (from Table 1, pages 11 and 12 of the investigators report):

Weeks:		Control	Low	Mid	High
0-13	M	402	430	408	399(99)[1]
	F	197	195	196	173(88)
1-13	M	355	376	359	348(98)
	F	157	154	155	133(85)

[1] = percent of control

There is a 12-15% decrease in body weight gain the in the high dose females, the males were relatively unaffected.

c. Food consumption, food efficiency and compound intake

The investigators provided group mean, group range and graphical depiction data only, no individual animal data were provided. The following table presents the food consumption (g/rat/day) calculated by the reviewer from the group mean data provided:

Weeks:		Control	Low	Mid	High
1-13	M	170	181	179	182
	F	129	126	131	127

The following table presents the food efficiency calculated by the reviewer from the above data:

Weeks:		Control	Low	Mid	High
1-13	M	16.1	16.0	15.4	14.7
	F	9.4	9.4	9.1	8.1

Food consumption was relatively unaffected but food efficiency in the high dose group was reduced, an indicator of toxicity.

Compound intake was not calculated, rather it was presented in graphical form.

011335

2. Hematology and Clinical Chemistry

The investigators provided group mean and individual animal data for the five animals per sex per dose group examined.

a. Hematology

The following table (extracted from Table 2, pages 13-20 of the investigators report) presents the hematological values for 1 and 3 months:

	MO.	Control	500	1000	5000
HCT	1	48.2/47.8[1]	48.2/45.4	47.2/45.2	48.4/44.3
	3	48.4/47.4	47.0/46.8	46.2/46.2	43.4/42.0
HGB	1	14.8/13.9	14.1/13.8	14.2/13.6	15.1/12.3
	3	15.6/14.2	14.6/14.4	14.3/14.3	13.2/12.5
RBC	1	5.00/5.52	5.35/4.93	5.38/5.07	5.30/4.23
	3	7.69/7.60	8.22/7.48	8.04/7.39	5.86/5.19
WBC	1	22.5/23.8	18.9/16.8	16.2/18.6	17.1/26.8
	3	24.9/17.9	22.2/13/7	26.4/14.2	23.3/22.1

[1] = male/female

There appears to be a decrease in hematocrit, hemoglobin and red blood cell counts in males and females at the 3 month time point; however, according to the investigators, this was within *normal variation*, no historical control data were provided.

b. Clinical Chemistry

The following table (extracted from Table 3, pages 21-28 of the investigators report) presents the clinical chemistry values for 1 and 3 months:

	MO.	Control	500	1000	5000
Sugar	1	76/83[1]	83/74	87/93	84/83
	3	87/74	104/111	103/96	101/86
BUN	1	16.5/19.1	17.7/18.7	16.1/22.0	18.5/18.2
	3	16.8/17.6	17.0/15.6	17.1/17.1	17.6/17.8
SG-PT	1	27/21	25/23	21/28	27/22
	3	18/21	21/24	16/24	30/18

[1] = male/female

A slight increase in blood glucose was noted in all treated males; however, no dose response was evident. No other treatment related effects were noted.

3. Urinalysis

The investigators provided group mean data only for 5 animals per dose group at 1 and 3 months. The following table (from Table 4, pages 29 and 30 of the investigators report) presents the results of the analysis; no treatment related effects were noted.

011335

ALANAP S 8 SUBCHRONIC RAT

LEVEL ppm	NO. OF RATS	SEX	APPEAR.	pH	SP. GR.	SUGAR	ACE-TONE	PRO-TEIN	BILI-RUBIN	OCCULT BLOOD	VOL.
								ONE MONTH			
ONTROL	5	M	T P YEL	7	1.009	0	0	0	0	0	100
ONTROL	5	F	T YEL	7	1.012	0	0	0	0	0	72
500	5	M	T YEL	7	1.010	0	0	0	0	0	105
500	5	F	T P YEL	7	1.007	0	0	0	0	0	100
1000	5	M	T YEL	9	1.010	0	0	T	0	0	100
1000	5	F	T YEL	7	1.008	0	0	0	0	0	100
5000	5	M	T YEL	6	1.022	0	0	T	3	0	50
5000	5	F	T YEL	5	1.020	0	0	0	3	0	35
								TERMINAL			
ONTROL	5	M	V T YEL	7	1.011	0	0	0	0	0	100
ONTROL	5	F	V T YEL	8	1.012	0	0	0	0	0	60
500	5	M	V T YEL	7	1.011	0	0	0	0	0	80
500	5	F	V T YEL	7	1.009	0	0	0	0	0	75
1000	5	M	V T YEL	9	1.014	0	0	T	0	0	80
1000	5	F	T YEL	7	1.005	0	0	0	0	0	100
5000	5	M	V T YEL	7	1.009	0	0	0	0	0	100
5000	5	F	V T YEL	7	1.010	0	0	0	0	0	75

011335

4. Sacrifice and Pathology

a. Organ weight

The investigators provided group mean data only, the following table presents the provided organ weight data (from Table 5, pages 31-34 of the investigators report):

	THYROID				HEART			
LEVEL	WEIGHT	S	RATIO	S	WEIGHT	S	RATIO	S
ppm	g.	g.	%	%	g.	g.	%	%
CONTROL	0.033	0.011	0.0065	0.0023	1.67	0.18	0.332	0.039
500	0.030	0.005	0.0057	0.0013	1.68	0.31	0.320	0.054
1000	0.032	0.005	0.0064	0.0014	1.69	0.19	0.336	0.051
5000	0.033	0.007	0.0066	0.0016	1.62	0.15	0.324	0.039
CONTROL	0.025	0.002	0.0089	0.0013	1.04	0.14	0.371	0.051
500	0.027	0.003	0.0095	0.0016	1.08	0.16	0.389	0.071
1000	0.023	0.002	0.0084	0.0009	1.04	0.10	0.370	0.040
5000	0.025	0.003	0.0095	0.0010	0.84[S-]	0.28	0.326	0.109

	LIVER				SPLEEN			
LEVEL	WEIGHT	S	RATIO	S	WEIGHT	S	RATIO	S
ppm	g.	g.	%	%	g.	g.	%	%
CONTROL	18.45	1.74	3.66	0.29	0.85	0.13	0.17	0.03
500	19.70	2.80	3.75	0.31	0.87	0.13[2/]	0.17	0.03[2/]
1000	20.26	3.95	3.96	0.37	0.81	0.11	0.16	0.02
5000	19.76	2.59	3.94	0.40	0.80	0.10	0.16	0.03
CONTROL	9.98	1.12	3.53	0.24	0.65	0.18	0.23	0.07
500	9.91	1.53	3.51	0.38	0.56	0.08	0.20	0.03
1000	10.07	1.15	3.58	0.19	0.61	0.10	0.22	0.03
5000	9.49	1.01	3.66	0.36	0.50[S-]	0.07	0.19	0.03

011335

ALANAP S 10 SUBCHRONIC RAT

KIDNEYS

LEVEL ppm	WEIGHT g.	S g.	RATIO %	S %
CONTROL	3.49	0.18	0.695	0.049
500	3.69	0.42	0.704	0.072
1000	3.63	0.51	0.715	0.064
5000	3.67	0.35	0.733	0.056
CONTROL	2.24	0.58	0.797	0.234
500	1.96	0.19	0.698	0.055
1000	1.97	0.19	0.703	0.058
5000	1.90	0.19	0.736	0.070

ADRENALS

WEIGHT g.	S g.	RATIO %	S %
0.060	0.014	0.012	0.003
0.064	0.011	0.012	0.003
0.068	0.010	0.014	0.001
0.063	0.007	0.013	0.001
0.070	0.006	0.025	0.002
0.074	0.013	0.026	0.005
0.077	0.011	0.027	0.004
0.073	0.014	0.028	0.005

TESTES

LEVEL ppm	WEIGHT g.	S g.	RATIO %	S %
CONTROL	3.51	0.38	0.699	0.085
500	3.42	0.68	0.644	0.095
1000	3.16	0.98	0.610	0.154
5000	3.41	0.31	0.683	0.078

The high dose females had statistically significantly lower absolute heart and spleen weights, with the relative organ weights also reduced.

b. Gross pathology

The investigators reported that there were no treatment related observations, this was supported by the provided data (pages 37-77 of the investigators report). The following presents a description of major observations:

011335

Gross necropsy examination at terminal sacrifice did not reveal any significant or consistent gross findings which could be directly attributed to the ingestion of Alanap S.

The lungs of three to six rats of each sex in each group including the control group showed dark red spots or areas which were apparently caused by aspiration of blood at the time of sacrifice. In addition, dark pink lungs were found in four to six rats from the control group and each test group.

Apparently incidental findings in both control and test rats included the following:

Lungs: Abscessed or consolidated areas on the lungs in one control rat and two test rats at the 1000 ppm level.

Kidneys: A dilated pelvis in one or both organs in two control rats and one test rat at each the 1000 and 5000 ppm levels; in addition, the left kidney of one of the control rats was greatly enlarged and was filled with a pink fluid and a dark red material, and the right kidney of the 1000 ppm rat was filled with fluid.

Uterine Horns: Distended with fluid in one control rat only.

