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

005873

MAY 14 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of dermal sensitization study and teratology study in rabbits with Naptalam

EPA ID #400-49 & 400-345; EPA Record #170807 & 170808; EPA Accession # 261889; Caswell #592; Tox Branch Project #1720 & 1721.

TO: Robert Taylor/Vickie Walters (PM #25)
Fungicide/Herbicide Branch
Registration Division (TS-767C)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/11/87
Pharmacologist, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T. Quang Bui 5/11/87
Acting Section Head, Review Section V
and
Theodore M. Farber, Ph.D., D.A.B.T. 5/14/87
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Uniroyal, Inc.
74 Amity Road
Bethany, CT 06525

Action Requested: Review acute toxicity data (dermal sensitization) to support "Warning" not "Danger" and review teratology study in rabbits.

Recommendations: The dermal sensitization study (Guideline §81-6) with Naptalam is classified as Core-Minimum Data. Under the conditions of this study, Alanap-L (Naptalam) produced dermal sensitization in the male and female quinea pig.

The teratology study in rabbits (Guideline §83-3) with Naptalam is classified as Core-Minimum Data. The No Observed Effect Level (NOEL) for Maternal Toxicity is 200 mg/kg/day. The Lowest Observed Effect Level (LOEL) for Maternal Toxicity is 650 mg/kg/day based on reduced body weight gain during the dosing period, mortality and clinical observation of reduced amount of stool. The NOEL for Developmental Toxicity is conservatively established at 200 mg/kg/day. The LOEL for Developmental Toxicity is 650 mg/kg/day based on the findings of increased numbers of litters (and fetuses)

presenting with forked scapula, hyoid arch(es) bent and misaligned sternebrae. However, the low number of dams for evaluation in this dose group may have restricted the adequate interpretation of the data for this group. The A/D ratio for this compound is 1, indicating that effects on the developing fetus may occur at doses that may be maternally toxic.

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Primary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/4/87
Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V, Toxicology Branch (TS-769C)

I. Study Type: Dermal Sensitization
Guideline §81-6

Study Title: Delayed Contact Hypersensitivity Study in Guinea Pigs of Alanap-L

EPA Identification Numbers: EPA Identifying No. 400-49
EPA Record No. 170807
EPA Accession No. 261889
Shaugnessy No. 030702-5
Caswell No. 592
Tox Branch Project No. 1720
Document No.

Sponsor: Uniroyal, Inc.
74 Amity Road
Bethany, CT 06525

Testing Laboratory: Hill Top Research, Inc.

Study Number: Hill Top Research Project No. 85-1583-21

Study Date: December 26, 1985

Study Author: Edwin V. Buehler, Ph.D.

Test Material: ANALAP-L (also known as Naptalam)
Benzoic acid, 2-((1-naphthalenylamino)carbonyl)-
CAS # 132-66-1
Lot No. G064001

Vehicle: The test substance was used undiluted for the sensitization test.
For the primary irritation test, test substance dilutions in distilled water of 50%, 25% and 10% w/v were used.

Test Animal: Male and Female Hartley Albino Guinea Pigs
Supplier: Murphy Breeding Laboratories, Inc.
Weight 300 to 400 gms

This study was designed to evaluate the potential of Alanap-L (Naptalam) to produce delayed contact hypersensitivity in Guinea Pigs.

II. Materials and Methods: A copy of the "purpose and general information" and "methods" section from the investigators report is appended. The following comments and highlights pertaining to the materials and methods are noted:

Test groups consisted of 10 animals per sex in the "test" group; 5 animals per sex in the control group; 2 animals per sex in the primary irritation phase.

Animals were kept under standard animals care conditions. They were quarantined for a period of at least 5 days before use. They received tap water and Purina Guinea Pig Chow ad lib.

The investigators employed the method of Buehler, 1965 and Ritz and Buehler, 1980.

The body weights of the animals at the start and completion of the test were not reported.

A Quality Assurance Statement was included.

III. Results:

A. Primary Irritation Phase (Pilot)

A mean grade of 0 was obtained at 24 and 48 hours (following a 6 hour patch application) for the undiluted, 50%, 25% and 10% w/v formulations in both male and female guinea pigs. No reaction was observed (see appended Table 1 from the investigators report).

B. Primary Challenge Phase

The control animals (distilled water) showed no evidence of dermal sensitization at 24 or 48 hours. For the test animals a mean skin score of 0.3 (1 animal with 1 and 11 with +) was obtained at 24 hours and a score of 0.2 (9 with +) at 48 hours. (see appended Table 2 from the investigators report). A score of 1 indicates slight confluent or moderate patchy erythema; a score of + indicates slight patchy erythema. These scores when compared to distilled water control indicated that Alanap-L induced dermal sensitization in male and female guinea pigs.

