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

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APR 15 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Phillip Hundemann, Product Manager
Registration Division (TS-767C)

Thru: Judith Hauswirth, Ph. D., Acting Head
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS-769)
Judith W. Hauswirth 4-14-87

FROM: Roger Gardner, Toxicologist
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS-769)
Roger Gardner 4-14-87
4/15/87

SUBJECT: Teratology Study in Rabbits with Thiophanate Methyl (EPA Reg. No. 4581-280) Tox. Proj. No. 7-0502. Tox. Chem. No. 375A.

Action Requested

Review of range-finding and full teratology studies in rabbits (see Appendix for Data Evaluation Records) to determine the possibility of adverse effects (6[a]2 data).

Recommendations and Conclusions

1. Based on limitations described in Section C. below, and the marginal nature of the effects observed (see point 3. and Section C. below), the submitted reports suggest an adverse effect [6(a)2 data]. However, circumstances described below indicate that another study is needed to confirm the effects observed.

2. Doses of 0, 2, 6, or 20 mg/kg were given orally to pregnant rabbits during gestation. Slight maternal toxicity (marginal and transient weight reductions up to 8.6% below controls, reduced food consumption, and decreased fecal output) were observed at 20 mg/kg/day. The no-observed effect level (NOEL) was greater than 20 mg/kg/day (see Appendix below).

3. Developmental toxicity (increased incidence of asymetric pelvis in treated groups) was observed in the study (see Sections B. and C., and the Appendix below), and the NOEL could not be determined because of the equivocal nature of results.

4. The study is considered to be supplementary (see Section C. and the Appendix below) because only marginal maternal effects were observed in the study and fetal effects need to be confirmed.

5. The adult to developmental toxicity ratio (A-D ratio) can not be determined for rabbits because of the limitations described in Section C. below.

A. Previously Submitted Developmental Toxicity Data

In one study, groups of pregnant rats were given daily doses by gavage of 0, 100, 300, or 1000 mg/kg on gestation days 6 through 19. Reduced fertility, generally decreased litter size, incidence of hair loss or matting, and ambiguous results in fetuses raise questions about the study, but no compound-related maternal or fetal effects were observed.

A second study in which pregnant rats received diets containing 0, 250, 1200, or 2500 ppm on days 6 through 19 of gestation indicated that thiophanate methyl decreased the palatability of test diets at the two highest levels. There were no fetal effects observed that could be directly associated with the test substance.

The data as presented in a mouse study did not demonstrate that the highest dose tested (1000 mg/kg/day) was sufficient to cause minimal toxicity in the dams or their fetuses. The report described the protocol and results so briefly that fetal examinations appeared to be incomplete (limited to the skeleton). Reported statistically significant differences in the number of live fetuses per litter in the high dose group with respect to the control group could not be confirmed by independent analysis (t test) of limited individual animal data. Administration of thiophanate methyl from Day 1 of gestation (well before implantation) could also have contributed to the decrease in litter size by causing a reduction in the number of implantation sites. (A slight decrease in implantation sites in dams given the highest dose was noted.) These considerations indicate that the mouse study is incomplete. Therefore, a teratology study in a second species (preferably the rabbit) is needed.

B. Developmental Toxicity Data in Rabbits

The new studies are described in detail in the Appendix below.

The two range-finding studies were conducted in rabbits to select doses for a teratology study with thiophanate methyl. In the first one, doses of 0, 150, 300, or 600 mg/kg/day were given to groups of 4 pregnant rabbits on days 6 through 19 of gestation. The results of the first study indicated that a maximum dose level should be less than 150 mg/kg based on the high incidence of mortalities, abortions, and total litter losses.

The second range-finding study tested doses of 0, 10, 30, and 100 mg/kg under similar conditions to those of the first study. The incidence of litter loss and abortions, body weight loss, reduced food consumption, and decreased fecal output in this study suggested that the highest dose for the main teratology study with thiophanate methyl should be less than 30 mg/kg/day.

