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

Chronic RAT, 2
CASWELL FILE

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

010741

JAN 25 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **NAPTALAM (Alanap):** Review of data waiver requests as part of a low volume/minor use waiver package. EPA DP Barcode: D192054; EPA Submission No. S442249; MRID#'s 427840-01, 427397-01 to -03; EPA Pesticide Chemical Code 030703, Caswell No. 780A.

TO: Lois Rossi/Susanne Cerrelli (PM 74)
Special Review and Reregistration Division (7508W)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 12/6/93
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y. M. Ioannou 12/6/93
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia van Gemert 1/14/94
Chief, Toxicology Branch II
Health Effects Division (7509C)

Registrant: Uniroyal Chemical Company, Inc.
74 Amity Road, Bethany Connecticut 06524-3402

Action Requested: Review data waiver requests as part of a low volume/minor use waiver package.

Recommendations: TB II has reviewed the Low Volume/Minor Use Waiver request from the registrant and has determined that, at present, based on the available toxicology database, the data waiver request for naptalam and Na-naptalam is denied. The RfD/Peer Review Committee will consider all the available data on naptalam and Na-naptalam and make appropriate recommendations.

LOW VOLUME/MINOR USE WAIVER REQUEST

BACKGROUND:

The registrant has 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). They have submitted upgrade data for the §83-1a and §83-2a and suggested to replace the §85-1 with a modified study. Further, the registrant submitted a study or upgrade data for the Acute Dermal Toxicity Study (§81-2), the Two Generation Reproduction Study in the Rat (§83-4), and two mutagenicity studies supporting gene mutation (§84-2a) and other genotoxic effects (§84-4). The mutagenicity study requirement for structural chromosome aberrations (§84-2b) *Will be reconducted contingent on 83-1(a) and 83-2(a) waivers*...otherwise a Low Volume/Minor Use Waiver is requested.

The following is the Low Volume/Minor Use Waiver request from the registrant:

Alanap-L (400-49) has been registered to control weeds on peanuts, soybeans and cucurbits. The peanut and soybean uses have been deleted from the label leaving only the uses on cucurbits, i.e. cantaloupe, cucumber, muskmelon and watermelon, which are Minor Use crops. The Low Volume/Minor Use waiver Section III-D of a typical Data Call-In Notice requests estimates of total company sales, product sales, the production costs of the product, and the sales forecast for the next ten years. This information is detailed in Tables a(i), a(ii), b, c, and e. Please note the Table numbers correspond to those in the Data Call-In Notice. Table e shows that the total sales of Alanap-L in 1993 on cucurbits balanced

[redacted]

which is insufficient to reconduct the required studies. In summary, a thorough review of the economics of the product and the costs necessary to continue to support the product shows that Alanap-L sales are not sufficient to justify expending the resources needed to satisfy the data requirements.

Alanap-L is an important herbicide to the cucurbit growers and is recommended by the State Agricultural Extension Services to control weeds such as lambsquarter redroot pigweed, common cocklebur and velvetleaf. The cucurbit growers have reiterated that Alanap-L is a necessary part of their weed control program. Please refer to Section III-Df of this submission.

To continue the Alanap-L registration, Uniroyal requests certain data waivers as outlined in Table d(i). This submission contains data to upgrade studies, new studies or proposals for bridging studies (Tables d(i) and d(ii). We feel this new information and proposed work are adequate to support the registration of Alanap-L on cucurbit minor uses. The four cucurbit crops are the only crops remaining on the label and we will not seek future registration for any additional food crops.

MRID# 42784001: *Combined Chronic/Oncogenicity Study in Rats Response to EPA Review Dated October 22, 1992,* April 1992; refers to **MRID # 00077053**, *104-Week Chronic Toxicity Study in Rats, 6Q8, Na Salt (Alanap Technical), Final Report,* Hazleton Laboratories America, Inc. for Uniroyal Chemical, Project No. 798-177, 5/20/81 (includes **MRID # 418388-01**, Composition of ALANAP Used in Chronic Toxicity Study Uniroyal Project No. 8969). The conclusions from the original review are as follows:

> Alanap was administered to 50 male and 50 female Sprague-Dawley rats for 2 years at dietary levels of 0, 120, 600, or 3000 ppm (estimated intake of about 5.6, 27, and 140 mg/kg/day). There was no carcinogenic response to dosing. At the highest dose level (3000 ppm), mean body weights and body weight gains in females were decreased 7% and 9%, respectively, compared to controls, but in males, mean weights and weight gains were similar to controls. Survival was not affected by dosing and ranged from 46% to 68% in male groups and from 56% to 62% in female groups at 104 weeks. No clear effects on any clinical parameters, on organ weight data or on macroscopic or microscopic findings were observed in treated rats. The dosing was not considered adequate to test for carcinogenicity. An effect level (LOEL) was not established in either sex; it was greater than the highest dose tested (HDT); the NOEL was equal to or greater than the HDT. Further, the MTD (maximum tolerated dose) was not achieved in this study. The study was classified as Core-Supplementary Data for both chronic toxicity and carcinogenicity and does not satisfy the guideline requirements for §83-1a, Chronic toxicity in the rodent and §83-2a, Carcinogenicity in the rat.