The following gross changes were seen in the test rats only:

500 ppm: A dark pink pancreas, mottled livers (two rats) and a light brown liver with dark purple-red areas, small testes (one rat), and a distended urinary bladder; in addition, one rat presented kidneys with a mottled surface, greenish brown cortex, and a dark purplish red outer medulla.

011335

1000 ppm: Livers with a mottled or yellow-tinged surface (four rats); dark red or purple-colored kidneys (two rats) and kidneys with a dark zone between the cortex and medulla (one rat); small, soft, bluish testes (two rats); and greatly distended urinary bladders (two rats).

5000 ppm: A dark zone between the renal cortex and medulla and a greatly distended urinary bladder (one rat each); in addition, one rat presented a dark reddish brown liver, enlarged adrenals, and one kidney with a dilated pelvis, green zone between the cortex and medulla, and a dark purplish pink outer medulla.

c. Microscopic pathology

The investigators provided individual animal data (pages 37-77 of the investigators report) and a pathologist's summary (pages 78-80 of the investigators report). The following is the summary from the report:

The dietary administration of 5000 ppm, Alanap S for approximately three months to male and female rats did not produce any distinct nor consistent compound-related cytologic changes in the tissues examined microscopically. The groups and levels were as follows: Group No. 1 (Control) and Group No. 4 (5000 ppm, Alanap S). The cytologic findings listed in the attached charts and summarized in the following paragraphs were considered spontaneous and not compound related.

One Group No. 1 rat (Rat No. 67-907) and one Group No. 4 rat (Rat No. 67-967) had minimal to slight focal encephalitis. Several small cysts were present in the anterior pituitary from one of nine Group No. 4 rats. Thyroid activity varied considerably from slight to moderate to high with the males in both Groups No. 1 and No. 4 having higher activity than the females in each group. The degree of activity appeared sex

related rather than compound related. The adrenals from seven of 10 Group No. 1 and five of 10 Group No. 4 rats were slightly to moderately congested. Minimal to slight focal lipidosis was present in the adrenal gland from one of 10 Group No. 1 and one of 10 Group No. 4 rats. The adrenals from two of 10 Group No. 1 and one of 10 Group No. 4 rats had small cortical nodules. Minimal extramedullary hematopoiesis was noted in the adrenal gland from one Group No. 4 rat.

The lungs from all Group No. 1 and Group No. 4 rats were slightly to moderately congested. Five of 10 Group No. 1 and three of 10 Group No. 4 rats had slight to moderate to severe agonal or terminal hemorrhage, mostly due to aspiration. Varying intensities of the murine pneumonia complex, characterized by peribronchiolar lymphoid hyperplasia and focal interstitial pneumonitis, were found in the lungs of most of Group No. 1 and Group No. 4 rats. The intensity of this pneumonia complex did not appear to be increased nor decreased when comparing the two groups. Abscessation of the lung was noted in one Group No. 1 rat (Rat No. 67-909). Most of the hearts from both Group No. 1 and Group No. 4 rats had slight to moderate congestion of the myocardial capillaries and blood vessels. One of 10 Group No. 1 and two of 10 Group No. 4 rats had minimal focal interstitial myocarditis.

Most of the livers from Group No. 1 and Group No. 4 rats had minimal to slight congestion. Minimal to slight pericholangitis was found in the livers from six of 10 Group No. 1 and seven of 10 Group No. 4 rats. Rather consistent findings in the spleen from both Group No. 1 and Group No. 4 rats were slight to moderate congestion, slight to moderate extramedullary hematopoiesis, and minimal to slight hemosiderosis. The kidneys from eight

011335

of 10 Group No. 1 and six of 10 Group No. 4 rats were slightly to moderately congested. Minimal focal interstitial nephritis was present in the kidneys from two of 10 Group No. 4 rats. Slight to moderate dilatation of the renal pelvis was noted in one of 10 Group No. 1 and two of 10 Group No. 4 rats. The kidney from one Group No. 1 rat had minimal mineralized deposits in the collecting tubules. Moderate to severe hydronephrosis was present in the kidney from one Group No. 1 rat (Rat No. 67-909).

The cytologic findings in the gastrointestinal tract were not remarkable. Minimal nodular lymphoid infiltrate was present in the lamina propria of the stomach from one of 10 Group No. 4 rats. One of 10 Group No. 4 rats had minimal focal periductal lymphocytic infiltrate in the pancreas. Minimal nodular lymphoid hyperplasia in the lamina propria of the small intestine was noted in three of 10 Group No. 1 and one of 10 Group No. 4 rats. Three of 10 Group No. 1 and three of 10 Group No. 4 rats had minimal to slight nodular lymphoid hyperplasia extending into the lamina propria of the large intestine.

The testes from both Group No. 1 and Group No. 4 rats indicated moderate spermatogenesis. The testes from one of five Group No. 4 rats had minimal spermatogenic giant cell formation.

The bone marrows from all Group No. 1 and Group No. 4 rats had moderate cellularity with megakaryocytes and active myelopoiesis and erythropoiesis. The following organs were within the limits of expected histologic appearance: eye, urinary bladder, ovary, and bone.

C. Discussion and Conclusions

Systemic toxicity was noted in the high dose group as reduced body weight gains in the females and reduced food efficiency in both males and females. High dose females also had decreased absolute and relative heart and spleen weights.

SYSTEMIC TOXICITY NOEL = 1000 ppm
SYSTEMIC TOXICITY LOEL = 5000 ppm

Study Deficiencies: purity of the test article was not provided (assumed 100%); little animal husbandry information was provided; platelet counts were not measured; calcium, blood creatinine, phosphorous, cholesterol, serum glutamic-oxaloacetic transaminase (serum aspartate aminotransferase, SGOT), sodium, potassium, chloride, total serum protein, albumin were not measured; aorta, salivary glands, periph. nerve, esophagus, spinal cord (3 levels), lymph nodes, thymus, cecum, lacrimal gland, mammary gland, rectum, parathyroids (possibly determined with thyroids), skeletal muscle, trachea, uterus, skin,all gross lesions and masses were not collected.

Page _____ is not included in this copy.

Pages __25__ through __33__ 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.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

__X__ FIFRA registration data.

__ _ __ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

__ _ __ Internal deliberative information.

_____ Attorney-Client work product.

__X__ Claimed Confidential by submitter upon submission to the Agency.

011335

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 7/15/94
Senior Pharmacologist, Review Section I, TBII (7509C)

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M.I. 7/15/94
Section Head, Review Section I, TBII (7509C)

DATA EVALUATION RECORD

Study Type: Subchronic Oral (Dietary) Toxicity
Species: Dog Guideline: §82-1b

EPA Numbers: EPA MRID# 00106277
EPA Pesticide Chemical Code 030703
Toxicology Chemical No. 592 (acid), 780A (Na salt)

Test Material: Alanap S

Synonyms: Naptalam

Title of Report: FINAL REPORT
13-WEEK Dietary Feeding - Dogs

Sponsor: Uniroyal Incorporated

Testing Facility: Hazleton Laboratories, Incorporated
Falls Church, Virginia

Study Number: Project No. 798-140

Author(s): G.C. Holsing, Ph.D.

Report Issued: March 1, 1968

Executive Summary: In a 13 week subchronic feeding study (MRID# 00106277), male and female adult beagle dogs (unknown source) received either 0, 300, 1000, or 3000-5000 ppm of Alanap S (equal to 11.4, 29.7, and 124.7 mg/kg/day in males and 9.7, 29.9, and 123.6 mg/kg/day in females).

Systemic toxicity was noted at the high dose (3000-5000 ppm) in the form of reduced body weight gains, reduced food efficiency and increased absolute and relative liver weights. **The LOEL for Systemic Toxicity is 3000 ppm and the NOEL for Systemic Toxicity is 1000 ppm based on reduced body weight gains, reduced food efficiency and increased absolute and relative liver weights.**

The study is classified as Core-Supplementary Data and does not satisfy the guideline requirements (§82-1b) for a subchronic oral toxicity study in non-rodents. This study cannot be upgraded due to numerous reporting and study deficiencies.

011335

A. Materials and Methods: A copy of the Materials and Methods section from the investigators report is attached.

1. Test compound: Alanap S (Naptalam)
Description - Fine, pale tan powder with a faint unpleasant odor
Lot # - C-465
Purity - assumed 100%
Received - July 27, 1967
Contaminants - none reported

2. Vehicle(s): None used

3. Test animals: Species: young adult male and female dogs
Strain: beagle
Age: not provided
Weight: 6.9-15.9 kg at study initiation
Source: not provided

4. Animal assignment

Animals were assigned to the following test groups; no indication as to method of assignment was provided:

Test Group	Dose in Diet (ppm)	# males	#females
1 Control	None	3	3
2 Low (LDT)	300	3	3
3 Mid (MDT)	1000	3	3
4 High (HDT)	3000 to 5000*	3	3

* study made reference to at least 3 dosages, 3000, 4000, and 5000 ppm; however, information on this was illegible

5. Diet preparation

Diet was prepared weekly, no storage method provided. There was no indication if samples of dietary admix were analyzed for stability and concentration.

6. Animal Husbandry

Animals were housed in metal cages and received Ground Wayne Dog Meal and water *ad libitum*. No other information was provided.

7. Clinical Observations

Animals were inspected daily for *appearance, behavior, appetite, elimination and signs of compound effect*. They were weighed weekly and food consumption was determined weekly.