In the main study, doses of 0, 2, 6, or 20 mg thiophanate methyl per kg body weight were given to groups of 15 pregnant rabbits on days 6 through 19 of gestation. The rabbits receiving the highest dose exhibited marginal and transient weight reductions (a maximum difference of 8.6% decrease below control group weight on day 10), reduced food consumption, and decreased fecal output.

Fetuses in the highest dosed group had increased incidences of minor skeletal variations including 13 pairs of ribs, ribs thickened at costel cartilage, 27 pre-sacral vertebrae, and asymmetric pelvis (illia associated with different sacral vertebrae). No teratogenic effects were observed.

C. Discussion

The 20 mg/kg dose in the main study was associated with an increased number of abortions and total litter losses. Two of the 15 inseminated rabbits in that group were not pregnant, and one doe died. Historical control data indicated an average incidence for abortion and total litter loss of 4.9% with a range from 0 to 33%, and the incidence of these effects in the main study (3/12 or 25%) was near the upper end of the historical range. The two control groups in the preliminary study showed a range of 0 (0/4) to 50% (2/4) for the incidence of abortions and total litter loss. The preliminary results and historical control data suggest that the reduced number of litters in the high dose group was a significant factor in the observed increased incidence of abortions and total litter losses.

The highest dose group also showed a lower number of implantation sites per doe. Since there were two non-pregnant animals in that group, and since thiophanate methyl was not administered until Day 6 (probably after implantation), the test substance is not likely to be the cause of the decreased number of implantation sites observed in the high dose group rabbits.

In addition, there were no signs of toxicity observed, with the exception of decreased food consumption and fecal output. Other signs such as changes in appearance, behavior or condition would be expected, but the report did not mention any other signs occurring in a dose-related manner.

These considerations suggest that factors other than toxicity may be associated with maternal effects observed in the main study, and the absence of clinical signs other than effects on food consumption and fecal output indicate that a wider dose range should be tested.

The 6 and 20 mg/kg doses in the main study were associated with minor skeletal alterations in the fetuses. Those results suggested that thiophanate methyl increased the incidence of 13 pairs of ribs and 27 presacral vertebrae. However, these increases were not reflected in numbers of litters containing one or more affected fetuses in mid and high dose groups. In addition, the percentage incidence of affected fetuses for those skeletal alterations were within historical ranges. Based on these considerations, the increased incidence of 13 pairs of ribs and 27 presacral vertebrae is probably not the result of administration of thiophanate methyl.

In the case of the incidence of fetuses and litters containing one or more fetuses with thickened ribs, there was a statistically significant increase, and the incidence in the high dose group was slightly higher than the historical range. There were 7 of 51 fetuses affected (13.8%) and 7 of 9 litters (78%) with affected fetuses in the high dose group compared to the maximum incidence of 12.8% of fetuses observed historically. Since historical control data did

not report results on the basis of litters with one or more affected fetuses. significance of results in the main study can not be assessed completely.

The rib effect is a minor variation occurring without other ossification anomalies such as wavy ribs, incomplete ossification, etc. In addition, the proportion of fetuses observed in each affected litter did not increase with the dose. In view of the conclusion stated above that a wider dose range should hgave been used, the absence of an increase in the proportion of affected fetuses in affected litters would not be unusual. Therefore, thickening of the ribs at the costel cartilage may not be the result of thiophanate methyl treatment, but existing data do not clearly support that conclusion.

There was no statistically significant overall difference between test groups with respect to the incidence of fetuses and litters with fetuses having asymetric pelvis, and there were no statistically significant differences between the control and high dose groups either. The report stated that the incidence of the effect was within the historical range, but the upper limit of the range was not legible as presented (see Addendum III for an example). Because of these considerations and the marginal maternal effects described above, the observed incidence of asymetric pelvis can only be interpreted as preliminary evidence that thiophanate methyl may cause developmental toxicity in rabbits. Those results should be confirmed in another study because of the relatively serious nature of the pelvic defect.