The following is the company response to the review:

EPA COMMENT:

Clinical chemistry parameters were determined for only five animals/sex/group and only on six of the required parameters at all intervals of blood sampling. The only electrolytes measured were calcium and potassium at 104 weeks. Cholesterol and SGOT were also measured only at 104 weeks.

COMPANY RESPONSE:

The available data in this study report indicate that there are no biologically important treatment related effects. This conclusion is supported by the data available in the chronic dog feeding study (MRID No. 410575-01) in which all the clinical chemistry parameters required by current rat chronic feeding protocols were evaluated (Appendix 1). It is important to note that the dosage levels were similar in both studies, i.e., approximately 150, 30 and 6 mg/kg/day in rats and 125, 25 and 5 mg/kg/day in dogs. In the rat study there was a reduction in serum LDH at 104 weeks in the mid and high dose males and high dose females, which was attributed to treatment. The significance of a decrease in this parameter is unclear, however. LDH was not effected by treatment in the dog study, which demonstrates possible species specificity. However, 5.7 mg/kg/day is the NOEL in the rat study which provides a considerable margin of safety.

EPA RESPONSE:

The 1977 Core Guidelines (prior to the 1984 Pesticide Assessment Guidelines) which would apply to this study due to the time period the study was conducted, only required 5 animals per sex per dose group and required testing of hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts and reticulocyte counts if anemia was present, further, calcium, phosphorus, fasting glucose, urea nitrogen, total protein, and hepatic enzymes were required for clinical chemistries. The company response is acceptable to the Agency.

EPA COMMENT:

Sufficient hematology parameters were analyzed to meet minimum guideline requirements, but only five animals/sex/group were used.

COMPANY RESPONSE:

Platelet count was apparently decreased by Alanap treatment in the rat chronic feeding study, but this effect was not dose dependent. No other hematological parameter was effected by Alanap treatment in rats. In the dog chronic feeding study, platelet count was not affected and neither were any of the other hematological parameters evaluated (Appendix 2). In the mouse oncogenicity study, MRID No. 119003, platelet count was not determined but Alanap had no effect on any of the hematological parameters evaluated (Appendix 3). Thus, while hematology was done on only 5 rats/group, there is no evidence to suggest that the hematopoietic system is a target organ for Alanap in rats, dogs or mice.

EPA RESPONSE:

As mentioned above, the 1977 Core Guidelines (prior to the 1984 Pesticide Assessment Guidelines) which would apply to this study due to the time period the study was conducted, only required 5 animals per sex per dose group and required testing of hematocrit, hemoglobin, erythrocyte count, total and differential leukocyte counts and reticulocyte counts if anemia was present, further, calcium, phosphorus, fasting glucose, urea nitrogen, total protein, and hepatic enzymes were required for clinical chemistries. The company response is acceptable to the Agency.

EPA COMMENT:

Compound intake was not calculated.

COMPANY RESPONSE:

The company provided the following table:

Compound intake has been estimated using food consumption and body weight tables (Appendix 4) and the diet analysis (Appendix 5).

	CONTROL		120 PPM		600 PPM		3000 PPM	
	MALE	FE-MALE	MALE	FE-MALE	MALE	FE-MALE	MALE	FE-MALE
Ave body weight (g)	558	325	550	326	557	326	552	307
Ave food consumption (g/day)	27.4	20.4	27.3	20.6	28.4	21.0	27.5	20.3
Dietary concentration (ppm)	0		116		588		3171	
Compound consumption (mg/kg/day)	0		5.7	7.3	30.0	37.9	158.0	209.7

EPA RESPONSE:

The provided data are acceptable to the Agency.

EPA COMMENT:

A protocol was not included.

COMPANY RESPONSE:

A copy of the original protocol is being submitted (Appendix 6).

EPA RESPONSE:

The provided data are acceptable to the Agency.

EPA COMMENT:

No ophthalmologic examination data were provided.

