10-1-83

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY 004272
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: October | -1983

SUBJECT: Long-Term Feeding Study in Mice with 5-Bromo-3-sec-butyl -6-methyluracil, INN-976, Bromacil ID#352-325 Acc. #244069, 244070 and 244071, Caswell number 111

FROM: Alex Arce, Tox Branch (TS-769)

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

THRU: W. Butler, Section III
W. Burnam, Chief
R. Coberly, Quality Control
Tox Branch (TS-769)

W. Butler 12/28/83

Request: To review a Mouse Long-Term Feeding Study - 18 months duration. Data gap listed in Registration Standard.

Registrant: Dupont

Recommendation

a) The "Long-term feeding study in mice with Bromacil," submitted to fulfill the data gap in the Bromacil Registration Standard, has been reviewed and graded as Core Minimum Data

b)
In the study the NOEL has not been established. A risk assessment evaluation will be required since oncogenic effects are reported at the 5000 ppm dose level.

The product may be a candidate for a Special Review.

Data Review

Haskell Laboratory #893-80
Medical Research Project No. 3155
December 1, 1980

Product: 5-Bromo-3-sec-butyl-6-methyluracil, INN-976, Bromacil - 95%

Subject: Mice, male & female CD-1

Purpose: "To evaluate the oncogenicity of 5-bromo-3-sec butyl-6-methyluracil (INN-976; Bromacil) in mice"

Dose levels: 0; 250; 1,250; and 5,000 ppm. 18 months study.

Background Information

Reported LD_{50} in rats = 5,175 mg/kg. Six male rats were tested with 10 oral doses of 1500 mg/kg for two weeks. Four died and two survivors showed signs of toxicity. Six rats were dosed with 10 daily doses of 1,035 mg/kg over a 2 week period. One rat died and the five survivors showed signs of toxicity including focal liver cell hypertrophy and hyperplasia.

In a subchronic test, 3-month rat feeding study, no abnormalities up to 500 ppm were detected. At higher dose levels, from 2,500 to 7,500 ppm, signs of toxicity observed were enlarged thyroid gland, increased liver weights and enlarged centrolobular hepatocytes.

Several other studies using rats and dogs exhibited toxic signs at dose levels higher than 250 ppm. Thus, the MTD was established at 5000 ppm.

Product: Bromacil INN-976. 95%

Procedure (18-month feeding study): The product was added to the ground chow as a suspension of 1% in corn oil. Diets were prepared fresh each week and analyzed for Bromacil content at intervals. Weights: each week, each animal, for the first 26 weeks. For the second weighing interval, weeks 26-52, mice were weighed every 2 weeks, and the third weighing interval, weeks 52-76, the mice were weighed every 4 weeks.

Observations: Daily

Food consumption: Determined each week as mean daily food consumption, mean food efficiency, and mean daily intake of Bromacil.

Hematology: At 1, 3, 6, 12, and 18 months, included RBC and WBC, differential hgb and Hct.

Mortality: Observed and recorded.

Sacrifice and necropsy: Started at the 78th week according to prearranged schedule. Major tissues and organs were examined and weighed, and sections were preserved for microscopic examinations. Masses and abnormal tissues were examined in all cases. Urine and feces were also analyzed before sacrifice.

Data from the submitted report: "All mice sacrificed at the terminal sacrifice and mice found dead or sacrificed in extremis during the study were necropsied

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and examined grossly. Whenever tissue integrity permitted, the brain, heart, lungs, liver, spleen, kidneys with adrenals attached, testes with epididymides attached, and thymus were weighed and mean organ/body weight ratios (relative organ weights) were calculated. When permitted by tissue integrity, the tissues listed above and other selected tissues listed below were prepared by conventional methods and representative sections were examined microscopically for histopathological nodes (mesenteric, cervical, mandibular, those that were abnormal, and those draining known and suspected tumor sites), aorta, salivary glands (parotid, sublingual and submaxillary), esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, gall bladder, pancreas, bladder, pituitary, thyroid, parathyroid, adrenals, epididymis, prostate, mammary gland, ovaries, uterus, cervix, vagina, spinal cord, peripheral nerve (sciatic), eye, Harderian glands, exorbital lacrimal gland, muscle (thigh, bone (femur), head (3 coronal sections which included nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx and middle ear), all gross lesions with border of normal tissue), and all masses (with adjacent normal tissue)."

