CASWELL FILE

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

009704

AUG 2 7 1992

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 5F03224; 8E03642. Baytan. Supplemental Data to the Rat Teratology Study

Tox. Chem. No. 074A
Project No. 1-1887
DP Barcodes: D167115, D167117, D167111

TO: James Stone, PM Team #22
Registration Division (H7505C)

FROM: Pamela M. Hurley, Toxicologist
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Pamela M Hurley 8/7/92

THRU: Roger L. Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Roger Gardner 8/14/92 KB 8/18/92

Submission: S400349, S400354, S400339

Background and Request:

Mobay Corporation had submitted developmental toxicity studies in the rat and rabbit in support of registration of Baytan. The Agency determined that both of the developmental toxicity studies did not meet the Agency's current standards and graded both studies as Core Supplementary. Mobay has conducted new developmental toxicity studies in both the rat and rabbit and has submitted the results to the Agency. The rabbit study will be reviewed in a separate memorandum. The new rat study has already been reviewed and was again graded Core Supplementary because of several deficiencies. However, the Agency review stated that the study may be upgradable upon receipt of additional data. The following additional data on the rat study was requested by the Agency:

1. Complete statistical assessments including:

   a. Skeletal, including litter data.
   b. Grouping of related findings (e.g., rib and associated abnormalities, dilated renal pelves and distended ureters, etc.).
   c. Soft tissues (both fetal and litter assessments).

(1)

2. Historical control data and appropriate comparisons to study data.

Mobay Corporation has submitted the requested data and the Toxicology Branch (TB-I) has been asked to review the data and upgrade the study, if appropriate.

Toxicology Branch Response:

Conclusions: TB-I has reviewed the additional data submitted by Registrant and has determined that the developmental toxicity study in the rat is acceptable for regulatory purposes and is reclassified as Core Minimum. The NOEL for maternal effects is 5 mg/kg/day and the LOEL for maternal effects is 15 mg/kg/day based on decrease in body weight gains during the dosing period. The NOEL for developmental effects is 25 mg/kg/day and the LOEL is 60 mg/kg/day, based on an increased incidence of extra ribs.

Review:

A. Summary of Design and Conduct of Study:

Baytan was tested for potential to induce developmental effects in rats at the following dose levels: 0, 5, 15, 25 and 60 mg/kg/day in a volume of 10 ml/kg. The doses were administered by gavage once daily from days 6 through 15 of gestation, for a total of 10 doses. Dose levels were selected on the basis of a range-finding study, in which groups of 5 dams were tested at 0, 25, 60, 95, 130 or 165 mg/kg/day. Decreases in body weight gain in the dams were noted at doses of 60 mg/kg/day and above and increased levels of resorptions were observed at 130 and 165 mg/kg/day. Five fetuses from 1 litter had cleft palate at 165 mg/kg/day and all but 1 fetus of this litter had protruding tongues. In the main study, the following parameters were measured and/or examined:

Dams: Mortality and clinical signs, body weights, food consumption, serum liver enzyme levels, pregnancy rate, # abortions, # corpora lutea, liver and uterine horn weights, examination of uterus, # implants and resorptions, # live and dead fetuses, placental weight, gross pathological examination of abdominal and thoracic viscera.

Fetuses: Viability, mean fetal weight, sex, external examinations, examination of abdominal and thoracic viscera (one half of fetuses), examination of skeletal development (one-half of fetuses).

B. Summary of Results (Taken From Data Evaluation Report):

**Dams:**

There was a significant reduction in mean body weight gain during the dosing period in the 15, 25 and 60 mg/kg/day dams.

Slight but statistically significant reductions in food consumption were observed on day 7 in the 15 and 60 mg/kg/day dose groups. Food consumption was increased on day 20 at the highest dose level.

No dams died on the study and no treatment-related clinical signs of toxicity were observed in any of the treated groups.

No treatment-related gross necrospy effects were observed.

No treatment-related effects in liver enzyme values or in absolute and relative liver weights were observed.

**Cesarian Section Observations:**

No toxicological effects were observed in the incidence of maternal death, abortion, number of live or dead fetuses or litter size. Placental weight increased in the high dose only ($p < 0.01$) and "both the mean number of resorption sites/litter and percent postimplantation loss increased slightly in the 15, 25 and 60 mg/kg/day dose 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."

**Fetal Observations:**

External and soft tissue examinations:

The study report presented external and soft tissue findings together and total incidences of individual abnormalities were not tabulated. A statistical assessment was not presented in the study report. The incidences of dilated renal pelves and dilated ureters were increased in all dose groups. These incidences are summarized in a table later in this memorandum.