011335

8. Ophthalmological examination

Ophthalmological examinations were not performed as they are not required in subchronic studies.

9. Hematology and Clinical Chemistry

Blood was collected before treatment and at 1 and 3 months for hematology and clinical chmeistry analysis from all animals.

a. Hematology

The following parameters were measured:

Erythrocyte count (RBC)*
Leukocyte count (WBC)*
Leukocyte differential count*
Hematocrit (HCT)*
Hemoglobin (HGB)*
* Required for subchronic studies

The following parameters required for subchronic studies were not determined:

Platelet count*

b. Clinical Chemistry

The following parameters were measured:

Blood sugar (Glucose)*
Blood urea nitrogen*
Serum glutamic-pyruvic transaminase (Serum alanine aminotransferase, SGPT)*
Serum glutamic-oxaloacetic transaminase (Serum aspartate aminotransferase, SGOT)*
Alkaline phosphatase (ALK)
Serum electrolytes (Sodium*, Potassium*, Chloride*)
Total serum Protein (TP)*
Albumin*
* Required for subchronic studies

The following parameters required in subchronic studies were not determined:

Calcium*, Blood creatinine*, Phosphorous*, Cholesterol*

011335

10. Urinalysis^

Urine was collected prior to study initiation and at 1 and 3 months; there was no indication if animals were fasted. The following parameters were examined:

Appearance (volume also?)	Protein
pH	Bilirubin
Specific gravity	Occult Blood
Sugar (Glucose)	Sediment (microscopic)
Acetone (Ketones)	

^Not required for subchronic studies

11. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination and the following tissues were collected for histological examination, the bolded organs, in addition, were weighed (the organs with **M** were examined microscopically in the control and high dose groups only):

Brain*+
Pituitary*
Eyes (optic nerve?)*#**M**
Thyroids*++**M**
Lung*
Heart*
Liver*+**M**
Gall bladder*
Spleen M
Kidneys*+**M**
Adrenal gland*
Stomach*
Pancreas***M**
Duodenum*, Jejunum*, Ileum*, Colon*
Urinary bladder*
Ovaries*+
Bone*# (costochondral junction)
Bone marrow* (sternum)
Testes*+

The following required for subchronic studies were not examined: Aorta*, Salivary glands*, Periph. nerve*#, Esophagus*, Spinal cord (3 levels)*#, Lymph nodes*, Thymus*, Cecum*, Lacrimal gland#, Mammary gland*#, Rectum*, Parathyroids*++ (possibly determined with thyroids), Skeletal muscle*#, Trachea*, Uterus*, Skin*#,All gross lesions and masses*

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

011335

12. Statistics

There was no indication of statistical procedures utilized.

13. Compliance

No statements of data confidentiality claims, compliance with GLP's quality assurance or flagging criteria were provided.

011335

B. RESULTS:

1. Clinical Observations

a. Clinical signs of toxicity/mortality

No clinical signs of toxicity were reported.

b. Body weight

Only individual animal data were provided. The following table presents body weight gain data (kg) calculated by the reviewer from the individual animal data:

Weeks:		Control	300	1000	3000
1-13	M	0.4	1.3	0.6	0
	F	0.5	1.2	0.5	0.3

Although only 3 animals per sex per dose group were used, it is apparent that the high dose group gained less weight than the control.

c. Food consumption, food efficiency and compound intake

Only individual animal data were provided. The following table presents food consumption data (kg/wk) calculated by the reviewer from the individual animal data:

Weeks:		Control	300	1000	3000
1-13	M	2.4	2.9	2.4	2.5
	F	2.1	2.1	1.9	2.0

The following table presents the food efficiency calculated by the reviewer from the above data:

Weeks:		Control	300	1000	3000
1-13	M	1.3	3.5	2.0	0
	F	1.9	4.4	2.0	1.2

Although food consumption seemed relatively unaffected, the food efficiency was reduced compared to control in the high dose group.

011335

The following table presents the compound intake (mg/kg/day) calculated by the reviewer from the individual animal data:

	Low	Mid	High
M	11.4	29.7	124.7
F	9.7	29.9	123.6

2. Hematology and Clinical Chemistry

a. Hematology

No treatment related effects were noted; the following table presents data from the tables provided in the investigators report:

DOG NO.	S E X	TIME INTERVAL months	HCT. %	HGB. g.%	RBC 10^6/cmm	WBC 10^3/cmm	DOG NO.	S E X	TIME INTERVAL months	HCT. %	HGB. g.%	RBC 10^6/cmm	WBC 10^3/cmm
CONTROL													CONTROL
12117	M	0	44.0	15.1	5.26	16.1	12185	F	0	50.0	18.2	6.92	10.5
		1	44.0	16.1	6.04	16.8			1	45.0	17.6	5.78	8.3
		3	45.0	16.3	6.77	15.6			3	50.0	17.0	7.62	9.2
12288	M	0	51.0	18.4	6.83	11.8	12189	F	0	58.0	18.9	7.81	11.5
		1	51.0	19.5	6.69	9.1			1	53.0	20.6	5.70	8.8
		3	54.0	18.3	7.70	9.1			3	51.0	17.6	7.71	9.0
12103	M	0	49.0	16.7	6.53	15.3							
		1	48.0	18.4	6.18	8.7	12246	F	0	47.0	16.5	7.22	14.0
		3	48.0	16.8	7.53	14.8			1	47.0	18.2	6.36	11.3
									3	48.0	16.5	7.03	24.9
300 PPM													300 PPM
12144	M	0	42.0	15.4	5.13	17.7	12186	F	0	55.0	19.7	7.90	10.7
		1	39.0	15.9	5.06	15.0			1	50.0	18.7	4.91	7.6
		3	46.0	15.7	6.45	8.7			3	48.0	17.0	7.58	11.7
12302	M	0	54.0	18.6	5.03	10.6	12188	F	0	55.0	19.5	7.62	14.6
		1	49.0	16.9	4.24	8.9			1	54.0	19.6	5.49	11.7
		3	51.0	17.6	7.36	7.8			3	51.0	18.1	7.67	13.2
12305	M	0	50.0	18.4	6.83	13.8							
		1	48.0	17.6	6.58	12.1	12328	F	0	46.0	16.5	6.28	11.8
		3	47.0	16.1	6.85	10.4			1	50.0	19.4	4.81	7.1
									3	50.0	17.6	7.97	15.8

011335

DOG NO.	SEX	TIME INTERVAL (weeks)	HCT. %	HGB. g/%	RBC x10⁶/cmm	WBC x10³/cmm	DOG NO.	SEX	TIME INTERVAL (weeks)	HCT. %	HGB. g/%	RBC x10⁶/cmm	WBC x10³/cmm
			1000 PPM										1000 PPM
12304	M	0	49.0	18.2	5.96	12.2	12251	F	0	49.0	17.6	6.63	11.0
		1	44.0	17.1	3.92	10.6			1	48.0	17.6	5.04	8.6
		3	42.0	14.1	6.04	11.5			3	48.0	16.3	6.98	9.5
12307	M	0	53.0	19.5	6.40	13.1	12253	F	0	47.0	16.5	6.73	10.4
		1	49.0	19.7	5.81	8.7			1	47.0	18.6	4.96	8.4
		3	47.0	16.5	6.89	8.8			3	47.0	16.3	6.78	10.4
12316	M	0	47.0	16.9	6.77	15.0	12327	F	0	44.0	14.4	5.04	12.6
		1	44.0	17.6	4.03	20.2			1	43.0	17.8	5.21	11.8
		3	49.0	16.3	7.27	30.8			3	[illegible]	15.2	6.47	13.3
		REPEAT				32.2							
			3000 TO 5000 PPM										
12282	M	0	52.0	19.5	7.16	16.8	12244	F	0	47.0	16.7	7.12	12.7
		1	51.0	19.4	5.50	20.5			1	49.0	19.6	6.20	11.0
		3	47.0	16.8	6.64	9.6			3	47.0	16.8	7.67	8.8
12306	M	0	47.0	17.2	5.89	12.7	12254	F	0	51.0	17.8	6.09	8.8
		1	45.0	17.4	4.32	9.2			1	46.0	17.4	5.20	9.5
		3	41.0	14.3	5.69	10.9			3	47.0	15.9	6.84	8.5
12315	M	0	47.0	16.7	6.20	12.7	12278	F	0	46.0	17.2	5.97	17.1
		1	52.0	19.6	6.96	10.4			1	44.0	17.4	5.68	11.2
		3	50.0	17.4	7.36	12.3			3	45.0	15.9	7.03	8.4

b. Clinical Chemistry

No treatment related effects were noted; the following table presents data from the tables provided in the investigators report:

D11335

ALANAP S [redacted] 9 DOG SUBCHRONIC

DOG NO.	SEX	TIME INTERVAL weeks	[redacted] mg. %	BUN mg.%	% DEP SULFOBR. 30 min.	SGPT (ALT) U/L	SGOT (AST) U/L	ALK. PHOS. U/L	PROTH. TIME secs.	BA mEq/L	K mEq/L	Cl mEq/L
						CONTROL						
12117	M	0	69	16.0		20	35	5.4		152	4.65	123
		1	101	15.0		10	30	1.6		146	5.00	123
		3	110	15.0		24	115	1.4		152	5.20	123
12288	M	0	84	16.0		23	18	1.3		148	5.00	117
		1	90	13.0		14	25	0.5		145	5.45	116
		3	88	15.5		17	25	.5		149	5.60	117
12303	M	0	72	15.0		25	19	1.8		144	4.80	118
		1	95	17.0		13	26	0.7		146	4.50	121
		3	90	19.0		17	16	0.8		146	4.90	114
12165	F	0	105	11.5		11	30	2.5		149	4.00	120
		1	84	15.0		9	30	1.1		148	4.90	119
		3	88	14.0		13	20	0.8		149	4.60	117
12189	F	0	105	18.0		14	32	2.3		152	4.55	113
		1	91	16.0		8	25	1.0		147	5.30	117
		3	86	17.0		13	20	0.7		148	4.80	116
12246	F	0	120	16.5		17	29	2.5		154	4.35	120
		1	107	17.0		14	28	1.0		155	5.20	124
		3	76	13.0		14	22	1.5		149	4.35	121
						300 PPM						
12144	M	0	80	11.0		19	31	2.9		148	5.20	117
		1	96	14.0		9	30	1.0		145	5.25	116
		3	87	10.0		16	22	0.9		146	5.20	116
12302	M	0	74	16.5		25	18	3.5		143	4.55	117
		1	95	15.0		9	24	1.9		145	5.60	119
		3	94	15.0		13	21	1.6		145	5.40	116
12305	M	0	80	16.0		16	18	1.5		144	4.05	117
		1	99	19.0		13	16	0.8		145	4.55	119
		3	91	17.0		16	29	1.0		150	4.80	116
[redacted]	F	0	91	19.5		20	28	1.4		149	4.10	117
		1	102	10.5		10	32	0.8		149	5.10	117
		3	86	11.0		17	33	0.7		150	5.00	117
12166	F	0	115	14.0		11	30	2.9		150	3.75	116
		1	104	15.5		14	32	1.2		149	5.05	119
		3	99	13.0		13	33	0.9		149	4.60	115
12326	F	0	75	14.5		46	28	2.4		155	4.60	116
		1	97	14.0		12	27	1.4		149	5.90	114
		3	84	13.0		16	35	1.0		149	5.00	115

42

011335

ALANAP S

DOG SUBCHRONIC

ANIM. NO.	SEX	TIME INTERVAL (weeks)	WEIGHT (kg)	BUN (mg %)	% DEP (EXTENT 30 min.)	SGPT (I.U.)	SGOT (I.U.)	ALK. PO4 (B.-L.-B units)	PROTH. TIME (secs.)	NA (mEq/L)	K (mEq/L)	Cl (mEq/L)
						1000 PPM						
12304	M	0	75	13.0		30	19	1.0		144	4.65	116
		1	105	14.5		12	27	0.7		148	5.20	117
		3	91	17.0		16	27	0.7		148	4.95	116
12307	M	0	76	12.0		43	17	1.9		144	4.30	116
		1	100	12.5		8	22	1.1		146	5.75	116
		3	91	13.0		16	36	0.9		149	5.50	116
12316	M	0	97	14.0		21	20	2.5		149	5.00	122
		1	86	14.0		14	26	0.9		149	5.00	116
		3	96	13.0		6	32	0.8		149	5.35	119
12251	F	0	94	20.5		13	26	3.7		150	4.60	119
		1	99	18.5		7	27	1.6		149	4.80	121
		3	101	18.0		10	34	1.4		149	4.50	117
12253	F	0	94	11.5		16	21	2.4		147	5.20	117
		1	105	11.0		12	24	1.0		148	5.75	119
		3	116	13.0		20	32	0.9		152	4.40	114
12327	F	0	90	7.0		14	24	2.8		155	4.30	117
		1	91	12.5		8	26	1.2		148	5.10	116
		3	93	12.0		8	27	1.2		152	4.60	117
						3000 TO 5000 PPM						
12282	M	0	76	14.5		22	23	1.8		152	4.35	122
		1	120	17.0		9	31	1.2		153	5.90	123
		3	99	16.0		23	32	1.7		154	4.50	119
12306	M	0	80	10.0		26	22	1.3		149	3.95	120
		1	96	12.0		14	22	0.8		149	5.00	120
		3	99	10.0		12	28	1.0		149	4.60	119
12315	M	0	90	14.0		32	30	3.0		148	4.20	116
		1	105	16.0		12	35	1.2		148	5.20	116
		3	104	18.0		16	33	1.2		152	4.70	117
12244	F	0	90	17.5		16	30	3.5		151	4.25	116
		1	115	20.0		12	30	2.1		150	4.65	121
		3	99	21.0		9	32	2.0		152	4.95	116
12294	F	0	87	15.0		27	23	2.0		151	4.65	120
		1	90	17.0		16	34	1.4		150	4.80	121
		3	91	19.0		18	39	2.2		152	4.40	117
12278	F	0	71	13.5		34	30	2.9		153	4.25	120
		1	104	23.0		11	27	1.6		151	4.50	124
		3	104	24.0		16	30	2.3		152	4.60	120

43

011335

ALANAP S

DOG SUBCHRONIC

DOG NO.	SEX	TIME INTERVAL (months)	TOTAL PROTEIN G. %	ALBUMIN G. %	DOG NO.	SEX	TIME INTERVAL (months)	TOTAL PROTEIN G. %	ALBUMIN G. %
			CONTROL						CONTROL
12117	M	0	6.5	2.0	12185	F	0	6.5	1.9
		1	6.4	1.7			1	7.0	1.5
		3	6.8	2.4			3	7.0	2.2
12288	M	0	7.3	2.1	12189	F	0	6.7	2.2
		1	6.5	1.9			1	6.7	2.0
		3	7.1	2.3			3	6.8	2.4
12303	M	0	7.1	1.7	12246	F	0	6.5	2.0
		1	6.4	1.5			1	7.1	1.7
		3	6.6	2.2			3	7.1	2.2
			300 PPM						300 PPM
12144	M	0	6.3	1.8	12186	F	0	7.6	1.8
		1	6.1	1.5			1	6.2	1.7
		3	6.2	2.2			3	6.6	2.5
12302	M	0	7.6	1.8	12188	F	0	7.5	2.8
		1	7.3	1.7			1	7.0	2.0
		3	7.6	2.4			3	7.0	2.7
12305	M	0	6.7	2.1	12328	F	0	6.6	2.2
		1	6.6	1.9			1	6.7	2.1
		3	7.2	2.3			3	7.1	3.1
			1000 PPM						1000 PPM
12304	M	0	7.0	1.9	12251	F	0	6.5	2.1
		1	6.6	1.9			1	6.6	2.2
		3	6.6	2.6			3	6.8	2.8
12307	M	0	7.0	1.9	12253	F	0	6.6	2.2
		1	6.9	1.7			1	6.5	2.1
		3	6.7	2.5			3	6.9	2.4
12316	M	0	6.4	1.7	12327	F	0	6.7	2.0
		1	6.6	1.2			1	6.5	1.9
		3	6.5	2.2			3	6.5	2.5
			3000 TO 5000 PPM						
12282	M	0	7.1	2.0	12244	F	0	6.4	2.0
		1	7.2	1.7			1	6.6	1.6
		3	6.6	2.5			3	6.9	2.6
12306	M	0	7.7	2.0	12294	F	0	6.6	2.0
		1	7.1	1.6			1	6.6	1.6
		3	7.3	2.4			3	7.1	2.6
12315	M	0	6.0	1.6	14478	F	0	7.0	1.7
		1	6.3	1.7			1	6.8	1.8
		3	6.5	2.3			3	6.9	2.6

011335

3. Urinalysis

No treatment related effects were noted; the following table presents data from the tables provided in the investigators report:

DOG NO.	SEX	TIME INTERVAL months	APPEAR.	[redacted]	SP. GR.	SUGAR	ACE-TONE	PRO-TEIN	BILI-RUBIN	OCCULT BLOOD
		0							CONTROL	
12117	M	INITIAL	V T	YEL	7	1.041	U	U	1	0	0
		1	T	YEL	6	1.040	U	U	1	T	0
		3	VT	DY	7	1.034	U	U	1	T	T
12288	M	INITIAL	T	YLL	7	1.022	U	U	0	1	0
		1	T	YEL	7	1.041	U	U	1	T	0
		3	T	YEL	8	1.030	U	U	1	1	U
12303	M	INITIAL	V T	YEL	7	1.046	U	U	1	1	0
		1	T	YEL	7	1.056	U	U	1	T	0
		3	T	YEL	5	1.025	U	U	T	T	0
12185	F	INITIAL	T	YEL	7	1.030	0	U	1	0	0
		1	V T	YLL	8	1.036	U	U	1	U	U
		3	T	YEL	7	1.040	U	U	1	0	0
12189	F	INITIAL	V T	YEL	7	1.030	U	U	T	0	0
		1	V T	YEL	7	1.030	U	U	1	T	1
		3	T	YEL	7	1.046	U	U	1	0	0
12246	F	INITIAL	T	YEL	6	1.040	U	U	1	0	T
		1	T	YEL	6	1.045	U	U	1	0	0
		3	T	YEL	5	1.060	U	U	1	0	T
		MEAN				1.033					