Results

Mortality: After the first year, mortality was greater for the treated than for controls at the 1250 and the 5000 ppm dose level, male and female.

Body Weight: The body weight was significantly lower than controls at 5000 ppm for males and females throughout the study.

Food Consumption: No remarkable changes. The daily intake in this type of study is not accurately calculated due to spillage. Clinical observations of alopecia and dermatitis in all animals.

The palpable or absorbable masses observed during the study were not the results of administration of the product.

Serology.

Hematology: A mild increase in HcT, Hgb;was not significant.

Pathology

At 5000 ppm, increase in the mean liver weight for male and female mice was observed. This observation is significant. At the other dose levels, the increase was not significant. 5000 ppm dose level: male control 2.417 - high dose 3.1019, female control 1.9114 - high dose 2.3638.

Oncogenicity (Refer to the attached table extracted from the submitted report)

At 5000 ppm, an increase in neoplasms in the liver of the male mice was observed. Control, 10 hepatocellular adenomas and carcinomas. At the 5000 ppm level, there were 19 adenoma-carcinomas, and this was signficantly different from control (p. <.05). Also 11 and 8, at 250 and 125 ppm respectively, were reported. Thus the hepatocellular adenomas were present in the male mice and recorded at each dose level, including the 0 control group, but the incidence was almost double at the high-dose level.

Summary Tables extracted from the submitted data are presented as an attachment of this report (Refer to page 5)

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Non - Neoplastic Abnormalities

Observed at all treatment groups, including the lowest at 250 ppm. Thus, the NOEL is not established in this study.

5000 ppm - diffuse hepatocellular hypertrophy - male and female

1250 ppm - some but in male only

250 ppm - centrolobular vacuolization - males

Other Abnormalities Observed

Testicular abnormalities were observed at all dose levels in a dose-related increment.

250 ppm - seminal vesicular distension.

Focal atrophy of seminoferous tubules at all dose levels. At 1,250 and 5000 ppm - spermatocyte necrosis, sperm calculi and interstitial cell hypertrophy/hyperplasia.

5000 ppm - Atrial trombosis - male.

The NOEL for this study has not been established, since at the lowest dose level of 250 ppm abnormalities are reported.

Conclusion: The submitted study is classified as Core Minimum Data

The dose levels used were 250, 1250 and 5000 ppm. These levels were incorperated into the diet.

The NOEL = Has not been established

The LEL = At 250 ppm

The principal effects observed were:

Oncogenicity - Hepatocellular adenomas and carcinomas at all dose levels including the control, but with a much higher incidence at the 5000 ppm dose (♂) level. The increase in combined carcinomas and hepatocellular adenomas was significant to a $p. \leq 0.05$ level of probability.

NOTE: I have reviewed the submitted study and found it to be acceptable. Any resemblance of my report to the submitted original does not have the intention of plagiarism.

If I have quoted from the original, it is because I believe, to the best of my ability, that the submitted data are thorough, and by adding or changing words I would have only increased the amount of paperwork with no valid or useful purpose.

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Table - Summary of combined incidence of neoplasms observed during the Hispathological Examination .

NOTE .- The following table was extracted from the submitted data.

The largest number of neoplasms were found at the high dose level .

Treatment Group (ppm INN-976:)	Male				Female			
	0	250	1,250	5,000	0	250	1,250	5,000
Combined Incidence of Hepatocellular Adenomas and Carcinomas	10	11	8	19*	1	3	0	1
No. Tumor Bearing Mice	8	11	7	17*	1	3	0	1
No. Mice in Treatment Group	80	80	80	80	80	80	79	80

* Different from control at $p \leq 0.05$ level of probability.

Table - The following table, also extracted from the submitted data , shows the number of nodules observed at necropsy .

