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

APR 25 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Repeat Teratology Studies (Rat and Rabbit) on Metalaxyl

TO: Henry Jacoby
Product Manager (12)
Registration Division (TS-769)

THRU: Robert P. Zendzian, Ph.D. 4/25/85
Acting Head, Revew Section IV
Toxicology Branch
Hazard Evaluation Division (7S-769)

FROM: Chad B. Sandusky, Ph.D. Chad B Sandusky 4/18/85
Pharmacologist
Toxicology Branch
Hazard Evaluation Division (TS-769) 4/25/85

Compound: Metalaxyl

Tox. Chem. #: 375AA

Registration #: 100-601
(3 separate action sheets)

Registrant: Ciba-Geigy

Accession #: 255939, 255994, 257329 -rabbit
256380, 257329 - rat

Record #: 142545, 144211, 148362

Action Requested:

Ciba-Geigy has submitted for review the following two repeat teratology studies:

1) Range - Finding and Definitive Teratology Study in Rats; P.E. Traster, International Research and Development Coropration (Study #'s 382-099 and 382-100), Jan. 3, 1985; Submitted by CibaGeigy; Accession Number: 256380, 257329.

2) Range - finding and Definitive Teratology Studies Conducted in Rabbits, M.F. Kend; International Research and Development Corporation, (Study #'s 382-097/382-098; Nov. 28 and Dec. 4, 1984, Accession Nos. 255939, 255994, 257329.

Conclusions:

The following conclusions are based on an in-depth review of each of the above teratology studies:

1) Rat Study:

Metalaxyl was administred by gavage to rats on days 6-15 of gestation at 0, 50, 250, and 400 mg/kg/dy. On day 20, all surviving dams were sacificed and C-sectioned. Maternal toxicity was present at 250 and 400 mkd, as evidenced by convulsions and ataxia; NOEL=50 mkd; LEL=250 mkd. The fetotoxic NOEL = 50 mkd, LEL=250 mkd, based on an increase in sternebrae #5 and/or #6 being unossified. No embryotoxicity was observed at any dose. Finally, metalaxyl was not teratogenic, even in the presence of maternal toxiciity; NOEL = 00 mkd, the highest dose tested; LEL not established.

Core Classification: Minimum.

The following deficiencies were noted in this study:

1) No information on compound purity or composition was provided

2) No information, e.g., strain, age, weight, etc., was provided on the "stock males' used for mating.

2) Rabbit Study:

Dutch belted rabbits (18/group) were artifically inseminated, ovulation induced, and gavaged with technical metalaxyl on gestation days 7-19 at 0, 30, 150 or 300 mg/kg/day. Methylcellulose (1%) served as vehicle control. Slight maternal toxicity was noted at 300 mkd, as evidenced by a small decrease in mean body weight (2.3%) during the 13 day treatment period. The result of a preliminary dose range finding study supported this observation of maternal toxicity, i.e., 500 mkd produced greater maternal weight loss (7.4%) and 1000 mkd produced maternal mortality (100%). Therefore, the maternal toxic NOEL 150 mkd; LEL=300 mkd. Under the conditions of this study, metalaxyl was not embryotoxic, fetotoxic or teratogenic. The NOEL for these parameters = 300 mkd; LEL not established.

2

Core Classification: Minimum

The following deficiencies were noted in this study.

1) No information was provided on compound purity, stability or composition.

2) No information was provided on "proven males" used for artifical insemination, e.g., age, or number and frequency of semen donations.

3) There was only a marginal demonstration of maternal toxicity. Higher doses, i.e., >300 mkd, may have been used to more clearly demonstrate a maternal toxic effect.

Background:

These repeat teratology studies were submitted to support the data in two earlier teratology studies in the same species. All studies were submitted by Ciba-Geigy. The earlier studies were also conducted by Ciba-Geigy. These repeat studies were conducted at IRDC and submitted in response to Toxicology Branch concerns that the first 2 studies, when subjected to re-review, were judged to be Core Supplementary (see related action 100-607; Accession #'s 252935, 252936 and 253634).

DER's:

DER's on the following repeat teratology studies are attached:

1) Range - Finding and Definitive Teratology Study in Rats; P.E. Traster, International Research and Development Coropration (Study #'s 382-099 and 382-100), Jan. 3, 1985; Submitted by CibaGeigy; Accession Number: 256380, 257329.