011335

DOG NO.	SEX	TIME INTERVAL months	APPEAR.	pH	SP. GR.	SUGAR	ACETONE	PROTEIN	BILIRUBIN	OCCULT BLOOD
									300 PPM	
12144	M	INITIAL	V T YEL	7	1.051	0	0	1	0	0
		1	T YEL	5	1.041	0	0	T	0	0
		3	T YEL	7	1.040	0	0	1	1	0
12302	M	INITIAL	T YEL	6	1.045	0	0	1	1	0
		1	V T YEL	7	1.025	0	0	1	T	0
		3	T YEL	6	1.038	0	0	1	1	0
12305	M	INITIAL	T YEL	6	1.037	0	0	1	1	0
		1	T YEL	6	1.043	0	0	1	1	0
		3	T YEL	5	1.050	0	0	1	T	0
12186	F	INITIAL	V T YEL	9	1.032	0	0	1	0	0
		1	T YEL	9	1.025	0	0	T	0	0
		3	T YEL	8	1.036	0	0	1	0	0
12188	F	INITIAL	T YEL	8	1.030	0	0	1	0	0
		1	T YEL	6	1.040	0	0	T	0	0
		3	T YEL	6	1.035	0	0	T	0	0
12328	F	INITIAL	T YEL	6	1.060	0	0	1	0	0
		1	T YEL	6	1.035	0	0	T	0	T
		3	T YEL	6	1.039	0	0	T	0	0
					1000 PPM					
12304	M	INITIAL	V T YEL	8	1.035	0	0	1	1	0
		1	T YEL	6	1.030	0	0	T	T	0
		3	T YEL	5	1.045	0	0	1	2	0
12307	M	INITIAL	T YEL	7	1.035	0	0	1	T	0
		1	T YEL	5	1.030	0	0	1	1	0
		3	T YEL	6	1.045	0	0	T	2	0
12316	M	INITIAL	T YEL	7	1.050	0	0	1	0	0
		1	T YEL	7	1.010	0	0	T	0	T
		3	T YEL	7	1.010	0	0	0	T	0

011335

ALANAP S

14

DOG SUBCHRONIC

DOG NO.	SEX	TIME INTERVAL Months	APPEAR.	pH	SP. GR.	SUGAR	ACETONE	PROTEIN	BILIRUBIN	OCCULT BLOOD
				1000 PPM						
12251	F	INITIAL	T YEL	7	1.050	0	0	1	0	0
		1	T YEL	7	1.050	0	0	1	1	0
		3	T YEL	6	1.048	0	0	T	T	0
12253	F	INITIAL	T P YEL	7	1.015	0	0	T	0	0
		1	V T YEL	6	1.035	0	0	T	1	0
		3	T YEL	7	1.030	0	0	1	0	0
12327	F	INITIAL	T YEL	8	1.021	0	0	T	0	0
		1	T YEL	8	1.035	0	0	T	1	0
		3	T YEL	9	1.050	0	0	1	0	0
				3000 TO 10000 PPM						
12282	M	INITIAL	V T YEL	7	1.038	0	0	1	1	0
		1	T YEL	6	1.045	0	0	1	1	0
		3	T YEL	6	1.028	0	0	1	1	0
12306	M	INITIAL	T YEL	8	1.032	0	0	T	T	0
		1	T YEL	7	1.040	0	0	1	1	0
		3	V T YEL	5	*1.060	0	0	1	2	0
		REPLAT			1.014					
12315	M	INITIAL	T YEL	6	1.046	0	0	T	0	0
		1	T YEL	6	1.050	0	0	T	1	0
		3	V T YEL	6	*1.060	0	0	1	1	0
		REPEAT			1.040					
12244	F	INITIAL	T YEL	7	1.042	0	0	1	0	0
		1	T YEL	8	1.020	0	0	1	1	0
		3	T YEL	6	1.030	0	0	1	-	
12254	F	INITIAL	T P YEL	6	1.026	0	0	0	0	0
		1	T YEL	9	1.025	0	0	T	T	0
		3	T YEL	7	1.025	0	0	T	0	0
12278	F	INITIAL	T YEL	6	1.040	0	0	0	0	0
		1	T YEL	6	1.040	0	0	T	1	0
		3	T YEL	5	1.030	0	0	T	0	0

011335

4. Sacrifice and Pathology

a. Organ weight

According to the investigators, no treatment related effects were noted; however, it appears that there is a dose related increase in liver weight, both absolute and relative. The following table presents data from the tables provided in the investigators report:

Organ:	Control	Low	Mid	High
Thyroid				
M	0.979/0.0080[1]	0.790/0.0073	1.116/0.0100	0.910/0.0085
F	0.936/0.0095	0.959/0.0106	0.986/0.0110	1.006/0.0125
Heart				
M	98.333/0.8227	91.100/0.8470	91.533/0.8171	90.633/0.8462
F	82.133/0.8398	79.500/0.8735	81.200/0.8856	70.366/0.8950
Liver				
M	306.333/2.5488	316.666/2.9521	334.666/2.9842	377.666/3.5576
F	260.333/2.6399	262.666/2.8196	266.000/2.9125	301.333/3.7894
Spleen				
M	35.633/0.2935	26.666/0.2489	28.433/0.2568	30.466/0.2915
F	28.133/0.2818	25.833/0.2844	23.066/0.2509	23.600/0.3022
Kidneys				
M	61.900/0.5169	57.266/0.5320	59.166/0.5305	55.066/0.5175
F	48.766/0.4995	47.999/0.5297	42.999/0.4723	41.133/0.5222
Adrenals				
M	1.270/0.0106	1.029/0.0095	1.326/0.0119	1.110/0.0105
F	1.033/0.0105	1.093/0.0121	0.993/0.0109	0.999/0.0129
Testes	27.333/0.2324	23.300/0.2163	21.399/0.1927	22.833/0.2159

[1] = absolute/relative

Data extracted from Report 798-140, Table 5.

b. Gross pathology

No treatment related effects were noted (individual animal data only were provided). Observations were singular in nature.

c. Microscopic pathology

No treatment related effects were noted (individual animal data only were provided). Observations were singular in nature.

C. Discussion and Conclusions

Systemic toxicity was noted at the high dose (3000-5000 ppm) in the form of reduced body weight gains, reduced food efficiency and increased absolute and relative liver weights.

Systemic Toxicity NOEL = 1000 ppm
Systemic Toxicity LOEL = 3000 ppm

C43
2

INTRODUCTION

The purpose of this study was to characterize and evaluate the subacute oral toxicity of Alanap 8 in dogs. The study was started on August 30, 1967, and terminated on December 13, 1967.

MATERIAL

Identification: Alanap 8 (Lot No. C-465).

Received: July 27, 1967, from Uniroyal Incorporated.

Description: Fine, pale tan powder with a faint unpleasant odor.

Purity: Assumed 100%.

METHODS

Experimental Animals

Breed: Young adult purebred beagles.

Number: Twelve males and 12 females.

Body Weight (at initiation): 6.9 to 15.9 kg.

Housing: [redacted] individually in metal cages.

Diet: [redacted] Wayne Dog Meal and water ad libitum.

Treatment Levels

GROUP NO.	NO. OF ANIMALS	
	male	female
1 (Control)	[redacted]	[redacted]
2		
3		
4		

Diet Preparation

The test material was incorporated into the basal diet on a weight per weight basis and thoroughly mixed in a twin-shell blender to provide the appropriate dietary levels. Fresh compound/diet mixtures were prepared weekly.

Compound Administration

The compound/diet mixtures were available to the compound treated dogs continuously for 13 weeks. The control dogs received the basal diet only.

Observations and Records

Daily: Appearance, behavior, appetite, elimination, and signs of compound effect.

Weekly: Body weights and food and compound consumption.

Clinical Laboratory Studies

Performed: Once initially and at one and three month-

Hematology: Erythrocyte counts, total and differential leukocyte counts, [redacted] and hematocrit and hemoglobin determinations.

Biochemistry: Blood sugar, blood urea nitrogen, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, serum electrolytes, total protein, and albumin.

Urine Analyses: Appearance, pH, specific gravity, sugar, acetone, protein, bilirubin, occult blood, and microscopic examination of the sediment.

D11335

RAVEN Augusta Maine 10-6-72

C45
4

- 4 -

Terminal Studies

Terminal Sacrifice: All dogs after 13 weeks of dietary feeding.

Gross Necropsies: On all sacrificed dogs.

Organs Weights: Thyroids, heart, liver, spleen, kidneys, adrenals, and testes.

Tissues Preserved: In 10% neutral buffered formalin - brain, pituitary, eyes, thyroids, lung, heart, liver, gallbladder, spleen, kidneys, adrenals, stomach, pancreas, duodenum, jejunum, ileum, colon, urinary bladder, ovaries, bone (costochondral junction), and bone marrow (sternum). In Bouin's fixative - testes.

Microscopic Examination: All cited tissues from the control and high level dogs, and eyes, thyroids, liver, kidney, and pancreas from all dogs at each of the two lower levels as well as the spleen of one animal from each of the two lower levels.

Tissue Storage: Wet tissues and paraffin blocks are being stored at Hazleton Laboratories, Inc., for possible future reference.

RESULTS

[redacted] Behavior, Body Weight Changes, Signs of Compound Effect

Checking body weights and food and compound consumption are presented in Table No. 1.