Based on the marginal maternal effects observed, a wider dose range could probably have been tested. The fetal effects observed suggest a potential for developmental toxicity, but circumstances of the experiment described above indicate that those results should be confirmed in another study in order to fully assess the potential for developmental toxicity.

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APPENDIX

Data Evaluation Records for the Following Studies

Tesh, J. M., F. W. Ross, and T. J. Wightman. April 25, 1986. Thiophanate Methyl: Effects of Oral Administration on Pregnancy in the Rabbit. 1. Dose Range Finding Study. Unpublished report prepared by Life Science Research, Suffolk, England. Submitted by Pennwalt Corp., Philadelphia, PA. EPA Acc. No. Unassigned. MRID No. Unassigned.

Tesh, J. M., F. W. Ross, T. J. Wrightman, et al. May 20, 1986. Thiophanate Methyl: Teratology Study in the Rabbit. Unpublished report no. 86/MIS010/111 prepared by Life Science Research, Suffolk, England. Submitted by Pennwalt Corp., Philadelphia, PA. EPA Acc. No. Unassigned. MRID No. Unassigned.

DATA EVALUATION RECORD 005840

1. CHEMICAL: Thiophanate methyl; 1,2-bis (3-methoxycarbonyl-2-thioureido) benzene; Topsin (Tox. Chem. No. 375A)

2. TEST MATERIAL: Technical grade thiophanate methyl (96.2% purity; pale brown powder) was used.

3. STUDY/ACTION TYPE: Teratology (range-finding) - rabbit

4. STUDY IDENTIFICATION: Tesh, J. M., F. W. Ross, and T. J. Wightman. April 25, 1986. Thiophanate Methyl: Effects of Oral Administration on Pregnancy in the Rabbit. 1. Dose Range Finding Study. Unpublished report prepared by Life Science Research, Suffolk, England. Submitted by Pennwalt Corp., Philadelphia, PA. EPA Acc. No. Unassigned. MRID No. Unassigned.

5. REVIEWED BY:

Name: Roger Gardner
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Organization: Review Section 6
Toxicology Branch
Signature: Roger Gardner
Date: 4-14-87

6. APPROVED BY:

Name: Judith Hauswirth, Ph. D.
Title: Acting Head
Organization: Review Section 6
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Signature: Judith W. Hauswirth
Date: 4-14-87

7. CONCLUSIONS: Two range-finding studies were conducted in rabbits to select doses for a teratology study with thiophanate methyl. In the first one, doses of 0, 150, 300, or 600 mg/kg/day were given to groups of 4 pregnant rabbits on days 6 through 19 of gestation. The results of the first study indicated that a maximum dose level should be less than 150 mg/kg based on the high incidence of mortalities, abortions, and total litter losses. The second study tested doses of 0, 10, 30, and 100 mg/kg under similar conditions to those of the first study. The incidence of litter loss and abortions in the second study suggested that the highest dose for the main teratology study with thiophanate methyl should be less than 30 mg/kg/day.

Core classification: Supplementary

8. MATERIALS AND METHODS

Test species: Approximately 18 to 24 week old female New Zealand white rabbits were used. The day the animals were artificially inseminated and given luteinizing hormone intravenously was designated Day 0 of gestation.

Experimental procedures: The test substance was suspended in 1% (w/v) aqueous methyl cellulose and administered by gavage on days 6 through 19 of gestation. Doses of 0, 150, 300, or 600 or 0, 10, 30, or 100 mg test substance per kg body

8. MATERIALS AND METHODS (continued)

weight were given to groups of 4 inseminated does. Because of extensive losses in the first range-finding experiment (at higher doses), a second experiment was conducted.

Each doe was observed at least once daily for occurrence of toxic signs and mortality. Body weight determinations were made daily throughout the study. Food and water consumption were determined for each animal for days 1-5, 6-12, 13-19, 20-23, and 24-28 of gestation.

Animals found dead or sacrificed in extremis were examined to determine the cause of their condition or death, and those that aborted were sacrificed and examined. Observations recorded for aborted does included the numbers of corpora lutea and implantation sites. Fetuses were examined for abnormalities when possible.