Skeletal examinations:

The Data Evaluation Report (DER) stated that the incidences of extra cervical and "lumbar" ribs appeared to be increased in a dose related manner. The incidences in the two highest dose levels were statistically significant when compared to controls. However, in the report tables, some items were combined and others were excluded, thus making it difficult to conduct a

complete assessment. The incidences of cervical ribs as well as other variations were not provided in the historical control data. Hence, it was difficult to ascertain what the range of incidences for extra ribs (0.5 to 15.7%) actually included. The historical control data that was presented in the report contained only one study from 1988 and no other studies from 1989 or 1990 (the present study was completed in 1990). The fetal skeletal summary table in the study report did not include litter incidences, which limited proper assessment of the data. Litter incidences were included in a summary table which combined all skeletal, visceral and external malformations and variations together into one table. Thus, although it was recognized the supernumerary ribs commonly occur, it was tentatively concluded on the basis of apparent trends for "extra ribs", that a NOEL could not be estimated for this finding. The incidences at the 25 and 60 mg/kg levels were clearly elevated and were significantly different from controls at $p < 0.01$.

The study was classified as Core Supplementary and the following NOEL's were tentatively estimated:

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 (tentative)

C. Review of Additional Data Provided by the Registrant:

Post-implantation loss and resorption sites/litter: The Registrant commented on the statement in the DER concerning the non-statistically significant increases in post-implantation loss and mean number of resorption sites/litter. The Registrant states that "the incidence of post-implantation loss was relatively low and quite comparable across all groups. There was an extremely low occurrence of late gestational deaths; only one non-viable fetus was observed and this occurred in a single 60 mg/kg litter. With regard to resorption, all categories dealing with resorption...were well within the historical control range for the performing laboratory...The actual percentage of dams possessing resorption was identical between the control and 60 mg/kg group (57.1%) and was lower than control for both the 15 and 25 mg/kg groups (56.0% in each case). In addition, the range finding study showed an even higher dose (95 mg/kg) than those employed in the definitive study appears to be devoid of counter-gestational potential."

The following table gives the actual summary data that was discussed by the Registrant above:

| Reproductive Efficacy and Fetal Data | | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg | 5 mg/kg | 15 mg/kg | 25 mg/kg | 60 mg/kg |
| No. of Litters | 28 | 22 | 25 | 25 | 28 |
| No. With Resorption Sites Only | 0 | 0 | 0 | 0 | 0 |
| # Corpora Lutea/Dam | 14.9 | 14.9 | 15.4 | 14.2 | 15.2 |
| # Implantations/Dam | 14.1 | 14.2 | 14.6 | 13.8 | 14.7 |
| # Dead Fetuses (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1(.3) |
| Litter Size/Dam | 13.3 | 13.6 | 13.4 | 12.7 | 13.7 |
| # Resorption Sites/Dam | 0.8 | 0.6 | 1.1 | 1.1 | 1.0 |
| Median Resorption Sites/Dam (range) | 1.0 (0-2) | 0.0 (0-2) | 1.0 (0-4) | 1.0 (0-6) | 1.0 (0-4) |
| Mean % Pre-Implantation Loss (range) | 6.4 (0-53.3) | 5.9 (0-43.8) | 7.7 (0-40.0) | 7.7 (0-66.7) | 4.9 (0-40.0) |
| Mean % Post-Implantation Loss (range) | 5.8 (0-16.7) | 4.0 (0-13.3) | 7.9 (0-22.2) | 7.6 (0-35.3) | 6.8 (0-23.5) |

Number of resorption sites/litter: The historical control data for six studies conducted between the years 10/80 and 2/82 (somewhat earlier than this study) indicates that the number of resorption sites/dam ranged from 0.7 to 1.4. The ranges of resorption sites/dam for each of the studies were from 0-3 to 0-11. The median number of resorption sites/dam were from 0 to 1. **The Toxicology Branch (TB-I) agrees with the Registrant that the data in the study and the historical control data indicate that Baytan does not have an effect on the number of resorption sites/litter at any dose level tested under the conditions of the study.**

Percent post-implantation loss: The changes in the percent post-implantation loss are not dose related. The mean % post-implantation losses in the historical controls ranged from 5.7 to 13.7. The ranges were from 0-18.2 to 0-66.7. As the Registrant has stated, the values for the present study are well within the historical control range. **Again, the Toxicology Branch (TB-I) agrees with the Registrant that the data in the study and the**

**historical control data indicate that Baytan does not have an effect on the percent post-implantation loss at any dose level tested under the conditions of the study.**

