6-21-82

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

002156

MEMORANDUM

TO: J. S. Ellenberger, PM-12
Registration Division (TS-767)

FROM: Robert. P. Zendzian, Ph.D.
Toxicology Branch/HED (TS-769)

THRU: William Burnam, Head
Review Section III

and

William Burnam, Deputy Chief
Toxicology Branch, HED

SUBJECT: Baygon(R) PP# 2F1244, Review of Two-year Mouse Oncongenicity Study and Teratogenicity Study, Caswell #508

Attached are my reviews of Bayer Report No. 9954 and Bayer Report # 10183 submitted by Mobay Chemical Corporation in relation to PP# 2F1244. The results of my reviews are summarized as follows:

BOE 5812315 (Propoxur, the Active Ingredient of Baygon) Chronic Toxicity Study in Mice (Two-Year Feeding Experiment)
E. Bomhard and E. Loeser
Histopathology
D. R. Patterson

Bayer Report No. 9954
Bayer AG
Institut Fuer Toxikologic
Wappertal, F.R.G.
May 12, 1982

The study shows no evidence of oncogenicity in mice at doses up to 6000 ppm (1191 mg/kg/day males and 1374 mg/kg/day females). The study satisfies the requirements for mouse oncogenicity; however, there is a discrepancy between the doses used and the acute oral toxicity of the compound.

In this study the calculated high-dose animals consumed 1191 mg/kg/day for males and 1374 mg/kg/day for females. The compound is a carbamate cholinesterase inhibitor and its reported LD_{50} in rats is on the order of 100 mg/kg orally. Feeding studies with carbamate cholinesterase inhibitors often show an apparently lesser toxicity than the acute oral studies but the difference here appears excessive. Several possible explanations exist for this difference.

1. The mouse may be considerably less sensitive to Baygon than the rats and the large difference is illusionary.

2. The compound deteriorates when mixed with food.

3. The compound bonds to the feed.

4. Preparation of the dosed feed was in error, and the true dose was lower than calculated.

In order to clarify this matter the following information is requested from the registrant:

1. An acute oral LD_{50} in males and females of the strain of mice used for the oncogenicity study.

2. A stability test of Baygon in the mouse diet at the doses used in the studies.

3. Photo or xerographic copies of the laboratory records of dose preparation for this study.

4. If the first three requirements do not clarify the toxicity discrepancy, a metabolism study utilizing radio-labeled Baygon in feed may be necessary.

BOE 5812315 [Propoxur, the Active Ingredient in Baygon(R)] Study of Embryotoxic and Teratogenic Effects on Rabbits After Oral Administration. G. Schlueter, Bayer A.G.; Institut Fuer Toxikologic; Bayer Report # 10183; Mobay ACD Report # 80034, September 9, 1981.

Teratogenic and/or fetotoxic effects were not demonstrated in rabbits at doses of Baygon(R) up to 10 mg/kg/day (days 6 through 18 of pregnancy). No toxic and/or pharmacologic effects occurred in the dams at any dose. Proper performance of this type of study requires that the high dose produce some effect in the dam (or be as high as can be practically administered). The study should be repeated at higher doses.

In relation to this petition, Toxicology Branch wishes to remind you of the data requested by Dr. Dykstra in his memo of June 26, 1981.

002156

"Recommendation:

The chronic rat and dog studies with Baygon submitted with PP# 9G0765 and 2F1244 did not adequately characterize the NOEL for cholinesterase inhibition (for plasma, RBC, and brain). Therefore, two 90-day feeding studies (rat and dog) with technical Baygon designed to measure these cholinesterase activities and to demonstrate a NOEL are required to be submitted."

002156

Data Evaluation Report

Teratology Study in Rabbits

Compound: BOE 5812315, Propoxur, Baygon(R) Technical

Citation: BOE 5812315 [Propoxur, the Active Ingredient in Baygon(R)] Study of Embryotoxic and Teratogenic Effects on Rabbits after Oral Administration. G. Schlueter, Bayer A.G.; Institut Fuer Toxikologic; Bayer Report # 10183; Mobay ACD Report # 80034, September 9, 1981.

Reviewed by: Robert P. Zendzian, Ph.D. 6/8/82
Pharmacologist
Toxicology Branch/HED

Core Classification: Minimum

Conclusion: Teratogenic and/or fetotoxic effects were not demonstrated in rabbits at doses of Baygon(R) up to 10 mg/kg/day (days 6 through 18 of pregnancy). No toxic and/or pharmacologic effects occurred in the dams at any dose. Proper performance of this type of study requires that the nigh dose produce some effect in the dam (or be as high as can be practically administered). The study should be repeated at higher doses.

Materials: Technical BOE 5812315 (99.6%) received January 21, 1980 was used in this study.

Sexually mature Himalayan rabbits, 2 to 2.5 kg, CHBB:HM strain were used for the study. The rabbits were housed singly in rabbit cages, room temperature 20 to 23°C, and 12 hours light-dark cycle. Food and water were available ad libitum.