Surviving rabbits were sacrificed on day 29 of gestation. The numbers of corpora lutea, implantation sites, live and dead fetuses, and embryonic deaths were noted.

Placentae and fetuses were weighed, and fetuses were examined for external abnormalities. The fetuses were then killed, internally sexed, and their viscera were examined for variations and malformations. They were then eviscerated and fixed in industrial methylated spirit.

Interpretation and analysis of results: The report described the manner in which means, standard deviations, and other statistics were calculated, and that description is included below as Addendum I.

9. REPORTED RESULTS

Maternal observations: Signs observed during gestation and attributed to the test substance included reductions in food consumption and fecal output in all animals given the 150, 300, or 600 mg/kg/day doses. The report stated that these effects were also found in the 30 and 100 mg/kg/day dosed groups, but the condition of those rabbits given the 10 mg/kg/day dose was comparable to control animals.

Table 1 summarizes mortality and pregnancy status of the animals in the experiment. Maternal body weight results are summarized in Table 2, and Addendum II shows the body weight change results as they were presented in the report.

The reported food consumption during the dosing period was <5 g/day/rabbit for the survivors in the groups given the 150, 300, or 600 mg/kg/day doses. The control groups consumed an average of 170 to 273 g/rabbit/day during the same period. Rabbits given the 10 mg/kg/day dose consumed amounts of food comparable to that of control animals during dosing, and the 30 mg/kg/day survivors consumed approximately 1/3 to 1/2 that in the control groups. Food consumption remained below the control group rates after the dosing period for those rabbits given 30 mg/kg/day or higher doses.

005840

9. REPORTED RESULTS (continued)

Table 1

Pregnancy data summary

Parameter	Dose (mg/kg/day) 0	150	300	600	0	10	30	100
Number inseminated	4	4	4	4	4	4	4	4
Deaths during dosing	0	1	1	2	0	0	0	0
Not pregnant	0	0	0	0	2	1	0	0
Abortions	0	0	3	0	0	0	1	2
Total litter loss	0	2	0	1	0	0	0	2
Number of litters	4	1	0	1	2	3	3	0

Litter observations: Because of the low number of pregnancies in those animals given the 150, 300, and 600 mg/kg/day doses, litter results are not discussed further (see Addendum III below for those results as they were presented in the report). Table 3 summarizes results for those rabbits given doses below 150 mg/kg/day along with the appropriate control group.

Table 2

Summary of maternal weight results (kg)

Dose (mg/kg/day)	Mean weight (kg) on gestation Day 0	Day 10	Day 28
0	4.03	4.13	4.41
150	4.20	4.07	3.87
300	--	--	--
600	3.78	3.43	3.57
0	3.89	4.18	4.36
10	4.11	4.39	4.65
30	3.80	3.67	3.86
100	--	--	--

Fetal observations: Because of the small number of litters available, fetal observations are not discussed in detail. However, Addendum IV shows those data as they were reported.

10. DISCUSSION

The results of the first range finding study indicated that a maximum dose level should be less than 150 mg/kg based on the high incidence of mortalities, abortions, and total litter losses (see Table 1 above). The incidence of litter loss and abortions in the second study also suggested that the highest dose for the main teratology study with thiophanate methyl should be less than 30 mg/kg/day.

005840

Table 3

Litter data summary

Parameter	Dose (mg/kg/day) 0	10	30	100
Number pregnant (Day 29)	2	3	4	0
Corpora lutea per doe	11.0	17.3	9.0	--
Implantations per litter	8.0	11.7	8.3	--
Live fetuses per litter	8.0	8.0	8.0	--
Total litter resorptions	1	0	0	1
Resorptions per litter				
Early	0.0	3.3	0.0	--
Late	0.0	0.3	0.3	--
Total	0.0	3.7*	0.3	--

*As reported.