The control dogs maintained normal appearance and behavior, ate well, and had normal elimination during the study. Four dogs gained body weight, the gains ranging from 0.6 to 1.8 kg., and the other two dogs lost 0.4 and 0.5 kg.

146

011335

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 6/22/94
Senior Pharmacologist, Review Section I, TBII/HED (7509C)

Secondary Review by: James N. Rowe, Ph.D. James N. Rowe 6/22/94
Section Head, Review Section III, TBII/HED (7509C)

DATA EVALUATION RECORD

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

EPA ID No.s: EPA MRID No. 00106320
EPA Pesticide Chemical Code 030703
Toxicology Chemical Code 780A (Na salt), 592 (acid)

Test Material: Alanap S Technical (Na Salt)

Synonyms: Naptalam, C465

Title of Report: Teratologic Evaluation of Alanap S Technical in Sprague-Dawley Rats

Sponsor: Uniroyal Chemical, Bethany Conn 06526

Testing Facility: Food and Drug Research Laboratories, Inc. (FDRL)

Study Number(s): 5888a

Author(s): Michael Knickerbocker, Thomas A. Re, Ph.D.

Report Issued: December 22, 1978

Executive Summary: In a developmental toxicity (teratology) study (MRID# 00106320), sexually mature Sprague-Dawley rats of the BLU: (SD) BR strain from Blue Spruce Farms, Inc., Altamont, NY received either 0, 15, 115, or 500 mg/kg/day Alanap S Technical (Na Salt; unknown purity) by oral gavage in corn oil. The study originally had a high dose of 900 mg/kg/day of which all animals died after the first few doses; a new group was substituted using 500 mg/kg/day.

Maternal toxicity was noted at 115 mg/kg/day and above in the form of reduced body weight gain during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20), for the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period (except 115 mg/kg/day). The 900 mg/kg/day dose group had complete deaths and there was increased maternal wastage at 500 mg/kg/day. **The Maternal Toxicity LOEL is 115 mg/kg/day and the Maternal Toxicity NOEL is 15 mg/kg/day based on reduced body weight gain.**

Developmental toxicity was noted in the 500 mg/kg/day dose

011335

group as lower mean fetal weight compared to the control group and there was an increased incidence of unspecified missing sternebrae, incomplete ossification of unspecified vertebrae, unspecified skull bones, unspecified extremities and increased missing or reduced hyoid bone in the 500 mg/kg/day dose group. **The Developmental Toxicity LOEL is 500 mg/kg/day and the Developmental Toxicity NOEL is 115 mg/kg/day based on reduced mean fetal weight and increased skeletal observations.**

The study is classified as Core Supplementary Data and does not satisfy the guideline requirement for a developmental toxicity (teratology) study (§ 83-3a) in the rat. The study may be upgraded if the deficiencies listed below are addressed to the Agency's satisfaction.

Study Deficiencies:

The percent active ingredient of the test compound was not provided.

No analysis of dosing solutions was performed (however, toxicity was noted so the animals did receive compound).

Bones that were affected in the fetuses were not identified.

Limited data were provided for maternal effects; however, this study was conducted prior to the 1984 Guidelines.

011335

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

Test Compound: Alanap S
Purity: not provided
Density: not provided
Description: light brown powder
Batch No. B19062, CC4035
Receipt date: April 22, 1980
Contaminants: none provided

Vehicle(s): corn oil

Test Animal(s): Species: sexually mature Sprague-Dawley rats
Strain: BLU: (SD) BR
Source: Blue Spruce Farms, Inc., Altamont, NY
Age: not provided
Body Weight: females - 248.6-269.1 g - day 0
Males - same strain

B. Study Design

This study was designed to assess the developmental toxicity potential of Alanap S when administered by oral gavage (intragastric intubation) to Sprague-Dawley rats on gestation days 6 through 15, inclusive.

Mating Procedure

Natural mating was used, the females were mated with males at a 1:1 ratio (female:male). *Observation of the vaginal sperm plug was considered day 0 of gestation.*

Animal Husbandry

Animals were kept under standard animal care conditions and there was no indication as to the time period the animals were acclimated to the laboratory conditions. They received ground Charles River Rat/Mouse/Hamster Formula (Agway) and tap water *ad libitum.*

Group Arrangement:

Test Group	Dose Level (mg/kg)	Number Assigned
Control	Corn Oil	40
Positive Control	Aspirin: 250 mg/kg/day)	45
Low Dose	15	30
Mid Dose	115	25
High Dose	900/500*	34

** = Level terminated after two weeks due to excessive deaths of dams. New level of 500 mg/kg/day Alanap added to study 8/7/78.*

No indication was given as to how doses were chosen.

011335

Dose Administration:

All doses were administered in a volume of 10 ml/kg of body weight/day prepared weekly during the dosing period. The dosing solutions were not analyzed for concentration and stability. Dosing was based on gestation day 6 body weight.

Observations

The animals were checked daily for mortality or abnormal condition and body weights were taken on gestation days 0, 6, 11, 15, and 20. Dams were sacrificed on day 20 of gestation. Examinations at sacrifice consisted of the following (from the investigators report):

> At the time of sacrifice on day 20 (or if the animal died [redacted] sacrificed moribund) the following observations were recorded for each female: numbers of corpora lutea, implantation sites, resorption sites, live and dead fetuses; sex of fetuses; and body weights of fetuses.

The fetuses were examined in the following manner (from the investigators report):

> At the time of uterine examination, all fetuses were examined grossly for the presence of external congential abnormalities. One-third of the fetuses from each litter were randomly selected and placed in Bouin's solution of detailed visceral examination employing the Wilson free-hand slicing technique. Any fetus showing external abnormalities was selected for examination by this technique.
>
> The remaining fetuses were eviscerated, fixed in 70% isopropyl alcohol, macerated in a 2% potassium hydroxide solution, stained with Alizarin-Red S dye, cleared in glycerine, and examined under low power magnification for skeletal anomalies and ossification variations. Each fetus was processed, examined and stored for possible further examination in a manner retaining the identity of both dam number and uterine position.

011335

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

Statistical analysis

The following statistical analysis methods were employed (from the investigators report):

> Incidences of occurence were expressed as percent, and comparisons between the control and test groups were made using 95% confidence intervals for proportions or by computation of exact probabilities. Continuous data were analyzed using a one-way completely random classification analysis of variance for fixed effects. Differences were deemed significant when the probability of rejecting the null hypothesis when true was less than 0.05. The least significant difference test was then employed to determine which test group(s) differed from the control.
>
> Continuous data from both test materials were evaluated simultaneously to increase the degree of freedom and better indicate differences.

Compliance

A signed and dated statement of no data confidentiality claims was not provided.

A signed and dated good laboratory practices statement of compliance was not provided.

A signed and dated review by the quality assurance unit was not provided.

A Flagging Criteria statement was not provided.

011335

C. Results

Analysis of Dosing Solutions

No analysis was presented in the report.

1. Maternal Toxicity:

Mortality

All animals died at the 900 mg/kg/day dose group after 3 or 4 doses; therefore an additional dose level of 500 mg/kg/day was added. No data were provided for the 900 mg/kg/day dose group animals.

Clinical Observations

No clinical signs related to treatment were reported.

Body Weight

The investigators provided group mean, and individual animal data. The following table presents body weight gain data calculated by the reviewer from the supplied mean body weight data (except for 0-20):

Table I: Body Weight Gains (grams)[a]

Group:	0-6	6-15	15-20	6-20	0-20
Control	19.4	32.1	62.8	94.9	114.3
Aspirin	19.1	15.6[48.6][1]	38.9[61.9]	54.5[57.4]	73.6*[64.4]
LDT	19.2	31.6	63.0	94.6	113.6
MDT	17.4	28.4[88.5]	57.0[90.8]	85.4[90.0]	102.8[89.9]
HDT	18.2	9.8[30.5]	55.7[88.7]	65.5[69.0]	83.7*[73.2]

* = 0.05 as compared to control [only data analyzed statistically]
[1] = percent of control
[a] = Data extracted from Laboratory No. 5888a, Table 2.

From the provided data it is apparent that the mid and high dose groups gained less weight than the control during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20), the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period.

Food Consumption

Food consumption was not measured and Food Efficiency could not be calculated.

Gross Pathological Observations

No data were provided.

011335

NAPTALAM 7 RAT TERATOLOGY

Cesarean Section Observations

Table II: Cesarean Section Observations[a]

Dose: rol	Control	LDT	MDT	HDT	Pos.Cont.
#Animals Assigned	40	30	25	34	45
#Animals Mated/Inseminated	40	30	25	34	45
#Animals Pregnant	36	23	23	30	42
Pregnancy Rate (%) 90	77	92	88	93	
Maternal Wastage - dead or abortions	0	0	2*	6*	4*
Total litters available	36	23	21	24	38
Total Corpora Lutea	data not available				
Corpora Lutea/dam					
Total Implantations	418	276	233	274	428
Implantations/Dam	11.6	12.0	11.1	11.4	11.3
Total Live Fetuses	407	266	216	253	212
Live Fetuses/Dam	11.3	11.6	10.3	10.5	5.6*
Total Resorptions	11	7	17	21	215
Dams affected	8	5	5	7	30*
Total litter resorptions	0	0	0	0	11
Mean Fetal Weight (gm)	3.50	3.48	3.51	3.17*	2.21*
Preimplantation Loss(%)	could not be calculated - no corpora lutea data				
Postimplantation Loss(%)[1]	2.63	3.62	7.30	7.66	50.47
Sex Ratio (% Male)	data not available				

* = p < 0.05 compared to control; [1] = calculated by reviewer
[a] = Data extracted from Laboratory No. 5888a, Table 1.