MALES

GROUP NUMBER	I	III	V	VII
DOSE LEVEL	0 PPM	250 PPM	1250 PPM	5000 PPM
NUMBER NECROPSIED	80	80	80	80
LIVER:				
Cystic lobe-mass/nodule	1	0	2	0
Heavy	0	0	0	1
Pale brown	4	4	2	0
Dark red mottling, dark red cystic nodules	0	0	0	1
Mass, left lobe	1	0	0	0
Cystic lobe, left side-thick irregular	1	0	0	0

MALES

GROUP NUMBER	I	III	V	VII
DOSE LEVEL	0 PPM	250 PPM	1250 PPM	5000 PPM
NUMBER NECROPSIED	80	80	80	80
Heavy with scattered nodules	1	0	0	0
Left lobe-dark	1	0	0	0
Right lobe-raised area	1	0	0	0
Pale brown; right lobe-lacerated	1	0	0	0
Dark	1	0	1	2
Nodules, left and right lobes	0	0	0	1
Pale brown, nodular, swollen, heavy	1	0	0	0
Left lobe-ruptured, filled with clotted blood	1	0	0	0
Left lobe-cystic masses	1	0	0	0
Pale brown, slightly coarse surface	0	0	0	1
Dark red mottling scattered throughout	1	0	0	0
Mass, right and median lobes	1	0	0	0
Lobular markings prominent	2	0	1	3
Cystic and caudate lobes-nodule	0	0	0	1
Cystic lobe-nodular/nodule	1	0	0	2
Heavy; mass, caudate lobe	0	0	0	1
Left lobe-nodule	1	3	0	2
Right lobe-nodule	1	2	0	2
Ventral surface-nodule	0	1	0	0
Cystic structure, cystic lobe	0	1	0	0
Pale brown, lobular markings prominent	0	1	1	0
Nodules throughout	0	1	0	0
Pale brown; red foci, left lobe	0	1	0	0
Caudate lobe-swollen pale brown	0	1	0	0
Cystic structure, caudate lobe	0	1	0	0
Pale brown; right side, adhesions	0	1	0	0
Pale brown; nodules throughout; mass, cystic lobe	0	1	0	0
Pale, nodular throughout; left lobe-nodule	0	1	0	0
Median lobe-cystic structure	0	1	0	0
Heavy; left lobe-mass/nodule	0	0	0	2
Heavy; right side-cystic mass	0	0	1	0
Swollen large, heavy, friable	0	0	0	1
Coarse	0	0	1	2

FEMALES

GROUP NUMBER	II	IV	V	VII
DOSE LEVEL	0 PPM	250 PPM	1250 PPM	5000 PPM
NUMBER NECROPSIED	80	80	79	80

LIVER:

Clear cysts throughout	1	0	0	0
Pale brown, lobular markings prominent	1	0	0	0
Pale brown	7	9	4	2
Yellow-brown nodules throughout	1	0	0	0
Apex-clear cyst	1	0	0	0
Lobular markings prominent	2	0	1	0
Heavy, red focal areas; right lobe-cystic mass	1	0	0	0
Cystic lobe-brown nodule	1	1	0	0
White foci throughout	0	3	0	0
Pale brown areas	0	1	0	0
Cystic lobe-clear cyst	0	2	0	1
Cystic lobe-swollen nodular, mottled brown	0	1	0	0
Left lobe-brown nodules	0	1	0	0
Dull brown	0	1	0	1
Dark red	0	1	0	0
Pale brown, nodular mass; median lobe	0	1	0	0
Heavy	0	0	1	1
Median lobe-clear cyst	0	0	1	0
Cystic lobe-white nodule	0	0	1	0
Large, heavy, granular surface	0	0	1	0
Lobular markings prominent, coarse	0	0	1	1
Coarse surface	0	0	0	3
Cystic lobe-nodule	0	0	0	1
Median lobe-white foci	0	0	0	1
Granular, coarse, irregular on surface	0	0	0	1
Coarse, appeared swollen	0	0	0	1
Right lobe-cyst	0	0	0	1
Left lobe-cyst	0	0	0	1
Dark	0	0	0	1