ADDENDUM I

Descriptions from the original report
of definitions, interpretations, and
statistical analyses used

Thiophanate-methyl tox review

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DATA EVALUATION RECORD

1. CHEMICAL: Thiophanate methyl; 1,2-bis (3-methoxycarbonyl-2-thioureido) benzene; Topsin (Tox. Chem. No. 375A)

2. TEST MATERIAL: Technical grade thiophanate methyl (96.2% purity; pale brown powder) was used.

3. STUDY/ACTION TYPE: Teratology - rabbit

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Title: Acting Head
Organization: Review Section 6
Toxicology Branch
Signature: Judith W. Hauswirth
Date: 4-14-87

7. CONCLUSIONS: Doses of 0, 2, 6, or 20 mg thiophanate methyl per kg body weight were given to groups of 15 pregnant rabbits on days 6 through 19 of gestation. The rabbits receiving the highest dose exhibited marginal and transient weight reductions (a maximum difference of 8.6% decrease below control group weight on day 10), reduced food consumption, and decreased fecal output. Fetuses in the highest dosed group had increased incidences of minor skeletal variations including 13 pairs of ribs, ribs thickened at costel cartilage, 27 pre-sacral vertebrae, and asymmetric pelvis (illia associated with different sacral vertebrae). No teratogenic effects were observed.

Based on the marginal maternal effects observed, a wider dose range could probably have been tested. The fetal effects observed suggest a potential for developmental toxicity, but circumstances of the experiment described above indicate that those results should be confirmed in another study in order to fully assess the potential for developmental toxicity.

Core classification: Supplementary for reas ons described above.

8. MATERIALS AND METHODS

Test species: Approximately 18 to 24 week old female New Zealand white rabbits were used. The day the animals were artificially inseminated and given luteinizing hormone intravenously was designated Day 0 of gestation.

8. MATERIALS AND METHODS (continued)

Experimental procedures: The test substance was suspended in 1% (w/v) aqueous methyl cellulose and administered by gavage on days 6 through 19 of gestation. Doses of 0, 2, 6, or 20 mg test substance per kg body weight were given to groups of 15 inseminated does.

Each doe was observed at least once daily for occurrence of toxic signs and mortality. Body weight determinations were made daily throughout the study. Food and water consumption were determined for each animal for days 1-5, 6-12, 13-19, 20-23, and 24-28 of gestation.

Animals found dead or sacrificed in extremis were examined to determine the cause of their condition or death, and those that aborted were sacrificed and examined. Observations recorded for aborted does included the numbers of corpora lutea and implantation sites, and fetuses were examined for abnormalities when possible.

Surviving rabbits were sacrificed on day 29 of gestation. The numbers of corpora lutea, implantation sites, live and dead fetuses, and embryonic deaths were noted.

Placentae and fetuses were weighed, and fetuses were examined for external abnormalities. The fetuses were then killed, internally sexed, and their viscera were examined for variations and malformations. One-third of the fetuses were decapitated, and the heads were fixed in Bouin's solution for subsequent examination by free-hand serial sectioning. Torsos and the remaining fetuses were eviscerated and fixed in industrial methylated spirit. Skeletons were stained using a modification of the Dawson Aliqirin staining technique according to the report.

Interpretation and analysis of results: The report described the manner in which means, standard deviations, and other statistics were calculated, and that description is included below as Addendum I.

9. REPORTED RESULTS

Maternal observations: Signs observed during gestation and attributed to the test substance included reduced food consumption and fecal output. The report noted that these effects were found primarily in the highest dosed group. Table 1 summarizes mortality and pregnancy status of the animals in the experiment. The report attributed the 5 deaths to "respiratory and/or gastrointestinal disturbances." Maternal body weight results are summarized in Table 2, and Addendum II shows the body weight change results as they were presented in the report. Weight loss was observed in the does given the 20 mg/kg/day dose level during the first four days of dosing. The investigators also noted a smaller weight loss in the mid dose group during the same period. After the first four days of dosing, weight gain in the mid and high dose groups was greater than or similar to that for the control group.

