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

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MAY 23 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **NAPTALAM (Alanap):** Review of mouse carcinogenicity study.
EPA DP Barcode: D197639; EPA Submission No. S455257;
MRID# 00119003; EPA Pesticide Chemical Code 030703,
Caswell No. 780A (Na salt); 592 (acid).

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

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 5/6/94
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 5/10/94
Section Head, Review Section I
and
Marcia van Gemert, Ph.D. Marcia van Gemert 5/18/94
Chief, Toxicology Branch II
Health Effects Division (7509C)

Registrant: Uniroyal Chemical Company, Inc.

Action Requested: Review of mouse carcinogenicity study with Alanap.

Recommendations: TB II has reviewed the study: *Lifetime Carcinogenicity Study in Mice* (IRDC for Uniroyal Chemical, Study No. 399-002b, August 24, 1982). The following are the conclusions from that review:

In a 84 week carcinogenicity study (MRID No. 119003), Naptalam was administered in the feed to 50 male and 50 female Charles River CD-1 mice at concentrations of 50, 2500, or 5000 ppm (males - 8, 376 or 737 mg/kg/day and females - 9, 437, or 870 mg/kg/day). The control group had 75 mice/sex.

Naptalam seemed to have affected the survival rate of the female 2500 ppm dose group because it was significantly lower when compared to the controls (48% vs 24%). Statistically significant reductions in body weights were observed during week 26 (50 ppm males and 5000 ppm females), week 38 (5000 ppm females), and week 62 (5000 ppm females). No dose response relationships or trends were evident in any of the body weight changes. No treatment-related effects were noted in food consumption or food efficiency in the test groups relative to controls.

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The only treatment-related gross pathology finding was pink/reddish discoloration of the urine. Compound-related microscopic liver changes were noted in the 2500 and 5000 ppm dose groups. The liver changes were hypertrophy of the centrilobular parenchymal cells with the males having higher incidences than females. It occurred in 20 males and 3 females of the 5000 ppm dose group, and in 25 males and 2 females of the 2500 dose group. No effects were seen in the 50 ppm dose group. Amyloidosis occurred in many tissues of Naptalam treated and control animals; this was a commonly occurring condition for Charles River CD-1 mice during the early 1980's and it was not considered to be treatment-related.

No statistically significant changes were noted in the incidence of tumor types for the treated groups when compared with the control group. The liver hepatocellular carcinomas did not display a dose-response, but the incidence (3, 4, 2 and 10% for the control, low, mid and high dose groups, respectively) was higher in the high dose group males compared to controls. The malignant lymphomas noted in the male 5000 ppm dose group had a higher incidence than the control group (10% vs 4%, respectively). Both of these findings may be compound-related even though they did not reach statistical significance. In females, the incidence of lung adenomas was 10/74 (13.5%), 3/50 (6%), 2/50 (4%) and 12/50 (24%) for the control, low, mid, and high dose groups, respectively and 1 adenocarcinoma (13/50 or 26%).

TOXII has concluded that the MTD was achieved. At the dose levels tested, Naptalam might have some carcinogenic potential in mice based on the increased incidence of tumors in the high dose groups.

The systemic NOEL is equal to 50 ppm (8-males & 9-females mg/kg/day) and the systemic LOEL is 2500 ppm (376-males & 437-females mg/kg/day) based on the decreased body weight gain in both sexes and liver hypertrophy of the centrilobular parenchymal cells in males.

The study is Core Supplementary and does not satisfy the guideline requirements for a §83-2 carcinogenicity study in mice.

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).

DISCUSSION:
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. Based on the positive findings in the mouse carcinogenicity study (discussed in this memo), the data waiver for the chronic/carcinogenicity study in the rat and the general metabolism study is denied.

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

Technical: Naptalam and Na-Naptalam
Use Pattern: food use
Action Type: Reregistration

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 dermal study - rat	Yes	NO
§82-1(b)90 day feeding - dog	Yes	NO
§83-1(a)2-year feeding - rodent	Yes	NO
§83-1(b)1 year feeding - nonrodent	Yes	NO
§83-2(a)Carcinogenicity - rat	Yes	NO
§83-2(b)Carcinogenicity - mouse	Yes	NO[1]
§83-3(a)Teratology - rat	Yes	Yes
§83-3(b)Teratology - rabbit	Yes	NO
§83-4 Multigeneration reproduction-rat	Yes	Yes
§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.