COMPANY RESPONSE:

No ophthalmologic examination was conducted. Alanap had no effect on the eyes of dogs fed for 1 year at similar dosage levels (Appendix 7).

EPA RESPONSE:

The 1977 Core Guidelines (prior to the 1984 Pesticide Assessment Guidelines) which would apply to this study due to the time period the study was conducted, did not require ophthalmologic examination data. The company response is acceptable to the Agency.

EPA COMMENT:

Non-neoplastic findings were not summarized.

COMPANY RESPONSE:

The company provided a summary of the histopathology (Appendix 8 of the submission under **MRID# 42784001**).

EPA RESPONSE:

The data provided by the registrant are acceptable to the Agency. No treatment related observations were noted.

EPA COMMENT:

The summary tabulations of histologic findings did not include the number of tissues examined; the reviewer provided the number derived from individual animal tabulations.

COMPANY RESPONSE:

The company provided this information with the summary of the histopathology (Appendix 8 of the submission under **MRID# 42784001**).

EPA RESPONSE:

The data provided by the registrant are acceptable to the Agency. No treatment related observations were noted.

EPA COMMENT:

The tabulations of histologic findings grade the severity of only a few lesions; the entry P (present) was entered for most.

COMPANY RESPONSE:

The severity of lesions was graded where deemed appropriate; however the fact that some lesions were not graded does not affect the report conclusions.

EPA RESPONSE:

The company provided some of this information with the summary of the histopathology (Appendix 8 of the submission under **MRID# 42784001**). It should be noted that toxicity of a test article sometimes follows a path of increasing severity.

EPA COMMENT:

Several pages of tabulated data were not fully legible.

COMPANY RESPONSE:

To expedite this submission we suggest that the agency identify the pages that are not legible and we will promptly submit replacement copies of these pages.

EPA RESPONSE:
No further response is necessary, a legible copy was obtained.

EPA COMMENT:

The rats should have been able to tolerate a higher dose than they were administered. A LOEL [registrant submission stated NOEL] was not achieved in either sex; body weight gains were decreased only 3% for males and 9% for females compared to controls; and no toxicologically important effects on any parameter were observed.

COMPANY RESPONSE:

Alanap administration did not have a significant effect on any toxicological parameter evaluated, including carcinogenicity. Alanap was also not carcinogenic in a mouse oncogenicity study at doses up to approximately 750 mg/kg/day (Appendix 9).

While the rat chronic feeding/oncogenicity study did not achieve the MTD as defined by a 10% reduction in body weight gain, it did demonstrate that Alanap is not oncogenic to rats at doses up to 158 mg/kg/day in males and 210 mg/kg/day in females.

In an effort to estimate any potential carcinogenic risk to humans, dietary exposure to Alanap on cucurbits was determined using TAS Exposure 1 Chronic Dietary Analysis. The daily exposure to Alanap in the general population was found to be 1.6×10^{-5} mg/kg/day (Appendix 10). In addition, a cancer potency factor ($q1^*$) was calculated using Tox Risk Version 3, Toxicology Risk Assessment based upon a hypothetical worst case scenario. Although 3000 ppm did not produce an increased tumor incidence in the present study, we have decided that a hypothetical worst case scenario would be one in which 3001 ppm would produce a tumor incidence of 50/50. To further exaggerate the worst case scenario we have assumed a rare tumor is formed with a control incidence of 0/50 (Appendix 11). The following table describes the hypothetical worst cause cancer risk associated with the low exposure to Alanap on cucurbits.

Dietary Exposure mg/kg body wt./day	Hypothetical Potency Factor ($q1^*$) mg/kg body wt./day	Hypothetical Cancer Risk
1.6×10^{-5}	2.727×10^{-2}	4.37×10^{-7}

It is apparent that even under a hypothetical worst case scenario, the carcinogenic risk to humans can be considered negligible based upon the very low dietary exposure to Alanap on cucurbits. It is our position that if this study was re-conducted at higher doses there are two possible results. First, the study could be negative for oncogenicity. Secondly, if positive oncogenic results were found, the potency factor would be lower than that obtained with the hypothetical worst-case scenario previously described which presented a negligible hypothetical cancer risk to humans. Thus, there is little practical basis to justify re-conducting this study at higher doses to evaluate carcinogenic potential, since an adequate margin of safety currently exists to support the use of Alanap on cucurbits. No other food registrations will be petitioned for this chemical.

EPA RESPONSE:

Naptalam and Na-naptalam will be presented to the RfD/Peer Review Committee 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. For the present time this study remains classified as **Core-Supplementary Data** for both chronic toxicity and carcinogenicity.