Methods: Mating - One male and one female were caged for breeding. The day on which two copulations occurred was taken as day zero.

Dosing: The compound was suspended in 0.5% Cremophor in water solution and administered by oral intubation on day 6 through day 18 of gestation. Doses were 0 (control), 1, 3, and 10 mg/kg/day.

Observations: The animals were weighed daily and observed for abnormalities during the gestation period.

Terminal Observations: On gestation day 29, the females were sacrificed and the fetuses removed by cesarean section.

All fetuses were examined for:

1. Weight and number

2. Sex

3. External malformations

5

4. Gross necropsy of thoracic and abdominal organs

5. Brain malfunctions by slicing fixed sections with a razor blade.

6. Cleaning and staining the skeletal system.

Statistics

1. The non-parametric rank sum test of Wilcoxen was used for weight gains, number of implantations, number of fetuses, number of resorptions, fetus weight and placenta weight.

2. The Chi-square test was used for number of fetuses with skeletal alterations, number with malformations and number stunted.

3. Either the Chi-square test or the Fisher exact test was used for the indices of fertilized and pregnant animals.

Results:

1. Effect on the dams: No toxic effects on the females were observed at any dose. No deaths occurred nor were abnormalities of appearance or behavior observed. No significant differences in weight gain between control and treated animals occurred.

There was no difference in fertilization and pregnancy indices between control and treated groups.

2. Effects on embryo and fetal development: No compound-related effects on the fetuses were observed in this study.

Discussion: The study as reported was properly performed and negative for fetal effects of doses of up to 10 mg/kg/day during gestation. However, since the highest dose produced no effects on the dam and a higher dose is technically feasible, the study does not fully satisfy the equirement for a teratogenicity study.

7

Data Evaluation Report

002156

Two-Year Mouse Oncogenicity Study

Compound Propoxur, Baygon(R), BOE 5812315, Technical

Citation

BOE 5812315, (Propoxur, the Active Ingredient of Baygon) Chronic Toxicity Study in Mice (Two Year Feeding Experiment)
E. Bomhard & E. Loeser
Histopathology
D.R. Patterson
Bayer Report No.: 9954
Bayer AG
Institut Fuer Toxikologic
Wappertal, F.R.G.
May 12, 1982

Reviewed by

6/8/82

Robert P. Zendzian, Ph.D.
Pharmacologist
Toxicology, Branch HED

Core Classification Minimum, (may be upgraded).

Conclusion: The study shows no evidence of oncogenicity in mice at doses up 6000 ppm (1191 mg/kg/day males and 1374 mg/kg/day females). The study satisfies the requirements for mouse oncogenicity; however, there is a discrepancy between the doses used and the acute oral toxicity of the compound.

The doses ingested are 11 and 13 times the acute oral toxicity of Baygon(R) in rats. Since the explanation of this difference in toxicity can range from a much lower sensitivity in mice to an error in dose preparation it is necessary to secure additional information before accepting the study. The information required is presented in detail in the discussion part of this report.

Materials

1. Test Compound

Technical BOE 5812315, (Propoxur, Baygon(R), batch #75/40, purity 99.6%) was used for the first 6 weeks of the study. Starting with week 7 a 90% concentration of Propoxur in [redacted] was used. "The stability of the compound in the mouse feed over the time period involved was assured by analytical tests

performed before the start of the study." Results of these tests were not provided.

2. Experimental Animals

SPF mice (CF_1/W74, bred by Winkelmonn, Borchan, FRG) were used for the study. Mice were 5-6 weeks old at the start of the study. The mean weight of the males was 25 gm and of the females 22 gm. The animals were housed in Type I Mikrolen cages on wood shavings, room temperature 22 ± 2 o C and on a 12 hour light/dark cycle. Cages were cleaned and supplied with fresh food weekly. Water was available ad libitum. The number of animals housed per cage was not reported.

Methods

1) Duration

Approximately 24 months (June 1976 to July 1978).

2) Dosing

BOE 5S12315 was mixed with pulverized feed to produce concentrations of 0 (control), 700, 2000 and 6000 ppm. Sixty males and 60 females were used at each dose. Ten of each sex per dose level were used for laboratory examination and interim necropsy. The body weights and food consumption of these latter animals were not determined.

3) General Observations.

All animals were observed daily for visable abnormalities. Body weight was determined weekly for the first 13 weeks and at 2-week intervals thereafter. Weekly food consumption was determined by "sex within each test group."

4) Clinical Chemistry and Hematology

Blood analysis was performed on 5 males and 5 females from each test group at 6 and 12 months on study and on 10 males and 10 females from each group at termination of the study.