Food consumption was decreased for the high dose group during days 6 through 12 when compared with that of the control group (115 compared with 186 g/rabbit /day). No statistical significance was indicated. No consistent differences with respect to group mean water consumption were noted by the investigators.

005840

9. REPORTED RESULTS (continued)

Table 1

Pregnancy data summary

Parameter	Dose (mg/kg/day) 0	2	6	20
Number inseminated	15	15	15	15
Deaths during dosing	2	1	1	1
Not pregnant	0	3	1	2
Abortions	0	1	1	2
Total litter loss	1	0	0	1
Number of litters	12	10	12	9

Table 2

Summary of maternal weight results (kg)

Dose (mg/kg/day)	Mean weight (kg) on gestation Day 0	Day 10	Day 28
0	4.04	4.19	4.35
2	3.85	3.96	4.21
6	3.99	4.04	4.19
20	3.90	3.83	4.22

Those animals that aborted their pregnancies were observed to lose weight during the days preceeding their abortions.

Litter observations: According to the investigators, there were no consistent treatment or dose-related effects on litter observations (see Table 4 below).

Fetal observations: The authors stated that the majority of fetal alterations were frequently observed at their laboratory in rabbits of the strain used. Most of them did not occur in a treatment related manner according to the report. However, the report noted the increased incidences of fetuses with 13 pairs of ribs and/or 27 presacral vertebrae and/or asymmetric pelvis (illia associated with different sacral vertebrae). There was also an increased incidence of thickened ribs at the costel cartilage in the high dose group when compared with the control group. Table 5 summarizes the incidences of these alterations.

005840

Table 3

Litter data summary

Parameter	Dose (mg/kg/day) 0	2	6	20
Number pregnant (Day 29)	13	11	13	12
Corpora lutea per doe	11.4	11.8	10.2	10.6
Implantations per litter	8.10	7.94	8.0	6.9
Live fetuses per litter	7.3	7.8	7.9	5.7
Fetal weight (g)	40.8	43.9	42.5	45.2
Total litter resorptions	1	0	0	1
Resorptions per litter				
Early	0.7	0.0	0.0	0.9
Late	0.1	0.1	0.1	0.3
Total	0.8	0.1	0.1	1.2

Table 4

Summary of selected skeletal alterations noted by the investigators

Parameter	Dose (mg/kg/day) 0	2	6	20
No. fetuses examined	88	78	95	51
No. with:				
13 pairs of ribs***	36	36	60**	31**
Ribs thickened at costel cartilage†	1	3	1	7*
27 pre-sacral vertebrae††	14	14	36*	21*
Asymmetric pelvis	3	4	7	5
No. litters examined	12	10	12	9
No. with:				
13 pairs of ribs	10	10	11	9
Ribs thickened at costel cartilage	1	3	1	7**
27 pre-sacral vertebrae	7	8	7	9
Asymmetric pelvis	3	3	5	5

*Statistically significantly different from control (Chi square test ($p < 0.01$).

**Statistically significantly different from control (Fisher's Exact test; $p = 0.05$).

***Statistically significant overall (2 X 4 contingency; $p < 0.05$).

†Statistically significant overall (2 X 4 contingency; $p < 0.01$).

††Statistically signigicant overall (2 X 4 contingency; $p < 0.001$)

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10. DISCUSSION

Maternal effects: The report concluded that the 20 mg/kg/day dose of thiophanate methyl caused a transient weight loss in the does early in the treatment period (Table 2 above and Addendum II below). The difference between the high dose and control group mean body weights was greatest at the Day 10 observation according to tabulated results in the report. That difference was marginal (approximately 8.6%), and the two group mean body weights were comparable at the end of the study. In addition, no statistically significant difference was indicated in the report for the high dose and control group mean body weights.

In addition, there were no signs of toxicity observed, with the exception of decreased food consumption and fecal output. Other dose-related signs such as changes in appearance, behavior or condition would be expected, but the report did not mention any other signs occurring in a dose-related manner.