III. Data Gaps

The following are data gaps for technical Naptalam and Na-Naptalam:

§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
§82-1(a) 90 day dermal study - rat
§82-1(b) 90 day feeding - dog
§83-1(a) 2-year feeding - rodent
§83-1(b) 1 year feeding - nonrodent
§83-2(a) Carcinogenicity - rat
§83-2(b) Carcinogenicity - mouse
§83-3(b) Teratology - rabbit
§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.

IV. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

V. Reference Dose

An RfD (PADI) of 0.0375 mg/kg/day based on a 13 week feeding study in the dog with a NOEL of 75 mg/kg/day and a modifying factor of 2000 has been established (3/85). This package of additional data will be submitted to the HED RfD/Peer Review Committee for reevaluation of the RfD.

VI. Pending Regulatory Actions

None.

VII: 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

Although the mouse carcinogenicity study was classified as Core-Supplementary Data, it appears that Naptalam, at 5000 ppm, increases the incidences of hepatocellular carcinomas in males, malignant lymphomas in males and lung adenomas in females. There are one positive and one possible positive mutagenicity studies.

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Primary Review by: Deborah L. McCall 4/14/94
Review Section III, Toxicology Branch II (7509C)
Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. 4/4/94
Review Section I, Toxicology Branch II (7509C)

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity §83-2

EPA IDENTIFICATION Nos.: EPA MRID No. - 119003
Caswell No. - 780A (592 - acid)
PC Code - 030703 (030702 - acid)
DP Barcode - D197639
Submission No. - S455257

TEST MATERIAL: Naptalam

SYNONYMS: Alanap, N-1-naphthylphthalamic acid

STUDY NUMBER: 399-002b

SPONSOR: Uniroyal Chemical

TESTING FACILITY: IRDC, Mattawan, MI

TITLE OF REPORT: Lifetime Carcinogenicity Study in Mice

AUTHOR(S): [not indicated]

REPORT ISSUED: August 24, 1982

EXECUTIVE SUMMARY: In a 84 week carcinogenicity study (MRID No. 119003), Naptalam was administered in the feed to 50 male and 50 female Charles River CD-1 mice at concentrations of 50, 2500, or 5000 ppm (males - 8, 376 or 737 mg/kg/day and females - 9, 437, or 870 mg/kg/day). The control group had 75 mice/sex.

Naptalam seemed to have affected the survival rate of the female 2500 ppm dose group because it was significantly lower when compared to the controls (48% vs 24%). Statistically significant reductions in body weights were observed during week 26 (50 ppm males and 5000 ppm females), week 38 (5000 ppm females), and week 62 (5000 ppm females). No dose response relationships or trends were evident in any of the body weight changes. No treatment-related effects were noted in food consumption or food efficiency in the test groups relative to controls.

The only treatment-related gross pathology finding was pink/reddish discoloration of the urine. Compound-related microscopic liver changes were noted in the 2500 and 5000 ppm dose groups. The liver changes were hypertrophy of the centrilobular parenchymal cells with the males having higher incidences than females. It occurred in 20 males and 3 females of the 5000 ppm dose group, and in 25 males and 2 females of the 2500 dose group. No effects were seen in the 50 ppm dose group. Amyloidosis occurred in many tissues of Naptalam treated and control animals; this was a commonly occurring condition for Charles River CD-1 mice during the early 1980's and it was not considered to be treatment-related.

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No statistically significant changes were noted in the incidence of tumor types for the treated groups when compared with the control group. The liver hepatocellular carcinomas did not display a dose-response, but the incidence (3, 4, 2 and 10% for the control, low, mid and high dose groups, respectively) was higher in the high dose group males compared to controls. The malignant lymphomas noted in the male 5000 ppm dose group had a higher incidence than the control group (10% vs 4%, respectively). Both of these findings may be compound-related even though they did not reach statistical significance. In females, the incidence of lung adenomas was 10/74 (13.5%), 3/50 (6%), 2/50 (4%) and 12/50 (24%) for the control, low, mid, and high dose groups, respectively and 1 adenocarcinoma (13/50 or 26%).

