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

FEB 16, 1991
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008262

MEMORANDUM:

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: EPA Reg. No. 3125-347; Baytan
Related Actions: PP No. 5F3224 and 5H5468

FROM: George Z. Ghali, PhD G. Ghali 2.13.91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Susan Lewis, PM 21
Fungicides / Herbicides Branch
Registration Division (H7505C)

THRU: John Quest, PhD
Science Analysis and Coordination Branch
Health Effects Division (H7509C)
and
Reto Engler, PhD
Chief, Science Analysis and Coordination Branch
Health Effects Division (H7509C

Registrant: Mobay Corporation
Kansas City, MO 64120

Action Requested:

Review and evaluation of a developmental toxicity study in the rat with Baytan technical, EPA Guideline No. 83-3, Mobay Report No. 100175, Acc. No. 414984-01.

Conclusion and Recommendations:

The study was reviewed by L. Chitlik, SACB/HED. The following are excerpts of the Data Evaluation Records (DER) prepared for this study:

Maternal toxicity was noted in the 15, 25 and 60 mg/kg/day dose groups manifested as body weight gain decrease.

Slight and non-significant increases in post-implantation loss were observed in the 15, 25 and 60 mg/kg/day dose groups. Increased incidences of dilated renal pelves and distended ureters were noted in all treated groups. Comparison to

(1)

historical control was not possible. The study report did not include a statistical assessment of soft tissue findings. Therefore, a NOEL could not be established for these soft tissue findings at this time.

Supernumerary ribs were significantly increased in the 25 and 60 mg/kg/day groups, with trends apparent at the lower dose levels. A proper statistical assessment of all skeletal findings was not performed since litter data were not generally provided . In addition, the limited assessment of the data by the investigators did not include, for example, a combination of all the appropriate rib abnormalities. These, in turn, were not properly compared to historical control data. Tentatively, no NOEL for skeletal effects is apparent. The registrant must complete a new statistical assessment and generally re-evaluate the data.

The study is not designed to assess potential functional effects. The findings associated with the kidneys/ureters could be confirmed by postnatal study.

The study report was considered to be deficient in the following aspect:

Incomplete statistical assessment including;

1. Skeletal (litters)
2. Grouping of related findings (e.g., rib and associated abnormalities, dilated renal pelves and distended ureters, etc.)
3. Soft tissues (both fetal and litter assessments)

Inadequate historical control data and inappropriate comparisons to study data.

Maternal toxicity NOEL and LOEL were considered to be 5 and 15 mg/kg/day respectively. Developmental toxicity NOEL and LOEL were considered to be < 5 and 5 mg/kg/day.

The study is classified as Core-Supplementary data. However the study might be upgraded upon the receipt and evaluation of the additional information requested above.

# DATA EVALUATION REPORT

Primary Reviewer: Laurence D. Chitlik, D.A.B.T. LDC 12/24/90
Science Analysis and Coordination Branch/HED (H7509C)

Secondary Reviewer: Reto Engler, Ph.D.
Chief, Science Analysis and Coordination Branch

I. Study Type: Developmental Toxicity
Species:Charles River Crl:CD BR rats
Guideline {83-3

Study Title: Developmental Toxicity Study in the Rat with BAYTAN Technical

Sponsor: Mobay Corporation

Testing Laboratory: Toxicology Department Miles Inc.
P.O. Box 40
Echardt, IN. 46515

Study Number(s): MTD0156 or 100175

Study Date(s): May 8, 1990

Study Author(s): G.R. Clemens, C.M. Troup, and R.E. Hartnagel

Test Material: Baytan Technical 95% a.i., B-(4-chlorophenoxy)
-α-(1,1-dimethyl-ethyl)-1H-1,2,4-triazole-1-ethanol
(CAS No. 55219-65-3)
Batch No.6-03-0140
$C_{14}H_{18}ClN_3O_2$
White to tan crystalline
Slightly soluble in isopropanol, methylene chloride, and water

Vehicle(s): suspension in CMC (0.5% w/v carboxymethylcellulose and 0.4% w/v polyoxyethylene sorbitan mono-oleate (Tween 80 NF) in distilled water

Dose:(s): Vehicle control - 10 ml/kg

Test compound - 5, 15, 25, 60 mg/kg
volume: 10 ml/kg

Route of administration: gavage

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Test Animal: Charles River Crl:CD BR rats, Portage, MI
Males were less than 24 weeks of age and weighing between 434 and 658 g prior to breeding and females were 12 weeks of age and weighing between 213

and 284 g at the time of breeding.

This study was designed to assess the developmental toxicity potential of Baytan Technical, 95% a.i, when administered by gavage to rats on gestation days 6 through 15, inclusive.