The highest dose was also associated with an increased number of abortions and total litter losses (Table 1 above) according to the authors. However, the high dose group showed a lower number of implantation sites per doe, and two of the 15 inseminated rabbits were not pregnant. Historical control data included in the report indicated an average incidence for abortion and total litter loss of 4.9% with a range from 0 to 33%; the incidence of these effects (3/12 or 25%) was at the upper end of the historical range. These considerations suggest that factors other than the test substance may be associated with these effects. Therefore, the data as presented in the report do not clearly support the conclusion that the test substance caused an increased incidence of abortions and litter losses.

Fetal effects: The high and mid doses were associated with minor skeletal alterations by the authors (Table 4 above). These effects included 13 pairs of ribs, ribs thickened at costel cartilage, 27 pre-sacral vertebrae, and asymmetric pelvis (illia associated with different sacral vertebrae). Statistically significant differences were not indicated in the report, but independent analyses (Chi square and Fisher's Exact tests) were done with the data shown in Table 4 above.

Those results suggest that thiophanate methyl at 6 and 20 mg/kg/day increased the incidence of 13 pairs of ribs and 27 presacral vertebrae. However, these increases were not reflected in numbers of litters containing one or more affected fetuses in those groups. In addition, the percentage incidence of affected fetuses for those skeletal alterations were within historical ranges according to the investigators (see Table 5 below). Based on these considerations, the increased incidence of 13 pairs of ribs and 27 presacral vertebrae seen in the mid and high dose groups is not the result of treatment.

In the case of the incidence of fetuses and litters containing one or more fetuses with thickened ribs, there was a statistically significant increase, and the incidence in the high dose group was slightly higher than the historical range. There were 7 of 51 fetuses affected (13.8%) and 7 of 9 litters (78%) with affected fetuses in the high dose group compared to the maximum incidence of 12.8% of fetuses observed historically. Since historical control data did not report results on the basis of litters with one or more affected fetuses, significance of results in the main study can not be assessed completely.

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10. DISCUSSION (continued)

Table 5

Summary of selected historical control data
along with appropriate experimental data

Parameter	Dose (mg/kg/day) 0	6	20	Historical data* Average	Range
Per cent fetuses with:					
13 pairs of ribs	40.9	63.2	60.8	35.91	11.9-61.0
Ribs thickened at costel cartilage	1.1	--	13.7	2.43	0.0-12.8
27 pre-sacral vertebrae	15.9	37.9	42.1	18.12	7.2-44.3
Asymmetric pelvis	3.4	7.4	9.8	3.54	0.0-**

*Data compiled from 86 studies and a total of 8655 fetuses.
**The righthand side of the Table 8 of the original report was not reproduced.

The rib effect is a minor variation occurring without other ossification anomalies such as wavy ribs, incomplete ossification, etc. In addition, the proportion of fetuses observed in each affected litter did not increase with the dose. In view of the conclusion stated above that a wider dose range should hgave been used, the absence of an increase in the proportion of affected fetuses in affected litters would not be unusual. Therefore, thickening of the ribs at the costel cartilage may not be the result of thiophanate methyl treatment, but existing data do not clearly support that conclusion.

There was no statistically significant overall difference between test groups with respect to the incidence of fetuses and litters with fetuses having asymetric pelvis, and there were no statistically significant differences between the control and high dose groups either. The report stated that the incidence of the effect was within the historical range, but the upper limit of the range was not legible as presented (see Addendum III for an example). Because of these considerations and the marginal maternal effects described above, the observed incidence of asymetric pelvis can only be interpreted as preliminary evidence that thiophanate methyl may cause developmental toxicity in rabbits. Those results should be confirmed in another study because of the relatively serious nature of the pelvic defect.

Based on the marginal maternal effects observed, a wider dose range could probably have been tested. The fetal effects observed suggest a potential for developmental toxicity, but circumstances of the experiment described above indicate that those results should be confirmed in another study in order to fully assess the potential for developmental toxicity.

ADDENDUM I

Descriptions from the original report
of definitions, interpretations, and
statistical analyses used

Thiophanate-methyl tox review

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Pages 28 through 34 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

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