IV. Conclusions:

Under the conditions of this study, Alanap-L produced dermal sensitization in the male and female quinea pig.

V. Core Classification: Core-Minimum Data.

Toxicity Category: Dermal Sensitizer.

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Pages __5__ through __10__ 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.

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_____ The product confidential statement of formula.

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__ _ __ Internal deliberative information.

_____ Attorney-Client work product.

__X__ Claimed Confidential by submitter upon submission to the Agency.

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Review Section V, Toxicology Branch/HED (TS-769C)

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V, Toxicology Branch/HED (TS-769C)

I. Study Type: Teratology - Guideline §83-3

Study Title: Teratology Study in Rabbits
(with Technical Alanap [Na Salt])

EPA Identification Numbers: EPA Identifying No. 400-345
EPA Record No. 170808
EPA Accession No. 261889
Shaugnessy No. 030702-5
Caswell No. 592
Tox Branch Project No. 1721
Document No.

Sponsor: Uniroyal, Inc.
74 Amity Road
Bethany, CT 06525

Testing Laboratory: International Research and Development Corporation
Mattawan, Michigan 49071

Study Number: IRDC Report No. 399-053

Study Date: May 31, 1985

Study Authors: Karen S. Arnold, B.S.
James L. Schardein, M.S.
Malcolm Blair, Ph.D.

Test Material: Technical Grade Alanap (as sodium salt)
(also known as Naptalam)
Benzoic acid, 2-((1-naphthalenylamino)carbonyl)-
monosodium salt
CAS # 132-67-2
Lot #3199300
Purity was not provided.

Vehicle: Deionized water.

Dosage: 0 (control), 50, 200 and 650 mg/kg/day. Test compound prepared daily as a suspension with a dosage volume of 3 ml/kg (based on most recent body weight). Administered by gavage as a single daily dose from Gestation Days 7 through 19. Dosing was conducted 3.25 to 7.5 hours into light cycle.

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Test Animal: Female Dutch Belted Rabbits
Received from Langshaw Farms, Augusta, Michigan
80 animals were used, received 11/1/84
Age = 4 to 4 1/2 months old

This study was designed to evaluate the developmental toxicity potential of Technical Alanap (Na salt).

II. Materials and Methods: A copy of the "Introduction" and "Methods and Procedures" is appended. The following comments and highlights pertaining to the materials and methods are noted:

Animals were kept under standard animal care procedures. All conditions were described in detail (see appended "Methods and Procedures").

Animals were treated by the supplier (Langshaw Farms) with 0.0032% sulfaquinoxaline one week prior to shipment to the investigators "...for control of cocciodosis".

Animals were quarantined for 27 days prior to use. During this period they were "...carefuly observed for changes in appearance and behavior. Animals were 5 to 5 1/2 months old prior to insemination and weighed between 2580 and 3320 gm on Gestation Day 0. They were superovulated 3 weeks prior to insemination with human chorionic gonadotropin (50 USP).

Animals were randomly assigned to study groups using a computer generated system.

The investigators employed 8 "proven" male rabbits as sperm donors. Description of the insemination procedure is appended in "Methods and Procedures". The authors stated that "Semen from one male was used to inseminate an equal number of females in each group". However, there are no data to substantiate their statement. The day of insemination was considered as Gestation Day 0.

Alanap was administered at dosage levels (as a suspension) of either 0, 50, 200 and 650 mg/kg/day by gavage as a single daily dose on Gestation Days 7 through 19.

The animals were observed twice daily prior to treatment for mortality and "overt changes in appearance and behavior". During the treatment period they were observed twice daily for mortality and once daily for "clinical signs of toxicity". Animals which died early, aborted or delivered prematurely were subjected to a post-mortem examination. The intact fetuses were examined and preserved for possible future evaluation as were the maternal tissues from the post-mortem examinations. No food consumption data were provided.

Individual maternal body weights were taken on Gestation Days 0, 7, 13, 20, 24 and 28. On Gestation Day 28 all surviving dams were sacrificed by injection of sodium pentobarbital into the marginal ear vein. They were then subjected to a post-mortem examination (maternal tissues were again preserved).

All fetuses were weighed, sexed and examined for external gross anomalies. They were then dissected, internally sexed and examined for visceral anomalies. The brain was examined by a mid coronal slice and the heart by a modified Staples method. All fetuses were then cleared and stained by a method similar to Dawson for skeletal examinations.

Statistical methodology was provided (see attached "Methods and Procedures").

A Quality Assurance Statement was provided.

III. Results

A. Maternal Clinical Observations

The investigators provided group mean and individual dam data. Table I presents the clinical observations.