External and visceral findings: The Registrant provided litter incidence tables for all external and visceral findings, including the statistical analyses. Historical control data were also provided which included more recent studies. The only findings that were statistically significant from controls were fetal incidences of dilated pelves of the kidney in the 15 mg/kg dose group and in the 60 mg/kg dose group. None of the litter incidences were statistically significant. There was no dose response and all of the values were within the historical control range except for the fetal incidences of dilated pelves at the high dose which was 4.3% versus 4.1% in the historical controls. In addition, it appears that in this study, the incidences in the control groups were especially low. **Taking all of the available data into consideration, TB-I does not believe that the incidences of dilated renal pelves and distended ureters in the treated groups are due to administration of Baytan.** The lesions of interest in the DER are summarized in the following table.

| External and Visceral Findings of Fetuses and Litters | | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg | 5 mg/kg | 15 mg/kg | 25 mg/kg | 60 mg/kg |
| **Kidney, bilateral pelvis (litters)** | 6(2) | 0(0) | 0(0) | 0(0) | 0(0) |
| **Kidney, dilated pelves** | | | | | |
| Litter (percent) | 0 (0) | 5 (22.7) | 4 (16.0) | 4 (16.0) | 5 (17.9) |
| Fetuses (percent) | 0 (0) | 5 (3.5) | 6* (3.7) | 4 (2.7) | 8* (4.3) |
| **Ureters, distended** | | | | | |
| Litter (percent) | 0 (0) | 3 (13.6) | 4 (16.0) | 4 (16.0) | 4 (14.3) |
| Fetuses (percent) | 0 (0) | 3 (2.1) | 6 (3.7) | 4 (2.7) | 6 (3.3) |
| **Historical Control Data (Ranges)** | | | | | |
| **Kidney, dilated pelves** | | | | | |
| Litter (percent) | 0 - 6 (0 - 23.1) | | | | |
| Fetuses (percent) | 0 - 6 (0 - 4.1) | | | | |
| **Ureters, distended** | | | | | |
| Litter (percent) | 0 - 5 (0 - 19.2) | | | | |
| Fetuses (percent) | 0 - 6 (0 - 3.4) | | | | |

* $p < 0.05$

It is of note that the Registrant observed that there was an unusual incidence of rudimentary kidneys in the control group which did not appear in the treated groups (6 fetuses in 2 litters). These findings have been communicated to the breeding laboratory, Charles River.

In this section, the Registrant also addressed the comment in the DER which suggested the need to perform a postnatal study to assess potential renal dysfunction. The Registrant stated that "the authors do not feel that this is justified. The literature supports the conclusion that these soft tissue variations are among the most common soft tissue findings in developmental toxicity studies conducted in the Sprague-Dawley rat." The

comments quoted several studies to support their objection to conducting the study. One study indicated that the dilation is merely a delay in renal development and not permanent damage. **TB-I agrees with the Registrant that postnatal studies to assess potential renal dysfunction are unnecessary at this time.**

Skeletal findings: The Registrant has provided a litter incidence table for skeletal findings and historical control tables for litter and fetal incidences of rib findings, including statistical analyses. The effect of concern in the DER appears to be extra ribs. According to the newly submitted data, this effect appears in the litters as well. In comparison to the historical control data, the incidence of extra ribs in the controls from this study appears to be slightly low. The fetal and litter incidences at the 25 mg/kg dose group were statistically significant. However, the incidences were well within the historical control range. Since the control incidences were low for this study, the effect in the 25 mg/kg dose is probably not toxicologically significant. There do not appear to be any other effects. **Therefore, the NOEL for developmental effects is 25 mg/kg and the LEL is 60 mg/kg, based on an increased incidence of extra ribs. TB-I agrees with the Registrant in that these should be considered to be variations, not malformations. TB-I also agrees with the statement from the Registrant that "it does not appear logical to combine or lump skeletal findings together, except perhaps in the case of malformations. For example, categories dealing with lagging ossification should not be combined with true malformations such as fused, missing or asymmetrical (e.g. scoliosis) skeletal elements. Nor should wavy ribs, or incompletely ossified ribs be combined with supernumerary ribs."** The following table summarizes the data on extra ribs.

| Extra Ribs (Fetal, Litter and Historical Control Incidences) | | | | | |
|---|---|---|---|---|---|
| | 0 mg/kg | 5 mg/kg | 15 mg/kg | 25 mg/kg | 60 mg/kg |
| Fetal Incidence (%) | 1 (0.5) | 6 (3.8) | 6 (3.4) | 13 (7.7)** | 42 (21.2)** |
| Litter Incidence (%) | 1 (3.6) | 6 (27.3) | 6 (24.0) | 9 (36.0)* | 20 (71.4)** |
| Historical Control Data | | | | | |
| Fetal Incidences (%) | 1 - 34 (0.5 - 18.6) | | | | |
| Litter Incidences (%) | 1 - 17 (3.7 - 65.2) | | | | |

* Significantly different from control ($p < 0.05$).
** Significantly different from control ($p < 0.01$).

cc: N. Thoa