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

a. Animals

The report is unclear as to how many animals were received for this study, but after an acclimation period of 13 days, 140 inseminated dams were randomly assigned to 5 groups of 28 animals each. The animals were kept under standard animal care procedures and received ground Purina Certified Rodent Chow #5002 and tap water ad libitum. Routine monitoring of the water supply for impurities or contamination was carried out. Slightly elevated iron levels were noted.

b. Mating and Group Arrangement

Rat: 2 females to 1 male overnight over a nine day period

Gestation Day 0 was the day when spermatozoa were identified microscopically.

The animals were assigned to the following groups:

| Group | Treatment | Dose | N |
|---|---|---|---|
| 1 | Vehicle control-CMC, (10 ml/kg) | 0 | 28 |
| 2 | | 5 mg/kg | 28 |
| 3 | | 15 mg/kg | 28 |
| 4 | | 25 mg/kg | 28 |
| 5 | | 60 mg/kg | 28 |

All dose levels were based on the results of a rangefinding study. This study was conducted from 9/6 to 9/29/89. Six groups of 5 rats each received doses of Baytan Technical at 0, 25, 60, 95, 130, or 165 mg/kg as a suspension in CMC. Weight gain effects were noted at levels of 60 mg/kg/day and above. Increased levels of resorptions were noted at 130 and 165 mg/kg/day. Five fetuses from one litter in the high dose level had cleft palate and all but one fetus of this litter had protruding tongues.

c. Dosing

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All doses were in a volume of 10 ml/kg/day prepared from stock solutions each day during the dosing period. The concentration and homogeneity of each stock test suspension was verified by high pressure

liquid chromatography. Dosing was based on body weights on day six of gestation. Dams were dosed once daily from days 6 to day 15 of gestation for a total of 10 doses.

d. Observations

The dams were checked for mortality and clinical signs on a daily basis. Body weights were obtained on Days 0, 6-16, and 20. Food consumption was measured on Days 1, 6, 7, 12, 16, and 20 of gestation. Dams were sacrificed on day 20 of gestation by $CO_2$ asphyxiation. Blood was drawn by cardiac puncture for the purpose of determining maternal serum liver enzyme levels. Corpora lutea were counted and recorded. The uterine horns and liver were weighed. The uterus was examined and implants and resorptions were counted. In addition the glass plate technique was utilized to assure that all implantation scars had been counted. Abdominal and thoracic viscera from dams received a gross pathological examination.

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The fetuses were examined in the following manner:

Viability of each fetus was determined. This was followed by an external examination. One-half of the fetuses from each dam were sacrificed by intracranial injection of barbiturate and received an examination of the abdominal and thoracic viscera. Following this exam these fetuses were fixed in Bouin's and later free-hand razor sections were made transversely through the mouth to the back of the head, and then sagittally through the eyes and cranium.

Fetuses not selected for visceral examination were fixed in toto in 70% ethanol. These fetuses were later eviscerated, cleared and stained with Alizarin Red-S and then evaluated for skeletal development. The report states that, "Skull, vertebrae, ribs, pelvis, appendages, scapulae, clavicles, and sternum were carefully examined and comparisons were made with the control."

Historical control data were provided to allow comparison with concurrent controls. However, these data were very incomplete and very difficult to utilize in the format provided. Findings such as dilated renal pelves and cervical ribs were not included although necessary for proper assessment of study data.

e. Statistical analysis

Analyses consisted of application of one or more of the following tests:

Chi-square, Dunn (1964), Dunnett's (1955; 1964), Fisher's (1934) exact (Pagano-Halvorsen, 1981), Kruskal-Wallis (1952), and Student's t.

A signed Statement of No Data Confidentiality Claims was provided. A signed Statement of compliance with EPA GLP's was

A Flagging Statement was provided and indicated that no criteria were exceeded.

A signed Quality Assurance Statement was not apparent.

III. Results

A. Maternal Toxicity

1. Mortality

No animals died on study.

2. Clinical Observations

No overt toxicity was observed in any dose group. In four high dose dams and 2 dams of the 25 mg/kg/day group, mild allopecia was observed. In controls, animal # RS1747, and high dose animal # RS1816, a reddish vaginal discharge was noted on days 15 and 13 respectively.