TABLE I: Maternal Clinical Observations[a]

Dose (mg/kg/day):	Control	50	200	650
# Dams	16	16	16	16
# Aborted	-	-	1	1
# Died	-	1	-	4
Nasal Discharge	3(6)[†]	-	-	2(5)
Ocular Discharge	-	-	1(5)	1(3)
Stained Haircoat	2(7)	1(3)	4(16)	3(15)
Hair Loss	1(5)	1(4)	-	-
Reduced Activity	-	-	-	2(2)
Gasping	-	-	-	1(1)
Ataxic	-	-	-	1(1)
Emaciated Appearance	-	1(8)	1(3)	2(4)
Sore in mouth	-	-	1(14)	-
Subcutaneous Mass in mouth	-	-	1(8)	-
Diarrhea	1(2)	-	2(2)	-
Soft Stool	-	1(1)	2(4)	1(4)
Reduced Amount of Stool	1(2)	1(10)	2(10)	7(26)
No Stool Apparent	-	-	1(3)	-
Red Fluid in Pan	-	1(3)	-	1(2)

[†] = # animals (# days observed)

[a] = Data extracted from IRDC Report No. 399-053 Table 1.

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There were increased clinical observations at the high dose consisting of reduced amount of stool and an increase in the number of dams that died. Of those animals which died, the investigators found no specific cause of death. One animal had a severely congested lining of the trachea.

B. Maternal Body Weight Gain

The investigators provided group mean and individual dam data for maternal body weights and body weight gains. Table II presents the maternal body weight gain data.

TABLE II: Maternal Body Weight Gain (gm)[a]

Dose (mg/kg/day): Gestation Days	Control	50	200	650
0 - 7	163±59.1[†]	143±128.8	180±72.9	191±82.5
7 - 13	40±101.1	82±89.2	56±113.6	-173±244.0
13 - 20	93±64.7	58±122.3	-37±222.9	-16±142.0
20 - 24	-6±97.4	-15±95.1	100±191.6	103±68.0
24 - 28	-13±104.6	7±81.4	17±62.2	15±75.8
7 - 20	133±98.1	140±159.0	19±281.0	-72±254.2
0 - 28	277±139.2	268±329.8	359±150.3	313±198.1

[†] = values are mean±s.d.

[a] = Data extracted from IRDC Report No. 399-053 Table 4.

The provided data indicated that the high dose animals gained less weight during the early part of the dosing period (Gestation Days 7 through 13) as well as during the entire dosing period (Gestation Days 7 through 20), when compared to the controls. After the dosing period, the high dose animals gained more weight than the controls during the same period. This rebound phenomena is indicative of toxicity of the compound during the treatment period. No food consumption data were provided to allow further analysis of this effect.

C. Cesarean Section Observations

The investigators provided group mean and individual dam data for the measured parameters. Table III presents the results of these observations.

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TABLE III: Cesarean Section Observations[a]

Dose (mg/kg/day):	Control	50	200	650
# Animals Used	16	16	16	16
# Died	0	1	0	4
# Gravid	0	0	0	0
# Non-Gravid	0	1	0	4
# Aborted	0	0	1	1
# Animals at C. Section	16	15	15	11
# Gravid	13	14	10	9
# Non-Gravid	3	1	5	2
Dams w/total resorptions	0	2	0	1
Dams w/viable fetuses	13	12	10	8
Mean Viable Fetuses	7.1±1.93	4.9±2.89	8.2±1.62	5.7±3.28
Mean Postimplantation Loss	0.5±0.78	1.3±2.09	0.6±0.97	1.2±2.05
Mean Implantations	7.5±1.81	6.2±2.19	8.8±1.40	6.9±2.80
Mean Corpora Lutea	10.1±1.38	9.3±1.83	11.4±3.60	10.2±4.02
Mean Preimplantation Loss (%)	25.2	32.1[†]	22.8	32.6
Mean Postimplantation Loss (%)	6.1	20.7	6.8	17.7
Mean Fetal Body Weight (gm)	31.2±4.67	35.1±4.72	31.5±2.40	34.2±3.78
Fetal Sex Distribution (m/f)	46/46	31/38	40/42	30/21

[†] = two animals were not included due to regressing corpora lutea
[a] = Data extracted from IRDC Report No. 399-053 Table 6.

No treatment related effects on the cesarean section parameters was noted. It also must be noted that the low dose group had a smaller mean litter size when compared to other study groups which may result from a lower number of corpora lutea and high preimplantation loss noted in this group.

D. Fetal Anomaly Observations

The investigators provided group totals and individual animal data as well as historical control data.

1. External and Visceral Examinations

The investigators did not separate observations into external and internal findings. These findings are summarized in the following Table IV. Apparently, no treatment related effects were evident.

