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

002777

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor, PM #25
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

SUBJECT: Alanap- EPA Reg. No. 400-75
CASWELL No. 592

Applicant: Uniroyal Chemical
Divisiion of Uniroyal, Inc.
74 Amity Road
Bethany, Connecticut 06525

Requested Action:

Review of Lifetime Carcinogenicity Study in Mice to support future registration of products containing alanap (N-1-naphthyl-phthalamic acid).

Recommendation(s):

The oncogenic evaluation of Alanap in mice is considered Core-Minimum and does not demonstrate an oncogenic potential in CD-1 mice.

Lifetime Carcinogenicity Study in Mice with Analap (International Research & Development Corporation, Study No. 399-002 b, July 23, 1982).

Procedure:

"Groups of albino mice (Charles River CD-1) 50 M and 50 F each weighing from 23 to 34 g were fed 50, 2500 and 5000 ppm of Analap for 18 months. A control group of 75 male and 75 female mice received the basal laboratory diet only. The animals were observed daily for signs of toxicity, moribundity and mortality.

Individual body weights and food consumption were recorded weekly for the first 14 weeks, then every other week for the next 12 weeks and once every 4 weeks thereafter. Hematology was conducted for five mice/sex/group at 3, 6, 12 and 18 months of study." [IRDC, Vol. 1 page 2 Acc. #248857].

At the conclusion of the study, all surviving mice were sacrificed and a complete post- mortem examination performed. Tissues were collected and preserved in phosphate buffered formalin. "Hematoxylin and eosin stained paraffin sections were prepared from all animals in all groups from the following tissues: abdominal aorta, adrenals (both), brain (3 levels), liver (2 lobes), lung & mainstem bronchi, eyes and contiguous Harderian glands (both), gonads (ovaries, tests with epididymis, prostate/corpus and cervix uteri, gallbladder, skeletal muscle, lymph nodes, mammary gland, mandibular salivary gland, sciatic nerve, pancreas, pituitary, skin, spinal cord (cervical and thoracic), spleen, heart (with coronary vessels), esophagus, stomach, large intestine (cecum and colon), kidneys, urinary bladder, thymus, trachea, thyroid/parathyroid, sternum (bone marrow) and any other tissue with lesions". [IRDC Vol. 1 pg. 9 Acc. #248857].

Body weights, food consumption and the hematologic parameters were compared by several statistical methods. Survival indices by sex, and tumor incidence of individual type were also statistically evaluated.

Results:

° Body Weight gain:

Body weight gain was not adversely affected in any of the treated groups when compared to controls.

° Food Consumption:

There was no statistically significant food consumption differences between the control group and test animals. However, during weeks 1-13, the females at the two highest dose levels showed a significant variation (Control 6.2; 2500 ppm, 5.4; 5,000 ppm, 5.5).

2

° Surival rate:

Alanap in the diet caused a significant lower survival in the mid-dose females ($p < 0.05$). This was not evident at other dose levels or control.

° Hematologic values:

There were no compound related effects on the parameters measured throughout the study.

° Non-neoplastic findings:

Compound related microscopic liver changes (hypertrophy of centrilobular parenchymal cells) were observed in the 5000 and 2500 ppm dietary levels.

Incidence of hepatocellular hypertrophy is as follows:

Males (Occurred/Examined)

Control 0 ppm	50 ppm	2500 ppm	5000 ppm
0/75	0/50	25/50	20/50

Females (Occurred/Examined)

Control 0 ppm	50 ppm	2500 ppm	5000 ppm
0/75	0/50	2/50	3/50

° Neoplastic Findings:

Among females in the highest dosage group (5000 ppm) a higher incidences of pulmonary adenoma/alveolar-bronchiolar adenoma was observed when compared to the control group:

Females (Occurred/Examined)

	0 ppm	50 ppm	2500 ppm	5000 ppm
adenoma/alveolar -bronchiolar adenoma	10/74	3/50	2/50	12/50
alveoloar-bronchiolar carcinoma	0/75	1/50	0/50	1/50

Hepatocellular carcinoma was observed in male mice. The incidence appears to be higher in the 5,000 ppm dose group when compared to controls; but is not statistically significant.

The incidence of hepatocellular carcinoma was observed as follows:

Males (Occurred/Examined)

	Control	50 ppm	2500 ppm	5000 ppm
hepatocellular carcinoma	2/75	2/50	1/50	5/50

A finding of malignant lymphoma was observed in both males and females in all dose groups and control group

Comparing the animals in which lymphoma was diagnosed there were no significant difference in latency and there were no significant differences between control and test groups as demonstrated in the table below:

Pathology Observations

MALES

	0 PPM	50 PPM	2500 PPM	5000 PPM
Malignant Lymphoma (Terminal Sacrifices)	1/37	2/29	4/33	0/21
Malignant Lymphoma (Unscheduled Sacrifices)	1/38	1/29	0/17	5/29

FEMALES

	0 PPM	50 PPM	2500 PPM	5000 PPM
Malignant Lymphoma (Terminal Sacrifices)	1/36	0/20	0/12	0/18
MALIGNANT Lymphoma (Unscheduled Sacrifices)	2/39	4/30	4/38	2/32

Statistical Evaluation:

All relevant data involving the histopathological observations of lung neoplasms, hepatocellular carciroma and malignant lymphoma in the highest dosage (5000 ppm) were compared to the control group. They were statistically evaluated for possible carcinogenicity and found not to be statistically significant. We have discussed these findings with Dr. L. Kasza (Staff Pathologist) and Mr. B. Litt (Staff Statistician).

Conclusion:

Alanap^{-1} is non-oncogenic to mice at 5,000 ppm in the diet (highest dose tested).

Systemic NOEL = 50 ppm

Systemic LEL = 2,500 ppm (liver hypertrophy of centrilobular parenchymal cells, lower survival rate in females).

Classification:

Core- Minimum Study

Carolos A. Rodriguez 5/9/83
Review Section #1
Toxicology Branch/HED (TS-769)

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