EPA COMMENT:

Individual animal body weights were not provided. No individual animal gross findings were provided; therefore, correlations could not be made with in-life masses or with histologic diagnoses.

COMPANY RESPONSE:

The company provided the individual body weights, food consumption and clinical observations (Appendix 12 of the submission under **MRID# 42784001**), and the company provided raw data for the individual animal gross findings (Appendix 13 of the submission under **MRID# 42784001**).

EPA RESPONSE:

The data submitted by the registrant to the Agency are acceptable.

EPA CONCLUSIONS:

As stated above, for the present time this study remains classified as **Core-Supplementary Data** for both chronic toxicity and carcinogenicity and the data will be presented to the RfD/Peer Review Committee for consideration.

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FINAL

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DATA EVALUATION REPORT

NAPTALAM

Study Title:
104-Week Chronic Toxicity Study in Rats
6Q8, Na Salt (Alanap Technical)

Prepared for:

Office of Pesticide Programs
Health Effects Division
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by:

Clement International Corporation
9300 Lee Highway
Fairfax, VA 22031-1207

September 30, 1992

Principal Reviewer: William L. McLellan Date Sept 30, 1992
William L. McLellan, Ph.D.

Independent Reviewer: John Liccione Date 9/30/92
John Liccione, Ph.D.

QA/QC Manager: Sharon A. Segal Date 9/30/92
Sharon Segal, Ph.D.

Contract Number: 68D10075
Work Assignment Number: 1-110
Clement Number: 93-71
Project Officer: James E. Scott

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Guideline §83-5: Combined Chronic/Oncogenicity Feeding Study in Rats

EPA Reviewer: Stephen C. Dapson, Ph.D. Signature: Stephen C. Dapson
Review Section I, Toxicology Branch II,
Health Effects Division Date: 10/1/92

EPA Section Head: Yiannakis M. Ioannou, Ph.D. Signature: Y. M. Ioannou
Section Head, Toxicology Branch II,
Health Effects Division Date: 10/21/92

DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding Study in Rats

TEST MATERIAL: Alanap Technical

EPA Pesticide Chemical Code: 030703

Tox Chem. Number: 780A and 592

MRID Number: 00077053, ~~41866-01~~ 41733-01

SYNONYMS: 6Q8 (Na Salt)

PROJECT NUMBER: 798-177

SPONSOR: Uniroyal Chemical
Bethany, CT

TESTING FACILITY: Hazleton Laboratories America, Inc.
Vienna, VA

TITLE OF REPORT: 104-Week Chronic Toxicity Study in Rats
6Q8, Na Salt (Alanap Technical)

AUTHORS: Serota, D. G.; Alsaker, R.D.; Dawkins, K.K.; Kundins, W.

REPORT ISSUED: May 20, 1981

CONCLUSIONS: Alanap was administered to 50 male and 50 female Sprague-Dawley rats for 2 years at dietary levels of 0, 120, 600, or 3000 ppm (estimated intake of about 5.6, 27, and 140 mg/kg/day).

There was no oncogenic response to dosing. At the highest dose level (3000 ppm), mean body weights and body weight gains in females were decreased 7% and 9%, respectively, compared to controls, but in males, mean weights and weight gains were similar to controls. Survival was not affected by dosing and ranged from 46% to 68% in male groups and from 56% to 62% in female groups at 104 weeks. No clear effects on any clinical parameters, on organ weight data, or on macroscopic or microscopic findings were observed in treated rats. The dosing was not considered adequate to test for oncogenicity. An effect level (LOEL) was not established in either sex; it was [redacted] greater than the highest dose tested (HTD); therefore, the NOEL cannot be determined. Further, the MTD (maximum tolerated dose) was not met in this study.

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CORE CLASSIFICATION: The study is considered Core Supplementary for both chronic toxicity and carcinogenicity. Several of the study deficiencies are presented in Section C--Reviewers' Discussion and Interpretation of Results.

A. MATERIALS AND METHODS

1. Test Article Description

Name: 6Q8 Na Salt (Alanap Technical)

Lot number: 3199300 E604

Purity: 92.6% Sodium Alanap by analysis

Physical property: Pale pink powder

Stability: Not reported

2. Diet Preparation

Premixes were prepared by weighing an appropriate amount of diet and test material and mixing in a Waring blender. Appropriate amounts of basal diet were then added to the premixes and mixed in a Patterson-Kelly blender (1 minute/kg diet) in order to obtain appropriate dose levels. Diets were prepared weekly.