3. Body Weight

Table I: Body Weight Gains and Corrected Body Weight (grams)[a]

| Group: | Prior to Dosing Period (d.0-6) | Dosing Period (d.6-16) | Post-Dosing Period (d.16-20) | Entire Gestation Period | Gravid+ Uterine Weight | Corrected† BW Gain Entire Gestation Period | N |
|---|---|---|---|---|---|---|---|
| Control | 27.8g | 52.5g | 54.6g | 134.9g | 73.2g | 61.7g | 28 |
| 5mg/kg | 24.6g | 51.7g | 55.9g | 132.2g | 74.9g | 57.3g | 22 |
| 15mg/kg | 23.5g | 45.8g* | 55.7g | 125.0g | 73.3g | 51.7g** | 25 |
| 25mg/kg | 23.5g | 45.9g* | 56.9g | 126.3g | 70.4g | 55.9g | 25 |
| 60mg/kg | 24.0g | 39.8g* | 62.5g | 126.1g | 78.3g | 47.8g (48.1** reported) | 28 |

† = corrected body weight gain for entire gestation period = body weight gain for entire gestation period minus gravid uterus weight.
* = Statistically different from control at the 0.05 level using Dunnett's test
** = Statistically different from control at the 0.01 level using Dunnett's test
+ = Data extracted from Appendix G and not statistically assessed.

The above table supports the contention that body weight gain was reduced in the 15, 25, and 60 mg/kg/day dose groups. This was most apparent during the dosing period and was supported by an apparent rebound effect only at the high dose level. In addition, the corrected body weight data is consistent with an effect at the 15, 25, and 60 mg/kg/day dose levels. Although the corrected body weight gain at the 25 mg/kg/day dose level is not reported as statistically significant, this is likely the result of inclusion of data from dam number 1862 which had only one implant and a uterine weight of only 7.7 grams.

4. Food Consumption

Table II of the submitted report presented the food consumption data for days 1, 6, 7, 12, 16, and 20. Data were not presented for various periods during the study as is normally preferred. Slight but statistically significant reductions (at the 0.05 level using Dunnett's test) were only noted on day 7 in the 15 and 60 mg/kg/day groups. Also the rebound in body weight gain noted previously at the high dose level appears to be supported by a statistically increased food consumption on day 20.

5. Gross and Clinical Pathology

Gross pathology findings were presented in Appendix D, on page 80 of the report. No compound related necropsy findings were apparent.

Appendix E included clinical chemistry findings for Aspartate Aminotransferase, Alanine Aminotransferase and Alkaline Phosphatase which were obtained on day 20 of gestation. No dose related alterations in clinical chemistry values were apparent from these data.

Liver weight and liver-to-body weight ratio data presented in table IV and in Appendix F did not suggest any compound related effects.

B. Cesarean Section Observations

Table V from the test report, titled "Reproductive Efficiency and Fetal Data" did not suggest any toxicological effects on the incidence of maternal death, abortion, number of live or dead fetuses, or litter size. Placental weight increased in the high dose only (statistically significant at the 0.01 level using the Kruskal-Wallis test). Both the mean number of resorption sites per litter and percent postimplantation loss increased slightly in the 15, 25, and 60 mg/kg/day levels but did not reach levels of statistical significance. Post-implantation loss, although slightly elevated in these groups did not appear to increase in a dose related manner.

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Table II: Cesarean Section Observations[a]

| Dose: | Control | 5 mg/kg | 15 mg/kg | 25mg/kg | 60 mg/kg |
|---|---|---|---|---|---|
| #Animals Assigned | 28 | 28 | 28 | 28 | 28 |
| #An. pregnant/Inseminated | 28 | 22 | 25 | 25 | 28 |
| Pregnancy Rate (%) | 100 | 78.6 | 89.3 | 89.3 | 100 |
| #Died | 0 | 0 | 0 | 0 | 0 |
| #Aborted | 0 | 0 | 0 | 0 | 0 |
| Corpora Lutea/Dam | 14.9 | 14.9 | 15.4 | 14.2 | 15.2 |
| Total Implantations | 395 | 312 | 364 | 346 | 411 |
| Implantations/Dam | 14.1 | 14.2 | 14.6 | 13.8 | 14.7 |
| Total Live Fetuses | 372 | 299 | 336 | 318 | 382 |
| % Viable | 100 | 100 | 100 | 100 | 99.7 |
| Resorptions/Dam | 0.8 | 0.6 | 1.1 | 1.1 | 1.0 |
| Total Dead Fetuses | 0 | 0 | 0 | 0 | 1 |
| Mean Placental weight | 0.52 | 0.52 | 0.51 | 0.55 | 0.63** |
| Mean Fetal Weight (gm) | 3.6 | 3.7 | 3.6 | 3.6 | 3.6 |
| Postimplantation Loss(%) | 5.8 | 4.0 | 7.9 | 7.6 | 6.8 |
| Sex Ratio (% Male) | 55.4 | 51.9 | 50.0 | 46.7 | 48.1 |

[a]=Data extracted from table V, pg. 24.