TOXII has concluded that the MTD was achieved. At the dose levels tested, Naptalam might have some carcinogenic potential in mice based on the increased incidence of tumors in the high dose groups.

The Systemic NOEL is equal to 50 ppm (8-males & 9-females mg/kg/day) and the systemic LOEL is 2500 ppm (376-males & 437-females mg/kg/day) based on the decreased body weight gain in both sexes and liver hypertrophy of the centrilobular parenchymal cells in males.

The study is Core Supplementary and does not satisfy the guideline requirements for a §83-2 carcinogenicity study in mice.

I. MATERIALS

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A. Test compound: Alanap technical, Lot No. C3199300, Description: pale lavender, chunky material. Purity - not reported.

B. Test animals: Species - Mouse; Strain - Charles River CD-1; Age - 6 weeks at study initiation; Weight - Males, 23-34 g and Females, 19-30 g at study initiation; Source - Charles River breeding Laboratories, Inc. North Wilmingtion, Mass.

C. Mice were individually housed in suspended wire-mesh cages and held in a temperature, relative humidity and light controlled room.

D. Animals received food Purina Laboratory Chow® from week 1 through week 80 and then Rodent Laboratory Chow® #5001 from week 81 through 84 and water ad libitum.

E. Statistics: The statistical procedures utilized in the study are listed in Attachment I.

F. Signed Quality Assurance and GLP Compliance statements, dated July 27, 1982 was presented.

G. STUDY DESIGN:

1. Selection of dietary levels: No justification was found in the study report for the dietary concentrations.

2. Animal assignment: Animals were assigned using a computer-generated randomization procedure to the following test groups:

Test Group	Dietary Concentration (ppm)	Main Study 84 Weeks	
		Males	Females
Control*	0	75	75
Low (LDT)	50	50	50
Mid (MDT)	2500	50	50
High (HDT)	5000	50	50

* Shared control group with another study performed at IRDC, study number 399-002a. Study was initiated on 5-20-77 and terminated on 12-29-78 because the mid-dose females survival rate approached 20%.

The test material was administered continuously in the diet for 84 weeks.

3. Diet preparation: Test diets were prepared using a premix of known concentration which contained both the basal diet and

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the test material. The diets were mixed using a Hobart mixer. The study report does not specify if the diets were prepared weekly or how they were stored prior to use. Samples of the diets were taken on 0 and 7 days at 3 months intervals.

Results: Homogeneity was not checked during the study and it could not be determined if stability of the test material was checked prior to the start of the study. The study report gives analyses of the diets for weeks 15, 27, 39, 53, 66, 78, and 84. Concentrations of the test diets were within acceptable ranges for the 2500 and 5000 ppm dose groups; actual concentrations ranged from 73% to 118% of target concentrations. However, the analyses of the 50 ppm dose group showed large discrepancies in this concentration. The 50 ppm diet contained approximately 490 ppm at week 15. [This reviewer assumes that for at least the first 15 weeks on test the low dose was receiving a dose close to 500 ppm and not 50 ppm since the first analysis wasn't performed until week 15.] At week 22 the problem was corrected and the diet contained approximately 56 ppm. However during the weeks of 66, 72, and 78 the levels were higher again (73-85 ppm).

II. METHODS AND RESULTS

A. Observations: Animals were inspected three times daily for clinical signs of toxicity and mortality. Furthermore, animals were subjected to detailed physical examinations weekly to detect palpable masses.

Results: No treatment-related clinical signs of toxicity were noted in the 50 ppm dose group. Some of the 2500 and 5000 ppm dose animals exhibited light pink to red urine during the first week on study. By the end of the study all of the mid and high dose animals had pink colored urine. Some of the signs noted during the study were: lacrimation, tremors, labored breathing, and abnormal gait. Mortality is summarized below.

The compound seemed to have affected the survival rate of the female 2500 ppm dose group because it was significantly lower when compared to the controls. Also, the overall female survival rate was slightly lower than males for all treatment groups (see below).