Results: A supplemental report (MRID No. 418388-01), dated April 5, 1991, presented analytical data for the test compound. The material was 90.48% pure. The major impurity was [redacted] of the sample. A supplemental report (MRID No. 418600-01) dated April 3, 1991, with a signed and dated QLP statement provided information on analysis of test compound in diet. The methodology had a recovery of 101 to 102% for spiked samples. Stability analysis indicated 82 to 85% recovery after 7 or 14 days storage of a diet fortified at 50 ppm. Homogeneity assays at week 82 gave ranges of 76-115%, 87-99%, and 70-82% of target for samples at three levels of the mixer for diets with target levels of 120, 600, or 3000 ppm. Mean (±SD) for analyses of diets at 13 intervals at nominal levels of 120, 600, or 3000 ppm, respectively, were 90.6±15.1%, 97.2±13.0%, and 98.8±12.4% of target.

3. Animals

Species: Rat

Strain: Sprague-Dawley

Age: Weanling

Weight at initiation: 94-190 g (group means) for males and 100-190 g (group means) for females

Source: Charles River Breeding Laboratories, Inc., Wilmington, MA

009801

Animals were acclimated to laboratory conditions for 16 days and were assigned to the following groups using a computerized randomization program:

Test Group	Dietary Level (ppm)	Main Study (24-months)	
		Males	Females
1 Control	0	50	50
2 Low-dose (LDT)	120	50	50
3 Mid-dose (MDT)	600	50	50
4 High-dose (HDT)	3000	50	50

Animals were examined for health status prior to study initiation. They were caged individually during the study. Environmental conditions were not reported.

Rationale for dose selection: Not provided.

4. Statistics

Body weight gains for individual animals were compiled for males at weeks 2, 4, 8, 17, and 51 and for females at weeks 2, 5, 11, 31, and 51. Weight gain, food consumption, and appropriate clinical laboratory data were analyzed by Bartlett's test and ANOVA (one way) for homogeneity of data. For homogeneous data, pairwise comparisons to controls were performed for means, and for nonhomogeneous data (with Bartlett's test), Scheffe's multiple comparison procedure was used. Organ weight data were similarly analyzed, and nonhomogeneous data were transformed by $\log_{10}$ or $\log_e$. Survival data were analyzed by Sach's life-table technique.

5. Compliance

Quality assurance statement, confidentiality statement, compliance with GLP's statement, and flagging statement were not provided.

B. METHODS AND RESULTS

1. General Observations

All animals were observed twice daily for mortality and signs of moribundity. Animals received detailed physical examinations (including palpations) weekly for 13 weeks, biweekly for weeks 14-27 and weeks 96-103, and every 4 weeks for weeks 28-95. Gross observations and clinical signs of toxicity were recorded at the above intervals.

Results: Table 1 indicates cumulative deaths/moribund sacrifices and percent survival at weeks 51, 79, and at study termination. No effects of dosing on survival were observed. Survival at 105-106

009801

weeks ranged from 46% to 64% in male groups and 54% to 62% in female groups.

No distinct treatment-related signs of toxicity were reported in animals that died during the study or in those that survived to terminal sacrifice. Antimortem signs (thinness, hunched appearance, labored respiration, anorexia, urine staining of fur, and red crusty eyes) occurred at comparable rates in dosed and control groups. Rats that survived to week 104 had similar signs, additional occurrence of sores and swelling in the extremities, tail, and body, and ocular changes. Suspected neoplasms (nodules, masses and wart-like lesions) were more frequent in females than in males, but no dose-related trends or increases were apparent. The following incidences of tissue masses were seen:

Test Group	Dose in Diet (ppm)	Incidence of Tissue Masses	
		Males	Females
1 Control	0	2	27
2 Low-dose (LDT)	120	9	32
3 Mid-dose (MDT)	600	6	31
4 High-dose (HDT)	3000	5	22

2. Body Weights/Food and Water Consumption/Test Material Intake

Body Weights

Body weights were recorded weekly until week 13, then they were recorded biweekly until week 27, and once every 4 weeks thereafter. Weight change data were determined for weeks 0-51 and 51-104.

Results: Table 2 presents mean body weights and body weight gains at representative intervals. At week 51, mean body weights in high-dose males were 2% lower than in controls and weight gains were decreased 3%. In dosed females, mean weights and weight gains were slightly higher than controls for the low-dose and mid-dose groups; mean weights at the high-dose were 7% lower than in the controls ($p<0.05$); and mean weight gains were 9% lower than in controls ($p<0.05$).

Food and Water Consumption

Food (Purina® Rodent Laboratory Chow) and water were available *ad libitum*. Food consumption was determine at the same time intervals as body weights.

Results: Normal variations in weekly food consumption were observed, but no effect of dosing on food consumption was observed.