Hemotological determinations
- Erythrocyte count
- Leukocyte count
- Thrombocyte count
- Reticulocyte count
- Differential WBC count
- Hemoglobin
- Hematocrit

Clinical Chemistry
- Alkaline Phosphatase
- Glutamate oxaloacetate transaminase
- Glutamate pyravate transaminase
- Creatinine
- Urea
- Blood Glucose
- Cholesterol
- Bilirubin
- Total Protein

5) Gross Necropsy and Histopathology

Gross necropsy was performed on all animals that died during the study, on 5 males and 5 females from each test group sacrificed at 6 months and on all remaining animals which were sacrificed at the end of the study. Samples of heart, lungs, liver, spleen, kidneys, testes, brain, pituitary, thyroid, adrenals, stomach, pancreas, urinary bladder, ovaries and uterus, epididymides, seminal vesicle, prostate, trachea, esophagus, femur with skeletal musculature and all abnormal tissue found during necropsy were collected and preserved for histopathological examination. The heart, lungs, liver, spleen, kidneys and testes were weighed.

Slide preparation and histopathological examination were performed by Hazleton Laboratories, Europe Ltd., Harrogate, England.

6) Statistical Analysis

Means, standard deviations and upper and lower confidence limits at 95% and 99% were calculated for each experimental group on all numerical data.

The U test of Mann, Whitney and Wilcoxon was used to compare control with test values at the 5% and 1% levels of significance.

Mortality rates of test and control groups were compared by means of Fishers exact test at significance levels of 5% and 1%.

Results

1) Observations

No differences in appearance and general behavior between test and control groups were reported.

2) Food and compound consumption

No differences in food consumption between control and treated animals was observed. The actual dose per animal was calculated as:

ppm	700	2000	6000
Males			
mg/kg/day	139	367	1191
Females			
mg/kg/day	192	478	1374

3) Body weights

Females at all doses and males at 700 and 2000 ppm gained weight in a similar manner as the controls. Males at 6000 ppm were significantly lower in body weight than controls for most of the study.

4) Mortality

The data present some evidence of decreased mortality at 2000 and 6000 ppm for the duration of the study. Percent mortality with time is summarized below.

Week	6	12	18	24
Sex	m/f	m/f	m/f	m/f
Dose ppm				
0	4/2	14/10	42/34	80/84
700	4/6	20/26	60/44	74/78
2000	2/2	10/14	38/36	68/68
6000	2/6	10/8	28/22	66/64

5) Hematology

No compound related abnormalities were observed in the cellular components of the blood. A few statistically significant variations from control were reported but they were inconsistent, following no apparent pattern in dose and/or time.

6) Clinical Chemistry

No dose and/or time related abnormalities were reported. Scattered values differed significantly from control but they followed no pattern.

7) Gross Pathology

No compound related effects were reported in the animals that died on study and in the animals that were sacrificed at 6 months and at termination.

8) Mean organ weights

Scattered mean values for the test animals at termination differed significantly from controls. Only the values for testes could be considered compound related but this is not considered a direct toxic effect. Control termination mean weight (181 mg) differed significantly from control 6 month mean weight (256mg). This is indicative of the normal decrease in testes weight in aged male mice. Treated testes mean weights were higher (215, 208 and 210 mg) at termination. This can be directly related to the compound induced increase in survival of the treated animals.

9) Histopathology

Nonneoplastic changes

No compound related changes were observed in any organs or tissues of the treated mice.

Neoplastic changes

The major tumor types observed were Adenoma and Adenocarcinoma of the lungs in both sexes, Adenoma and Adenocarcinoma of the liver in the males and malignant lymphoma in both sexes.

The incidence of these tumor types did not exceed that of historical controls and there was no evidence of a dose related increase. Occurrence of other tumor types was scattered with no dose relationship.

Discussion

The study follows the requirements for a mouse oncogenic study. The only compound related effects observed were a decrease in weight gain in the high dose males and an increase in survival time in both sexes. No oncogenic effect was observed. In and of itself the study satisfies all requirements for a mouse oncogenic study however there are some discrepancies between the doses used in this study and previous studies that require clarification.

In this study the calculated high-dose animals consumed 1191 mg/kg/day for males and 1374 mg/kg/day for females. The compound is a carbamate cholinesterase inhibitor and its reported LD_{50} in rats is in the order of 100 mg/kg orally. Feeding studies with carbamate cholinesterase inhibitors often show an apparently lesser toxicity than the acute oral studies but the difference here appears excessive. Several possible explanations exist for this difference and it is necessary to have this clarified.

1. The mouse may be considerably less sensitive to Baygon than the rat and the large difference is illusionary.

2. The compound deteriorates when mixed with food.

3. The compound bonds to the feed.

4. Preparation of the dosed feed was in error and the true dose was lower than calculated.

In order to clarify this matter the following information is requested from the registrant:

1. An acute oral LD_{50} in males and females of the strain of mice used for the oncogenicity study

2. A stability test of Baygon in the mouse diet at the doses used in the studies

3. Photo or xerographic copies of the laboratory records of dose preparation for this study

4. If the first three requirements do not clarify the toxicity discrepancy a metabolism study utilizing radio labeled Baygon in feed may be necessary.

TS-767:Zerdzim:DCR-07873:WANG-1344B:aa :Raven:479-2013: 6/3/82
REVISED:06/07/82:DCR-37634:SAME FILE-1344B