Dose level (ppm)	Percent Survival at week 50		Percent Survival at Week 62		Percent Survival at Week 84	
	male	female	male	female	male	female
0	97 (73/75)	93 (70/75)	84 (63/75)	87 (65/75)	49 (37/75)	48 (36/75)
50	94 (47/50)	100 (50/50)	78 (39/50)	94 (47/50)	56 (28/50)	40 (20/50)
2500	98 (49/50)	96 (48/50)	86 (43/50)	72 (36/50)	66 (33/50)	24* (12/50)
5000	98 (49/50)	96 (48/50)	70 (35/50)	72 (36/50)	42 (21/50)	36 (18/50)

(data was extracted from Table 1, pg 23 and statistics were not performed on week 62.)

* = significantly lower than the control group ($p < 0.05$).

B. Body Weight: Animals were weighed at study initiation, once weekly for the first 14 weeks, every two weeks for the next 12 weeks and once every 4 weeks for the remainder of the study.

Results: Mean body weights and mean body weight gains are summarized in Tables 1 and 2, respectively. Statistically significant reductions in body weights were observed during week 26 (50 ppm males and 5000 ppm females), week 38 (5000 ppm females), and week 62 (5000 ppm females). No dose response relationships or trends were evident in any of the above changes. A decrease in body weight gain was noted at the 13-week time point in all treated groups of the male and the mid- and high dose groups of female rats. Similar decreases were also seen in all treated male and female groups at the 26-week time point (see Table 2).

Table 1: Mean Body Weights (g) at Selected Intervals

Week	0		50		2500		5000	
	♂	♀	♂	♀	♂	♀	♂	♀
0	28	24	28	24	28	25	27	25
13	37	31	36	31	36	31	35	31
26	38	33	37**	32	37	33	36	32**
50	37	34	38	35	38**	35*	38**	35
84	37	35	38	35	39	36	37	35

* = Significantly different from controls ($p < 0.05$).
** = Significantly different from controls ($p < 0.01$).
(Data were extracted from Tables 2 and 3, pgs 24 & 25.)

Table 2: Mean Body Weight Gains (g) at Selected Intervals

Week	Males				Females			
PPM	0	50	2500	5000	0	50	2500	5000
0-13	9	8	8	8	7	7	6	6
% of control	-	89	89	89	-	100	86	86
0-26	10	9	9	9	9	8	8	7
% of control	-	90	90	90	-	89	89	78
0-50	9	10	10	11	10	11	10	10
% of control	-	111	111	122	-	110	100	100
0-84	9	10	11	10	11	11	11	10
% of control	-	111	122	111	-	100	100	91

(Data were extracted from Tables 2 and 3, pgs 24 & 25.)

C. Food consumption and compound intake: Food consumption was determined once weekly for the first 14 weeks, every two weeks for the next 12 weeks and once every 4 weeks for the remainder of the study.

Results: Food consumption data are summarized in Table 3. No treatment-related effects were noted in food consumption or food efficiency in the test groups relative to controls. Two statistically significant decreases were noted in the 2500 and 5000 ppm females, but due to the lack of a dose-response these were considered to be of little biological significance. The mean daily dosages in mg/kg/day were approximately 0, 8, 376 and 737 for males and 0, 9, 437, and 870 for females from the control, low-, mid-, and high-dose groups, respectively.

Table 3: t-Test Comparison between Means in Food Consumption (g/mouse/day)

Week	0		50		2500		5000	
	♂	♀	♂	♀	♂	♀	♂	♀
1-13	5.3	6.2	5.6	5.9	5.5	5.4**	5.2	5.5**
14-26	5.2	6.0	5.6	6.1	5.7	6.1	5.6	5.9
30-50	5.6	5.9	5.6	5.5	5.5	5.5	5.2	5.3
54-74	4.5	4.7	4.5	4.7	4.8	4.9	4.4	4.7
78-82	5.5	5.7	5.6	5.4	5.6	5.4	5.2	5.4

* = Significantly different from controls ($p < 0.05$).
** = Significantly different from controls ($p < 0.01$).
(Data was extracted from Table 4, pg 27.)

D. Hematology analysis: Blood was collected from the retro-orbital sinus from five mice/sex/group at 3, 6, 12 and 18 months of the study for hematology analysis. The CHECKED (X) parameters were examined.