Water consumption was not monitored. Food efficiency data were not provided.

Test Material Intake

Data were not provided. However, based on analytical levels in the diets, food consumption values, and mean body weights at week 52, the compound intake in males was approximately 5.6, 27, and 140 mg/kg/day (calculated by the reviewers) at nominal dietary levels of 120, 600, or 3000 ppm, respectively.

3. Ophthalmoscopic Examination

No data were presented.

4. Clinical Pathology

Blood was collected from five rats/sex/group at 13, 26, 52, 78, and 104 weeks for clinical laboratory tests. For hematology, samples were collected from the tail; for clinical chemistry, samples were collected from the tail (week 13), or by orbital sinus puncture (weeks 26, 52, and 78), or from the abdominal aorta (week 104). The checked (X) parameters were examined.

(a) Hematology

X Hematocrit*	X Leukocyte differential count
X Hemoglobin (HGB)*	Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*	Mean corpuscular HGB concentration (MCHC)
X Erythrocyte count (RBC)*	Mean corpuscular volume (MCV)
X Platelet count*	Coagulation: thromboplastin time (PT)
Reticulocyte count (RETIC)	
Red cell morphology	

*Recommended by Subdivision F (November 1984) Guidelines

Results: No clearly compound-related effects on hematology parameters were observed. Table 3 summarizes data for males on red cell parameters. The mean values for hematocrit (HCT), hemoglobin (HGB), and erythrocyte (RBC) counts were slightly depressed for high-dose males at weeks 58 and 78 and for mid-dose males at week 78, when compared with controls. There were no corresponding effects in females and no marked effects in males at 104 weeks. At weeks 78 and 104, morphological blood cell changes were noted but the changes were randomly scattered among groups and not considered compound related.

(b) Blood (Clinical) Chemistry: The checked (X) parameters were examined on 5 rats/sex/group only at week 104. The double-checked (XX) parameters were examined on 5 rats/sex/group at weeks 13, 26, 52, 78, and 104.

Electrolytes

X Calcium*
Chloride*
Magnesium*
Phosphorus*
X Potassium*
Sodium*

Enzymes

XX Alkaline phosphatase (ALP)
Cholinesterase
Creatine phosphokinase
X Lactic acid dehydrogenase
XX Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
Gamma glutamyltransferase (GGT)

Other

XX Albumin*
XX Albumin/globulin ratio
XX Blood creatinine*
XX Blood urea nitrogen*
X Cholesterol [total]*
XX Globulin
XX Glucose (fasting)*
XX Total bilirubin*
Direct bilirubin
XX Total protein*
Triglycerides

*Recommended by Subdivision F (November 1984) Guidelines

Results: No biologically important effects of dosing were observed for the clinical chemistry parameters examined. The study authors suggested that the decreased mean levels of lactic acid dehydrogenase seen in mid- and high-dose males were probably related to dosing.

(c) Urinalysis

Appearance*	X Sediment (microscopic)	X Bilirubin*
Volume*	X Protein*	Blood
X Specific gravity*	X Glucose*	Nitrate
X pH*	X Ketones	Urobilinogen

*Recommended by Subdivision F (November 1984) Guidelines

Results: No effects of dosing on any urinary parameters were observed.

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5. Sacrifice and Pathology

The checked (X) tissues were preserved for histological examination.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*[a]	X Brain (3 levels)[b]
X Salivary glands*	X Heart*[b]	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord (two levels)[a]
X Stomach*	X Lymph nodes*	X Pituitary*[c]
X Duodenum*	X Spleen[b]	X Eyes (with Harderian glands)
X Jejunum*	X Thymus	
X Ileum*		Glandular
Cecum*	Urogenital	
X Colon*		X Adrenals*[c]
Rectum	X Kidneys*[b]	Lacrimal gland
X Liver*[b]	X Urinary bladder*	X Mammary gland
Gallbladder*	X Testes*[b]	X Thyroids*[c]
X Pancreas*	X Epididymides[b]	X Parathyroids*
	X Prostate	X Harderian glands
Respiratory	X Seminal vesicle[a]	
	X Ovaries	
X Trachea*	X Uterus	
X Lung*		

Other

X Bone marrow (sternum)*
X Skeletal muscle*
X Skin
X All gross lesions and masses
Nasal septum

*Recommended by Subdivision F (November 1984) Guidelines

[a]Organ was preserved but did not undergo histopathology
[b]Organ was weighed before fixation
[c]Organ was weighed after fixation

(a) Organ Weights

Table 4 summarizes data on mean pituitary weights at study termination. The absolute and relative (to body) weights were increased in mid- and high-dose males and in high-dose females when compared to controls; the increases were not significant. No compound-related effects on weights of other organs were noted.