TABLE IV: Visceral Anomaly Observations[a]

Dose (mg/kg/day):	Control	50	200	650
# litters examined	13	12	10	8
# fetuses examined	92	69	82	51
Craniorachischisis	1(1)/1(8)[†,††]			
Ablepharia	1(1)/1(8)[††]			
Microphthalmia	1(1)/1(8)[††]			
Cleft palate	1(1)/1(8)[††]			
Omphalocele				1(1)/2(13)
Retroesophageal aortic arch				1(1)/2(13)
Ectromelia	1(1)/1(8)			
"Tail anomaly"			1(1)/1(10)	
"Major vessel variation"[†††]	10(3)/11(23)	4(3)/6(25)	4(3)/5(30)	1(1)/2(13)
Renal pelvis not developed	1(1)/1(8)			
Hemorrhagic thymus			1(1)/1(10)	

[†] = #fetuses(#litters)/%fetuses(%litters)
[††] = observations in the same fetus
[†††] = specific findings were included in individual animal data.
[a] = Data extracted from IRDC Report No. 399-053 Tables 9 and 11.

2. Skeletal Examinations

Table V presents the skeletal anomaly observations.

TABLE V: Skeletal Anomaly Observations[a]

Dose (mg/kg/day):	Control	50	200	650
# litters examined	13	12	10	8
# fetuses examined	92	69	82	51
Craniorachischisis[†]	1(1)/1(8)[††]			
"Tail anomaly"[†]			1(1)/1(10)	
Forked Scapula	3(3)/3(23)	3(3)/4(25)	2(1)/2(10)	4(3)/8(38)
27 presacral vertebrae	14(6)/15(46)	9(5)/13(42)	9(4)/11(40)	2(2)/4(25)
13th rudimentary rib(s)	17(10)/19(77)	14(9)/20(75)	12(4)/15(40)	9(5)/18(63)
12 full pairs of ribs	13(5)/14(39)	11(5)/16(42)	15(4)/18(40)	3(2)/6(25)
Accessory skull bones	2(2)/2(15)	2(2)/3(17)	2(2)/2(20)	1(1)/2(13)
Hyoid arch(es) bent	3(3)/3(16)	6(5)/9(42)	4(2)/5(20)	6(5)/12(63)
Hyoid body unossified		1(1)/2(8)	1(1)/1(10)	
Skull, reduced ossification	5(2)/5(15)	2(2)/3(17)		
Sternebrae #5 unossified	9(5)/10(37)	3(2)/4(17)	6(4)/7(40)	4(3)/8(38)
Misaligned sternebrae	2(2)/2(15)			2(2)/4(25)
Fused sternebrae		1(1)/2(8)	1(1)/1(10)	1(1)/2(13)
Vertebral variation				1(1)/2(13)
Carpal flexure	1(1)/1(8)			

[†] = noted in visceral examinations
[††] = #fetuses(#litters)/%fetuses(%litters)
[a] = Data extracted from IRDC Report No. 399-053 Table 11.

The utility of the high dose is restricted due to the small number of litters (8) as compared to the control group (13). However, there may be an indication of developmental toxicity in the high dose as noted by an increase in the number of litters (and fetuses) presenting with forked scapula, hyoid arch(es) bent and misaligned sternebrae.

IV. Conclusions:

The No Observed Effect Level (NOEL) for Maternal Toxicity is 200 mg/kg/day. The Lowest Observed Effect Level (LOEL) for Maternal Toxicity is 650 mg/kg/day based on reduced body weight gain during the dosing period, mortality and clinical observation of reduced amount of stool.

The NOEL for Developmental Toxicity is conservatively established at 200 mg/kg/day. The LOEL for Developmental Toxicity is 650 mg/kg/day based on the findings of increased numbers of litters (and fetuses) presenting with forked scapula, hyoid arch(es) bent and misaligned sternebrae. However, the low number of dams for evaluation in this dose group may have restricted the adequate interpretation of the data for this group.

The A/D ratio for this compound is 1, indicating that effects on the developing fetus may occur at doses that may be maternally toxic.

V. Core Classification: Core-Minimum Data.

Maternal Toxicity NOEL = 200 mg/kg/day
Maternal Toxicity LOEL = 650 mg/kg/day
Developmental Toxicity NOEL = 200 mg/kg/day
Developmental Toxicity LOEL = 650 mg/kg/day
A/D Ratio = 1

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__ _ __ Identity of product inert ingredients.

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Chemical:	**Benzoic acid, 2-((1-naphthalenylamino)ca**
PC Code:	**030703**
HED File Code	**13000 Tox Reviews**
Memo Date:	**05/14/87**
File ID:	**TX005873**
Accession Number:	**412-03-0114**

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