1. Hematology:

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Erythrocyte count*
X Leukocyte count*
Platelet count*
X Leukocyte (differential)*
Reticulocyte count (RETIC)
Red cell morphology
Mean corpuscular HGB concentration
Mean corpuscular volume
Mean corpuscular hemoglobin

* Required for subchronic and chronic studies

Results: In the males, a significant increase (15.4 compared to 14.1 in the controls) in the hemoglobin parameter occurred during the 12th month in the 2500 ppm dose group. In females, several significant effects occurred during the study. Hemoglobin was significantly decreased in the 50 and 5000 ppm dose groups (15.7 & 15.4 compared to 16.6 in the controls) at 3 months. The total

leukocytes in the 50 ppm dose group was significantly increased at 3 months (18.9 compared to 12.3 in the controls). Since none of these changes occurred in a treatment-related manner the changes were considered of little biological significance.

E. Sacrifice and Pathology: All animals that died or were sacrificed moribund or on schedule were subjected to a gross pathological examination. The CHECKED (X) tissues were collected for histological examination. Additionally, 3 coronal sections through the head, including the nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx and middle ear were examined in 10 randomly selected mice from the control and high dose groups.

Digestive System		Cardiovasc./Hemat.		Neurologic	
	Tongue	X	Aorta*	X	Brain*†
X	Salivary glands*	X	Heart*	X	Sciatic nerve
X	Esophagus*	X	Bone marrow*	X	Spinal cord*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Rectum*	X	Spleen*	X	Eyes* (optic nerve)
X	Colon*	X	Thymus		
X	Cecum*				
X	Ileum*				
X	Jejunum*	Urogenital		Glandular	
X	Duodenum*	X	Kidneys*†	X	Adrenals*
X	Liver*†	X	Urinary bladder*		Lacrimal gland
X	Gallbladder*	X	Testes*†	X	Mammary gland*
X	Pancreas*	X	Epididymis*	X	Thyroid gland*
		X	Prostate*	X	Parathyroid*
Respiratory		X	Seminal vesicle*	X	Harderian gland
	Trachea*	X	Ovaries*		
X	Lung*	X	Uterus*	Other	
	Nasal cavity		Vagina	X	Bone (sternum
				X	Skeletal muscle*
				X	Skin*
				X	All gross lesions & masses*

* Recommended by Subdivision F (October 1982) Guidelines.
† Organ weight required in chronic studies.

1. Organ weight: The Subdivision F guidelines recommends that the liver, kidneys, brain, and testes be weighed; however no organ weight data were found in the study report.

2. Gross pathology: The study authors considered the pink/reddish discoloration of the urine the only treatment-related finding. Other gross findings were: granular or pitted surface of the kidneys, pale kidneys, enlarged or cystic uteri, lung and liver masses (males had higher incidences), distended urinary bladder (males had a higher incidence) and abdominal distension. Amyloidosis was seen in higher incidences in the group of mice that died during the study. This is a common cause of death for Charles River CD-1 mice. All of these findings were considered to be within normal ranges and are commonly

seen in mice of this age and strain. 010989

3. Microscopic pathology: Non-neoplastic lesions found in this study are summarized in Tables 4 and 5, and neoplastic lesions are summarized in Table 6.

A. Non-neoplastic - Compound-related liver changes were noted in the 2500 and 5000 ppm dose groups. The liver changes were hypertrophy of the centrilobular parenchymal cells with the males having higher incidences than females (see Tables 4 & 5). It occurred in 20 males and 3 females in the 5000 ppm dose group, and in 25 males and 2 females of the 2500 dose group. The 50 ppm dose group did not have this finding. The other microscopic findings noted in these mice are typical for this age and strain of mice. Amyloidosis occurred in the lungs, thyroids, adrenals, liver, heart, stomach, intestines, kidneys, testes and ovaries. This is a commonly occurring condition for Charles River CD-1 mice during the early 1980's and it was not considered to be treatment-related.

B. Neoplastic - No statistically significant changes were noted in the incidence of tumor types for the treated groups when compared with the control group. The neoplastic lesions seen in this study are not unusual for this strain and age of mice (see Table 6). Although, the liver hepatocellular carcinomas did not display a dose response the male 5000 ppm dose group did have a higher incidence than the control group (10% vs 3%). The historical control range was 0-6.3% for males. The malignant lymphomas noted in the male 5000 ppm dose group had a higher incidence than the controls (10% vs 4%). The historical control range was 1.7-10% for males. These findings may be compound-related even though they did not reach statistical significance. In females, the incidence of lung adenoma was 10/74 (13.5%), 3/50 (6%), 2/50 (4%) and 12/50 (24%) for the control, low, mid, and high dose groups, respectively and 1 adenocarcinoma (13/50 or 26%). Even though the lung adenomas are outside of the historical control ranges (0-6.7% for females) the study included two pathology reports which concluded that the tumors were not compound-related.