(b) Macroscopic Pathology

No treatment-related findings were observed. Frequently occurring findings which were seen at similar incidences in all groups included enlarged and dark red pituitary, red areas in the lungs, enlarged liver, spleen, kidneys, and adrenals, ulcerated areas in the stomach, and thickened mammary glands (females). The incidences

were not markedly higher than normally experienced in chronic studies in rats (data not presented).

(c) Microscopic Pathology

Summary tabulations of nonneoplastic findings were not provided. Scanning of the individual animal histopathology tabulations (by the reviewer) for animals that died and were sacrificed moribund or those sacrificed at termination did not reveal any dose-related increase in incidence or severity of findings.

Table 5 summarizes the frequency of neoplasms. No compound-related increase in neoplastic findings was observed. Incidences of neoplasms were within the range normally expected for rats, and any increased incidences (e.g., astrocytoma of brain in 3/50 high-dose males compared to 1/50 control males) were related to normal biologic variation. No oncogenic response was seen.

C. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS

The study had a number of deficiencies:

- Clinical chemistry parameters were determined for only five animals/sex/group and only on six of the required parameters at all intervals of blood sampling. The only electrolytes measured were calcium and potassium at 104 weeks. Cholesterol and SGOT were also measured only at 104 weeks.

- Sufficient hematology parameters were analyzed to meet minimum guideline requirements, but only five animals/sex/group were used.

- Compound intake was not calculated.

- Individual animal body weights were not provided.

- A protocol was not included.

- No ophthalmologic examination data were provided.

- The summary tabulations of histologic findings did not indicate the number of tissues examined; the reviewer provided the number derived from individual animal tabulations.

- Nonneoplastic findings were not summarized.

- The tabulations of histologic findings graded the severity of only a few lesions; the entry P (present) was entered for most.

- No individual animal gross findings were provided; therefore, correlations could not be made with in-life masses or with histologic diagnoses.

- Several pages of tabulated data were not fully legible.

The rats should have been able to tolerate a higher dose than they were administered. A LOEL was not achieved in either sex; body weight gains were decreased only 3% for males and 9% for females compared to controls; and no toxicologically important effects on any parameters were observed.

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TABLE 1. Cumulative Mortality (percent survival) in Rats Fed Alanap for 104 Weeks[a].

Dietary Level (ppm)	Mortalities (percent survival) at: Week 51	Week 79	Termination
		Males	
0	4 (92)	9 (82)	27 (46)
120	0 (100)	5 (90)	27 (46)
600	1 (98)	8 (84)	26 (48)
3000	2 (96)	8 (84)	18 (68)
		Females	
0	1 (98)	5 (90)	20 (60)
120	0 (100)	5 (90)	19 (62)
600	1 (98)	6 (88)	22 (56)
3000	1 (98)	7 (86)	21 (58)

[a]Data extracted from Study No. 798-177, Table 1, pp. 24-27.

TABLE 2. Mean Body Weight Data in Rats Fed Alanap for 104 Weeks[a]

Dietary Level (ppm)	Mean Body Weight (g±SD) at Week						Mean Body Weight Gain and (% Change) at Weeks[b]		
	0	13	25	51	79	104	0-13	0-51	0-104
Males									
0	148±14.0	518±39.4	584±49.6	665±57.4	674±58.9	596±134.7	370	517	448
120	148±17.6	514±43.6	582±55.3	653±64.4	640±73.1	577±107.8	366 (-1.1)	505 (-2.4)	429 (-4.3)
600	150±18.2	515±52.5	587±56.8	658±63.3	653±72.0	609±95.9	365 (-1.4)	508 (-2.8)	459 (+2.4)
3000	151±14.6	506±37.2	577±43.3	653±58.1	656±83.7	584±95.9	355 (-4.1)	502 (-3.0)	433 (-3.4)
Females									
0	131±11.2	273±24.7	302±30.9	358±49.6	411±59.5	421±78.3	142	227	290
120	128±11.6	272±22.8	305±26.8	363±49.6	408±57.5	425±72.1	144 (+1.4)	235 (+3.5)	297 (+2.4)
600	128±10.8	274±27.3	310±35.8	367±58.3	405±69.4	424±79.8	146 (+2.8)	239 (+5.3)	296 (+2.1)
3000	127±11.1	259±21.9	288±26.1	334*±30.0	392±48.0	394±82.0	132 (-7.0)	207 (-8.9)	267 (-8.0)

[a]Data extracted from Study No. 798-177, Table 1, pp. 24-27

[b]These data are the differences between mean values. Since individual animal body weights were not provided, means of gains based on individual animal weight gains could not be calculated.