** Statistically significant increase ($p<0.01$). Also outside the historical range for placental weight (0.50 to 0.55).

C. Fetal Observations

1. External and Soft Tissue Examinations

The investigators presented data for external and soft tissue findings together in Table VII. Total incidences of individual abnormalities were not tabulated. Findings noted were essentially for kidney, brain, and major vessels and have been tabulated by this reviewer. A statistical assessment was not presented by the investigators, however, the incidences of dilated renal pelves and dilated ureters is increased in all dose groups.

| Dose level: mg/kg/day<br>fetuses (litters) | 0 | 5 | 15 | 25 | 60 |
|---|---|---|---|---|---|
| Kidney | | | | | |
| Bilateral Rudimentary | 6(2) | 0 | 0 | 0 | 0 |
| Dilated pelvis | 0 | 5(5) | 6(4) | 4(4) | 8(5) |
| Ureter distended | 0 | 3(3) | 6(4) | 4(4) | 6(4) |
| Brain | | | | | |
| Cerebrum diminished in size | 1(1) | 0 | 0 | 0 | 0 |
| Portion of cerebrum isolated above meninge causing herniation (segmented ?) | 0 | 2(2) | 0 | 0 | 0 |
| Craniorachischisis (sic) | 0 | 1(1) | 0 | 0 | 0 |
| Major vessel | 0 | 1(1) | 2(2) | 1(1) | 1(1) |
| Anal imperforate | 0 | 1(1) | 0 | 1(1) | 1(1) |
| Tail missing/ threadlike | 0 | 0 | 0 | 1(1) | 1(1) |

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3. Skeletal Examinations

Skeletal data were presented by the investigators in table VIII. The incidences of extra cervical and lumbar ribs appears to be increased in a dose related manner. In addition, separate headings exist in table VIII for cervical, extra, and other rib findings, but table IX simply combines only two headings (cervical and lumbar ribs) and excludes small, rudimentary, bulbous, etc. from this assessment of fetal and litter incidences. If these were included, the dose response may be even stronger. Further, the incidences of cervical ribs as well as other variations are not provided in the historical data. Hence, it is difficult to ascertain what the range of incidences for extra ribs (0.5 to 15.7%) actually includes. In order to use historical data correctly, it is important to relate specific study findings to specific findings in the historical data. In addition, this is better accomplished when the historical data are comprised of studies conducted during a similar period. In this case no other studies from 1989 or 1990 are included and only one study from 1988 is listed.

See tables VIII and IX attached. Note that table VIII does not include litter incidences for any of the reported findings. This limits proper assessment of the data since the litter is considered the proper unit for statistical assessment. Table IX includes a combined assessment on a litter basis for all skeletal, visceral, and external findings. This approach is one step above useless, except for the assessment of extra ribs which I have already indicated to be incomplete and misleading. In the absence of useful historical data and the lack of statistical assessments on a litter basis for all malformation and variation data, it is tentatively concluded on the basis of apparent trends for "extra ribs" that no NOEL exists for this finding. It is recognized that supernumerary ribs commonly occur, but the incidences at the 25 and 60 mg/kg levels are clearly elevated and are significantly different from controls at the 0.01 level using the Chi-square test.

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IV. Discussion/Conclusion

a. Maternal Toxicity: Maternal body weight gain effects were noted in the 15, 25, and 60 mg/kg/day dose groups. The determination of effects at this dose level were confirmed after assessment of corrected body weight gain at these same dose levels.

b. Developmental Toxicity:

i. Deaths/Resorptions: Slight and non-significant increases in post-implantation loss were observed at the 15, 25, and 60 mg/kg/day dose levels.

ii. Structural abnormality/altered growth: Increased incidences of dilated renal pelves and distended ureters were noted at all dose levels but not in controls. Comparisons to historical control data are not possible at this time. The report did not include a statistical assessment of soft tissue findings. Tentatively, it is concluded that no NOEL exists for these soft tissue findings.

Supernumerary ribs were noted to increase in this study especially at the highest two dose levels (statistically significant), with trends apparent at lower dose levels. A proper statistical assessment of ALL skeletal findings was not performed since litter data were not generally provided. In addition, the limited assessment of the data by the investigators did not include, for example, a combination of all the appropriate rib abnormalities. These, in turn, were not properly compared to historical control data. Tentatively, no NOEL for skeletal effects is apparent.

The registrant must complete a new statistical assessment and generally re-evaluate the data.

iii. Functional deficits: This study is not designed to assess potential functional effects. The findings associated with the kidney/ureters could be confirmed by a postnatal study.

c. Study Deficiencies:

Incomplete statistical assessment

1. Skeletal (litters)
2. Grouping of related findings (e.g., rib and associated abnormalities, dilated renal pelves and distended ureters, etc.
3. Soft tissues (both fetal and litter assessments)

Inadequate historical data and inappropriate comparisons to study data.

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V. Core Classification: Core-Supplementary Data.

Maternal NOEL = 5 mg/kg/day
Maternal LOEL = 15 mg/kg/day
Developmental Toxicity NOEL < 5 mg/kg/day (tentative)
Developmental Toxicity LOEL = 5 mg/kg/day

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