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TABLE 4. Summary of Non-neoplastic Lesions in Selected Tissues of Mice Fed Naptalam Continuously for 84 Weeks[a]

Finding	Dietary Concentration (ppm)							
	Terminal sacrifice				Deaths/unscheduled sacrifice			
	0		5000		0		5000	
	♂	♀	♂	♀	♂	♀	♂	♀
Lung:								
Atelectasis	0/37	0/36	1/20	1/18	8/38	8/38	3/27	7/32
Amyloidosis	2/37[b]	1/36	0/20	0/18	9/38	0/38	1/27	1/32
Thyroid:								
Amyloidosis	2/26	3/32	0/21	2/17	15/28	14/32	6/22	13/27
Adrenals:								
Spindle cell proliferation	21/37	34/36	10/19	17/18	16/38	25/38	11/28	23/32
Brown degeneration	15/37	15/36	6/19	5/18	13/38	14/38	5/28	3/32
Amyloidosis	6/37	10/36	3/19	9/18	29/38	28/38	22/28	25/32
Liver:								
Amyloidosis	7/37	10/36	0/21	6/18	27/38	20/39	17/29	25/32
Hypertrophy, centrilobular hepa.	0/37	0/36	15/21	1/18	0/38	0/39	5/29	2/32
Parenchymal mononuclear foci	15/37	25/36	11/21	8/18	5/38	16/39	2/29	7/32
Heart:								
Amyloidosis	2/37	10/36	2/21	7/18	29/38	22/39	19/29	18/32

[a]Data were extracted from Tables 9 & 10.
[b]First number is the incidence and the second number the number of tissues examined.

TABLE 5. Additional Non-neoplastic Lesions in the Livers of Mice Fed Naptalam Continuously for 84 Weeks[a]

Finding	Dietary Concentration (ppm)							
	Terminal sacrifice				Deaths/unscheduled sacrifice			
	50		2500		50		2500	
	♂	♀	♂	♀	♂	♀	♂	♀
Liver:								
Amyloidosis	1/28[b]	1/20	3/33	3/12	12/22	25/30	15/17	29/38
Hypertrophy, centrilobular hepa.	0/28	0/20	25/33	2/12	0/22	0/30	0/17	0/38
Parenchymal mononuclear foci	10/28	16/20	10/28	9/12	1/22	13/30	0/17	10/38

[a]Data were extracted from Tables 9 & 10.
[b]First number is the incidence and the second number the number of tissues examined.

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TABLE 6. Summary of Neoplastic Lesions in Selected Tissues of Mice Fed Naptalam Continuously for 84 Weeks[a,b]

Finding	Dietary Concentration (ppm)							
	0		50		2500		5000	
	♂	♀	♂	♀	♂	♀	♂	♀
Lung:								
Adenoma	13/75[c]	10/74	4/50	3/50	7/49	2/50	5/47	12/50
Carcinoma/Adenocarcinoma	0/75	0/74	2/50	1/50	1/49	0/50	2/47	1/50
Liver:								
Hepatocellular carcinoma	2/75	1/75	2/50	0/50	1/50	0/50	5/50	0/50
Cholangiocellular carcinoma	-	-	1/50	0/50	0/50	0/50	-	-
Hemangiosarcoma	-	-	1/50	0/50	0/50	0/50	-	-
Mammary Gland:								
Adenocarcinoma	-	0/53	-	1/50	-	0/50	-	1/50
Hematopoietic, Lymphocytic, Reticuloendothelial Systems:								
Malignant lymphoma	3/75	3/75	2/50	1/50	0/50	2/50	5/50	2/50
Reticulum cell sarcoma	0/75	1/75	0/50	1/50	2/50	1/50	1/50	2/50
Myeloma	0/75	1/75	0/50	0/50	0/50	0/50	0/50	0/50

[a]Data were extracted from Tables 11 - 14.
[b]Includes observation at Terminal sacrifice, deaths, and unscheduled sacrifices.
[c]First number is the incidence and the second number the number of tissues examined.
[NOTE: The control and high dose groups were evaluated by one pathologist and the low and mid dose groups were evaluated by a different pathologist.]