There was reduced mean fetal weight in the high dose group (statistically significant) along with increased maternal wastage. There was a slightly increased number of resorptions and postimplantation loss in the mid and high dose group along with slightly reduced litter sizes.

2. Developmental Toxicity

The following *Table 3* from the investigators report presents the fetal observations for skeletal examinations.

Table 3

Summary of Skeletal Findings in Fetuses[1]

Findings	Corn Oil Control[2] (10ml/kg)	Aspirin 250	Alenap 15	Alenap 115	Alenap 500
			mg/kg		
Live Fetuses Examined (at term)	205/36	166/27	183/23	148/21	175/24
Sternebrae					
Incomplete oss.	184/33	116/25	110/21	76/19	123/22
Bipartite		4/2			
Missing	5/4	113/26*	4/3	3/2	20/8*
Ribs					
Incomplete oss.					
Fused/split		14/8*			1/1
Wavy		1/1			
Less than 12		5/2			2/1
More than 13:					
Rudimentary	45/22	34/14	19/9	23/11	17/8
Extra		80/21*		2/2	
Vertebrae					
Incomplete oss.	22/14	105/25*	15/9	16/9	25/14*
Skull					
Incomplete oss.	1/1	54/18*		1/1	14/5*
Extremities					
Incomplete oss.		64/18*	1/1	2/2*	2/2*
Miscellaneous					
Hyoid; missing	1/1	27/11*			5/2
Hyoid; reduced	5/4	66/19*	3/3	2/2	7/6*

1 Numerator = number of fetuses affected; Denominator = number of litters affected.
2 All materials administered by gavage days 6-15 of gestation.
* Significantly different from control ($p<.05$)

From the data provided there is an indication that the high dose had increased incidence of missing sternebrae (slight; which not specified), incomplete ossification of the vertebrae (which not specified), skull (which bones not specified), extremities (which not specified) and increased missing or reduced hyoid bone.

011335

The following *Table 4* from the investigators report presents the observations for visceral observations.

Table 4

Summary of Soft Tissue Abnormalities of Fetuses

(Wilson Sections)

Treatment[1]/Findings	Fetus (No. affected/No. observed)	Litter (No. affected/No. observed)
Control: Corn Oil 10 ml/kg		
Gastroschisis	1/122	1/36
Hemorrhagic thorax	3/122	1/36
Hemorrhagic abdomen	10/122	8/36
Positive Control: Aspirin 250 mg/kg		
Spina bifida	10/66	7*/25
Encephalomeningocele	15/66	12*/25
Exophthalmos	1/66	1/25
Gastroschisis	3/66	2/25
Hemorrhagic abdomen	5/66	4/25
Pup(s) small	2/66	2/25
Fluid under skin	1/66	1/25
Alanap: 15 mg/kg		
Gastroschisis	2/83	2/23
Hemorrhagic abdomen	8/83	5/23
Alanap: 115 mg/kg		
Hemorrhagic abdomen	3/68	3/21
Pup small	1/68	1/21
Alanap: 500 mg/kg		
Hemorrhagic abdomen	2/78	2/24
Pup(s) small	7/78	4*/24

1 All materials administered by gavage days 6-15 of gestation.
* Significantly different from control ($p < .05$).

No specific treatment related effects were noted.

011335

D. Discussion/Conclusions

a. Maternal Toxicity:

Maternal toxicity was noted at 115 mg/kg/day and above in the form of reduced body weight gain during the dosing period (gestation days 6-15), the post dosing period (gestation days 15-20) and for the combined dosing plus post dosing period (gestation days 6-20) and for the entire gestation period. The 900 mg/kg/day dose group had complete deaths and there was increased maternal wastage at 500 mg/kg/day.

b. Developmental Toxicity:

i. Deaths/Resorptions:
There was a slightly increased number of resorptions and postimplantation loss in the 115 and 500 mg/kg/day dose groups along with slightly reduced litter sizes.

ii. Altered Growth:
There was reduced mean fetal weight in the 500 mg/kg/day dose group (statistically significantly different).

iii. Developmental Anomalies:
There was increased incidence of missing sternebrae (slight; which not specified), incomplete ossification of the vertebrae (which not specified), skull (which bones not specified), extremities (which not specified) and increased missing or reduced hyoid bone in the 500 mg/kg/day dose group.

iv. Malformations:
No treatment related effects were noted.

E. Study Deficiencies:

The percent active ingredient of the test compound was not provided.

No analysis of dosing solutions was performed (however, toxicity was noted so the animals did receive compound).

Bones that were affected in the fetuses were not identified.

Limited data were provided for maternal effects; however, this study was conducted prior to the 1984 Guidelines.

F. Core Classification: Core Supplementary Data.
Maternal Toxicity NOEL = 15 mg/kg/day
Maternal Toxicity LOEL = 115 mg/kg/day
Developmental Toxicity NOEL = 115 mg/kg/day
Developmental Toxicity LOEL = 500 mg/kg/day

01133

Y TAVAPA 10-4-82
RAVEN & RESEARCH SVT. INC.

BEST DOCUMENT AVAILABLE

FDRL

3

Introduction

This report describes the results of a study designed to evaluate the teratogenic potential of Alanap Technical following oral intubation in pregnant Sprague-Dawley rats during organogenesis. The study as outlined in Food and Drug Research Laboratories, Inc. (FDRL) Proposal No. 78005-A was authorized by Mr. Rene' Dupre', Product Specialist, Uniroyal Chemical in a letter dated April 26, 1978. Procedures used were defined in an FDRL Working Protocol prepared July 21, 1978 and ammended August 22, 1978.

Supplied by the sponsor, the test material was received at the Waverly Research Center of FDRL on June 1, 1978. A light brown powdered material contained in a glass pint jar, the label identified the contents as: ALANAP S TECHNICAL; C465; Na Salt; 200 grams; BL9062; CC 4035. Additional material from the same lot/batch was received August 10, 1978.

In conjunction with this study, another test chemical was evaluated in the same manner using common control groups for both materials. The evaluation of the other material (H719 Technical) is reported separately.

Procedures

Animals and Husbandry

All animals used in this study were sexually mature Sprague-Dawley rats -- BLU: (SD) BR. All rats were purchased from Blue Spruce Farms, Inc., Altamont, NY. All animals were

0113

FDRL

individually housed in wire-mesh bottom cages in temperature controlled (70 ± 3°F) quarters. Fresh tap water and ground Charles River Rat/Mouse/Hamster Formula (Agway) were provided ad libitum throughout the study.

Treatment

Females were mated 1:1 with males in sufficient numbers to produce 120 pregnancies at termination. Observation of the vaginal sperm plug was considered day 0 of gestation. The pregnant rats were then distributed into five treatment groups using a random number assignment sheet. One male was not allowed to impregnate more than one female per group. Three test groups each consisting of at least 20 pregnant females were established. In addition, a vehicle (negative) control group and a positive control group each consisting of at least 30 pregnant females were established. Extra females were assigned to each group to allow for false pregnancies and maternal deaths.

Beginning on day 6 of gestation and continuing daily through day 15 of gestation, the appropriate materials were administered by oral intubation to the pregnant females. The test material was prepared fresh weekly and administered as a suspension in corn oil on a 10 ml/kg basis. The positive control compound (aspirin) was given as an aqueous suspension. The amount of material administered to each animal was determined by the body weight on day 6 of gestation and maintained throughout the treatment period. The dosage regimen was as follows:

Group	Minimum No. Pregnant Females	Treatment/Level
A	30	Corn Oil: 10 ml/kg/day
B	30	Aspirin: 250 mg/kg/day
C	20	Alanap: 15 mg/kg/day
D	20	Alanap: 115 mg/kg/day
E*	20	Alanap: 90[illegible] mg/kg/day

* Level terminated after two weeks due to excessive deaths of dams. New level of 500 mg/kg/day Alanap added to study 8/7/78.

On day 20 of gestation, all females were killed by a 5-10 minute exposure to chloroform vapors. The uterine contents of each were removed and the reproductive performance recorded. The urogenital tract of each female was examined for anatomical normality. All females that died or were sacrificed moribund during the course of the study were weighed; the weights were recorded; and all were subjected to a thorough uterine examination.

Observations

Body weights of all females were recorded on days 0, 6, 11, 15 and 20 of gestation. All animals were observed daily for signs of toxicity and a record maintained.

At the time of sacrifice on day 20 (or if the animal di[illegible]was sacrificed moribund) the following observations were rec[illegible]d for each female: numbers of corpora lutea, implantation sites, resorption sites, live and dead fetuses; sex of fetuses; and body weights of fetuses.

FDAL

At the time of uterine examination, all fetuses were examined grossly for the presence of external congential abnormalities. One-third of the fetuses from each litter were randomly selected and placed in Bouin's solution of detailed visceral examination employing the Wilson free-hand slicing technique. Any fetus showing external abnormalities was selected for examination by this technique.