*Significantly different from control values ($p<0.05$)

TABLE 3. Mean Hematology Data for Male Rats Fed Alanap for 104 Weeks[a,b]

Parameter and Dietary Level (ppm)	Mean Hematology Data at Week:				
	13	26	52	78	104
Hematocrit (%)					
0	47.4±1.2	46.6±1.1	44.2±5.4	44.3±1.5	36.5±12.
120	45.6±2.3	47.0±1.2	45.2±0.8	44.8±1.2	37.6±4.9
600	46.1±2.1	45.8±2.6	45.6±1.7	38.1±5.0	43.2±3.1
3000	45.7±4.0	46.0±2.4	40.9±12.1	37.2±12.1	40.0±1.6
Hemoglobin (g/dL)					
0	16.2±0.3	15.0±0.7	14.5±1.5	14.4±0.8	12.0±4.7
120	15.8±0.7	15.1±0.4	14.3±0.5	15.0±0.3	11.8±2.2
600	15.8±0.7	14.2±0.9	14.6±0.6	13.0±2.0	14.4±1.7
3000	15.8±1.4	14.5±1.0	12.5±4.4	12.0±4.6	12.8±1.1
Erythrocyte Count					
0	8.1±0.4	8.4±0.7	7.3±1.1	7.5±0.3	6.3±2.2
120	8.1±0.6	8.2±0.2	7.8±0.9	7.9±0.4	6.1±1.0
600	8.1±0.4	7.6±0.5	7.4±0.2	7.1±0.8	7.1±0.7
3000	7.8±0.4	7.6±0.3	6.5±2.3	6.4±2.2	5.9±1.1

[a]Data extracted from Study No. 798-177, Table 2, pp. 32-34

[b]Based on five animals/sex/group

TABLE 4. Mean Pituitary Weight and Pituitary/Body Weight Ratio in Rats Fed Alanap for 104 Weeks[a]

Dietary Level (ppm)	Mean (g ± S.D.)		
	Body weight (g)	Pituitary Weight (g)	Ratio (%)
		Males	
0	591±113	0.030±0.020	0.0052±0.0030
120	570±105	0.037±0.084	0.0081±0.022
600	598± 92	0.045±0.089	0.0111±0.032
3000	573± 92	0.049±0.066	0.0095±0.014
		Females	
0	392±71	0.12±0.11	0.035±0.038
120	413±96	0.12±0.15	0.032±0.047
600	397±76	0.10±0.11	0.028±0.032
3000	364±89	0.16±0.19	0.059±0.084

[a]Data extracted from Study No. 798-177, Table 4, pp. 44-52

TABLE 5. Frequency of Neoplasms in Rats Fed Analap Technical for 104 Weeks[a].

Tissue/ Neoplasm	Dietary Level (ppm) Males 0	120	600	3000	Females 0	120	600	3000
Brain								
Astrocytoma	1	0	1	3	1	2	1	2
Pituitary								
Adenomas	18	23	20	24	40	38	41	38
Carcinoma	7	2	2	1	1	4	3	3
Thyroid								
C-cell adenoma	2	4	0	2	2	1	2	3
Adrenals								
Cortical cell								
Carcinomas	2	1	0	0	3	1	1	0
Adenomas	1	1	0	0	9	1	0	3
Pheochromocytoma	8	3	6	5	2	3	0	0
Liver								
Neoplastic nodule	1	2	1	3	6	0	1	5
Hepatocellular carcinomas	2	3	4	4	1	1	3	2
Testis								
Interstitial cell tumor	2	3	3	2	-	-	-	-
Mesothelioma	0	0	1	2	-	-	-	-
Mammary gland								
Adenoma	-	-	-	-	0	0	1	2
Fibroadenoma	-	-	-	-	16	14	18	13
Adenocarcinoma	-	-	-	-	9	6	7	9
Pancreas								
Islet cell								
Adenoma	3	2	5	4	1	1	1	0
Carcinoma	0	3	2	0	2	1	0	0
Reticuloendothelial system								
Malignant lymphomas	0	0	0	1	0	1	2	1
Fibrous histocytoma, malignant	1	0	1	1	4	2	1	0
Uterus								
Endometrial stromal polyp	-	-	-	-	2	3	1	2

[a]Data extracted from Study No. 798-177, Text Table pp.19-22 and Tables 5A and 5B

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Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca**
PC Code:	**030702**
HED File Code	**13000 Tox Reviews**
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