III. REVIEWERS' DISCUSSION/CONCLUSIONS: 010989

In the 84 week feeding study, Naptalam seemed to have affected the survival rate of the female 2500 ppm dose group because it was significantly lower when compared to the controls (48% vs 24%). Also, the overall female survival rate was slightly lower than males for all treated groups at week 84. Statistically significant reductions in body weights were observed during weeks 26 (50 ppm males and 5000 ppm females), 38 (5000 ppm females), and 62 (5000 ppm females). A decrease in body weight gain was noted at the 13-week time point in all treated groups of the male and the mid- and high dose groups of female rats. Similar decreases were also seen in all treated male and female groups at the 26-week time point. No dose-response relationships or trends were evident in any of the body weight changes. No treatment-related effects in food consumption or food efficiency were observed in the test groups relative to controls.

The only treatment-related gross pathology finding was pink/reddish discoloration of the urine. Other gross findings were pale or granular surfaces of the kidneys, enlarged or cystic uteri, lung and liver masses (males had higher incidences), distended urinary bladder (males had a higher incidence) and abdominal distension. Amyloidosis was seen in higher incidences in the group of mice that died during the study. This is a common cause of death for Charles River CD-1 mice.

Compound-related liver changes were noted in the 2500 and 5000 ppm dose groups. The liver changes were hypertrophy of the centrilobular parenchymal cells with the males having higher incidences than females. It occurred in 40% of the males and 6% of the females in the 5000 ppm dose group, and in 50% of the males and 4% of the females in the 2500 dose group. No effects were seen in the 50 ppm dose or the control groups. Amyloidosis occurred in the lungs, thyroids, adrenals, liver, heart, stomach, intestines, kidneys testes and ovaries of Naptalam treated and control groups. This is a commonly occurring condition for Charles River CD-1 mice during the early 1980's and it was not considered to be treatment-related.

No statistically significant changes were noted in the incidence of tumor types for the treated groups when compared with the control group. The liver hepatocellular carcinomas did not display a dose-response, but the incidence (3, 4, 2 and 10% for the control, low, mid and high dose groups, respectively) was higher in the high dose group males compared to controls. The malignant lymphomas noted in the male 5000 ppm dose group had a higher incidence than the control group (10% vs 4%, respectively). Both of these findings may be compound-related even though they did not reach statistical significance. In females, the incidence of lung adenomas was 10/74 (13.5%), 3/50 (6%), 2/50 (4%) and 12/50 (24%) for the control, low, mid, and high dose groups, respectively and 1 adenocarcinoma (13/50 or 26%).

TOXII has concluded that the MTD was achieved. At the dose levels tested, Naptalam might have some carcinogenic potential in mice based on the increased incidence of tumors in the high dose groups.

The Systemic NOEL is equal to 50 ppm (8-♂ & 9-♀ mg/kg/day) and the systemic LOEL is 2500 ppm (376-♂'s & 437-♀'s mg/kg/day) based on the decreased body weight gain in both sexes and liver hypertrophy of the centrilobular parenchymal cells in males.

The study is Core Supplementary and does not satisfy the guideline requirements for a §83-2 oncogenicity study in mice.

IV. STUDY DEFICIENCIES

The purity of the test compound was not reported.

The Subdivision F guidelines recommends that at least the liver, kidneys, brain, and testes should be weighed; however no organ weight data were found in the study report.

Homogeneity was not checked during the study and it could not be determined if stability of the test material was checked prior to the start of the study.

Analyses of the 50 ppm dose group showed large discrepancies in the concentration of the test material. The 50 ppm diet contained approximately 490 ppm at week 15. [This reviewer assumes that for at least the first 15 weeks on test the low dose was receiving a dose close to 500 ppm, since the first analysis wasn't performed until week 15.] At week 22 the problem was corrected.

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Pages __17__ through __18__ are not included in this copy.

The material not included contains the following type of information:

__ _ __ Identity of product inert ingredients.

__ _ __ Identity of product impurities.

__ _ __ Description of the product manufacturing process.

__ _ __ Description of quality control procedures.

__ _ __ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

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