The remaining fetuses were eviscerated, fixed in 70% isopropyl alcohol, macerated in a 2% potassium hydroxide solution, stained with Alizarin-Red S dye, cleared in glycerine, and examined under low power magnification for skeletal anomalies and ossification variations. Each fetus was processed, examined and stored for possible further examination in a manner retaining the identity of both dam number and uterine position.

Statistical Evaluation

Incidences of occurence were expressed as percent, and comparisons between the control and test groups were made using 95% confidence intervals for proportions or by computation of exact probabilities. Continuous data were analyzed using a one-[redacted]ately random classification analysis of variance for fi[redacted]ents. Differences were deemed significant when the probability of rejecting the null hypothesis when true was less than 0.05. The least significant difference test was then employed to determine which test group(s) differed from the control.

011335

FORL

Continuous data from both test materials were evaluated simulta... to increase the degree of freedom and better indicate differences.

011335

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 11/16/94
Senior Pharmacologist, Review Section I, TBII/HED (7509C)

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M.I 11/17/94
Section Head, Review Section I, TBII/HED (7509C)

DATA EVALUATION RECORD

Study Type: Primary Skin Irritation; Species: Rabbit; Guideline: §81-5

EPA Identification No.s: EPA MRID# 00060408
EPA Pesticide Chemical Code 030703
Toxicology Chemical Code 780A
EPA DP Barcode D207628
EPA Submission No. S473779

Test Material: Alanap (25.34% a.i., Lot# B1 #8554 and 074053)

Synonyms: Naptalam

Sponsor: UNIROYAL CHEMICAL COMPANY, INC., 74 Amity Road, Bethany, CT 06524-3402

Testing Facility: Product Safety Laboratories
New Brunswick, NJ 08901

Title of Report: Primary Skin Irritation in Rabbits - Alanap

Study Number(s): Laboratory Project ID T-210

Author(s): Ralph Shapiro

Report Issued: July 18, 1977

Executive Summary: In a primary skin irritation study (MRID# 00060408), New Zealand White Albino Rabbits were exposed to 0.5 ml Alanap (25.34% a.i., Lot# B1 #8554 and 074053) on unabraded and abraded skin areas.

Alanap produced a primary irritation score of 0.3, which is considered to be in the non-primary irritant category. There was slight irritation (erythema) present at 72 hours in both intact and abraded skin. **TOXICITY CATEGORY IV**

This study is classified as Acceptable and satisfies the guideline requirement (§81-5) for a primary skin irritation study in rabbits.

011335

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

Test Compound: Naptalam
Purity: 25.34% a.i.
Description: A crystal clear burgundy colored solution
Lot No.: P1 #8554 and 074053
Receipt date: 1/25/93

Vehicle(s): none used

Test Animal(s): Species: Albino Rabbit (sex not reported)
Strain: New Zealand White
Source: not provided
Age: not provided
Body Weight: 2.3-3.0 kg

B. Study Design

This study was designed to assess the primary skin irritation potential of Alanap in rabbits.

Animal Husbandry

No information provided.

Dose Administration:

The rabbits were prepared by clipping the skin of the trunk free of hair. Epidermal abrasions were made over a 2-3 cm² area on each rabbit. Two 2.5 cm2 gauze patches were placed over the intact skin, the second patch over the abraded skin. Five-tenths of a millimeter of test material was placed under each patch. The patches were secured with tape and covered with a plastic trunk band to prevent evaporation. The rabbits were immobilized in head stocks for 24 hours at which time the patches were removed and the rabbits returned to their cages.

Observations

According to the investigators: *Skin lesions were evaluated at 24 and 72 hours and scored in accordance with CFR Title 21, para. 191.11*...and evaluated by a scoring system in the attached materials and methods.

Statistical analysis

No statistical analysis methods were employed.

011335

Compliance

A signed and dated Statement of No Data Confidentiality Claims was provided. A signed and dated Statement of Non-Compliance with Good Laboratory Practice Standards was provided, this study was conducted prior to GLP's. A signed and dated Quality Assurance Evaluation Statement **was not** provided. A signed and dated FIFRA Flagging Statement **was not** provided; however, this study was not positive for skin irritation.

C. Results

1. Mortality

No mortality was reported.

2. Body Weights

Body weight changes were not reported.

3. Skin Irritation

The Primary Irritation Score (PIS) was 0.3, which is considered to be in the non-primary irritant category. There was slight irritation (erythema) present at 72 hours in both intact and abraded skin.

D. Discussion/Conclusions

Alanap produced a primary irritation score of 0.3, which is considered to be in the non-primary irritant category. There was slight irritation (erythema) present at 72 hours in both intact and abraded skin. **TOXICITY CATEGORY IV**

E. Core Classification: Acceptable.

This study satisfies the guideline requirement (§81-5) for a primary skin irritation study in rabbits.

011335

Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 11/16/94
Senior Pharmacologist, Review Section I, TBII/HED (7509C)

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M.I 11/17/94
Section Head, Review Section I, TBII/HED (7509C)

DATA EVALUATION RECORD

Study Type: Acute (Primary) Eye Irritation; Species: Rabbit; Guideline: §81-4

EPA Identification No.s: EPA MRID# 00078530
EPA Pesticide Chemical Code 030703
Toxicology Chemical Code 780A
EPA DP Barcode D207628
EPA Submission No. S473779

Test Material: Alanap (24.54% a.i., Lot# BL8881-CC0005 & 0036121)

Synonyms: Naptalam

Sponsor: UNIROYAL CHEMICAL COMPANY, INC., 74 Amity Road, Bethany, CT 06524-3402

Testing Facility: Hazleton Laboratories America, Inc. Vienna, Virginia 22180

Title of Report: Acute Eye Irritation Study in Rabbits - Alanap

Study Number(s): Laboratory Project ID 798-182

Author(s): Vincent J. Piccerillo

Report Issued: April 24, 1978

Executive Summary: In a primary eye irritation study (MRID# 00078530), New Zealand White Rabbits were exposed to 0.1 ml Alanap (24.54% a.i., Lot# BL8881 - CC0005 and 0036121) instilled into 1 eye with the other serving as a control. A comparison was made between unwashed and washed eyes.

Alanap produced primary eye irritation which included corneal opacities and eye irritation which were reversible in less than 7 days. TOXICITY CATEGORY III

This study is classified as Acceptable and satisfies the guideline requirement (§81-4) for a primary eye irritation study in rabbits.

011335

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

Test Compound: Alanap
Purity: 24.54% a.i.
Description: A pink liquid
Lot No.: BL8881 - CC0005 and 0036121
Receipt date: 1/25/93

Vehicle(s): none used

Test Animal(s): Species: Rabbit (sex not reported)
Strain: New Zealand White
Source: Bunnyville Farms, Littlestown, PA
Age: not provided
Body Weight: 2790-3100 g

B. Study Design

This study was designed to assess the acute eye irritation in rabbits.

Animal Husbandry

There was no indication if animals were acclimated to the laboratory conditions; they were singly caged under standard animal care conditions. The animals received Purina® Rabbit Chow® Checkers® and water (automatic system) *ad libitum*.

Dose Administration:

Animals were checked prior to use for corneal defects. *A 0.1 ml aliquot of the test material was instilled into the conjunctival sac of the left eye of each rabbit, and the eye held closed for one second following instillation.* The eyes of six rabbits were tested unwashed and 3 rabbits were tested washed. The washed eye animals received a rinsing with 20 ml of lukewarm water 30 seconds after instillation.

Observations

According to the investigators: *The treated eye of each rabbit was examined for gross signs of eye irritation at 24, 48, and 72 hours and 4 and 7 days postinstillation.* Scoring was according to Draize (scale provided).

Statistical analysis

No statistical analysis methods were employed.

Compliance

A signed and dated Statement of No Data Confidentiality Claims was provided. A signed and dated Statement of Non-Compliance with Good Laboratory Practice Standards was provided, this study was conducted prior to GLP's. A signed and dated Quality Assurance Evaluation Statement **was not** provided. A signed and dated FIFRA Flagging Statement **was not** provided; however, this study was positive for eye irritation.

C. Results

1. Mortality

No mortality was reported.

2. Body Weights

Individual animal data were provided by the investigators, no treatment related effects were noted.

3. Eye Irritation

a. Unwashed Eyes

Three of the six rabbits tested exhibited corneal opacities involving less than 25 percent of the corneal surface. The effects were noted during fluorescein staining at 24 hours in 2 rabbits and at both 24 and 48 hours in the third rabbit. Eye irritation consisting of slight to moderate conjunctival redness, chemosis and discharge was noted in all 6 rabbits at 48 hours. The slight conjunctival redness was found in 4 rabbits at 72 hours. No signs of irritation were noted at day 4.

b. Washed Eyes

All rabbits showed conjunctival redness at 24 hours which persisted in 1 rabbit at 48 hours. No signs of corneal damage were noted.

D. Discussion/Conclusions

Alanap produced primary eye irritation which included corneal opacities and eye irritation which were reversible in less than 7 days. **TOXICITY CATEGORY III**

E. Core Classification: Acceptable.

This study satisfies the guideline requirement (§81-4) for a primary eye irritation study in rabbits.

END