2) Range - finding and Definitive Teratology Studies Conducted in Rabbits, M.F. Kend; International Research and Development Corporation, (Study #'s 382-097/382-098; Nov. 28 and Dec. 4, 1984, Accession Nos. 255939, 255994, 257329.

Reference:

The above 2 teratology studies are repeat studies of the following 2 teratology reports:

1) Spoede, S.J. and Campbell, W.R. 1984. Expanded report on the Segement II reproduction study with CGA-48988 Technical in the rat (test for teratogenic or embryotoxic effects). Unpublished report (Study No. 227716) prepared and submmitted by CIBA-GEIGY Corporation, Agricultural Division, Greensboro, North Carolina. Accession #: 252936, 253634.

2) Buettler, B. and Campbell, W.R. 1984. Expanded report on a Segment II reproduction study in the rabbit with CGA-48988 Technical (test for teratogenic and embryotoxic effects). Unpublished reprot (Study No. 784868) prepared and submitted by CIBA-GEIGY Corporation, Agricultural Division, Greensboro, North Carolina. Accession #: 252935.

These studies are reviewed under Petition # 100-607.

Data Evaluation Report

Compound: Metalaxyl

Citation: Range - Finding and Definitive Teratology Study in Rats; P.E. Traster, IRDC (Study #'s 382-099 and 382-100), Jan. 3, 1985; Submitted by Ciba-Geigy; Accession Number: 256380

Report Number: IRDC 382-099 (Range Finding) and IRDC 382-100 (Definitive Study)

Reviewed By:

Chad B. Sandusky, Ph.D.
Pharmacologist
Toxicology Branch
Hazard Evaluation Division (TS-769)

Chad B Sandusky
4/10/85

Robert P. Zendzian, Ph.D.
Acting Section Head IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/13/85

Core Classification: Minimum.

The following deficiencies were noted in this study:

1) No information on compound purity or composition was provided.

2) No information, e.g., strain, age, weight, etc., was provided on the "stock males" used for mating.

Tox Category: N/A

Conclusion:

Metalaxyl was administered by gavage to rats on days 6-15 of gestation at 0, 50, 250, and 400 mg/kg/day. On day 20, all surviving dams were sacificed and C-sectioned. Maternal toxicity was present at 250 and 400 mkd, as evidenced by convulsions and ataxia; NOEL=50 mkd. The fetotoxic NOEL = 50 mkd, LEL=250 mkd, based on an increase in sternebrae #5 and/or #6 being unossified. No embryotoxicity was observed at any dose. Finally, metalaxyl was not teratogenic, even in the presence of maternal toxicity; NOEL = 400 mkd, the highest dose tested.

Materials:

1) Test article: Metalaxyl technical, FL 840049; light brown chunky solid. No further information on compound purity or composition was provided. However, data was reported which indicated that when mixed and suspended in the vehicle methylcellulose, metalaxyl is stable for up to one week.

2) Vehicle control article: 1% methylcellulose. No further information was provided.

3) Experimental animals: The following information is taken directly from the original report:

"The animals for this study were received in three separate shipments. One hundred thirty-four untreated 70-day old, and twenty-one, 45-day old virgin female Charles River COBS® CD® rats were received from Charles River Breeding Laboratories, Inc., Portage, Michigan on July 16, 1984. Eleven animals considered for this study were 28 days old when received from the same source on June 18, 1984."

The weights of the rats upon receipt was not given. However, the body weights during gestation are shown in Table 2.

Females were mated with "stock males utilized exclusively for this purpose". No other information on these "stock males" was provided.

Methods:

Animals were acclimated at least 10 days prior to mating. During the entire study the animals were housed individually (except during mating), provided standard rodent chow and water ad libidum and maintained under environmentally controlled standard laboratory conditions.

After acclimation, all animals were weighed and examined. One female and one male (of the same strian and source) were then placed together for mating. After copulation (determined by daily inspection for copulatory plugy or vaginal smear for sperm), the female was returned to an individual cage. The day of mating was designated day 0 of gestation.

After evidence of mating, females were consecutively assigned (by ear tag number) to one control or one of three treatment groups. The final doses used in this study and the number of mated females assigned to each group are shown below:

GROUP	NUMBER OF ANIMALS
Control (1% methylcellulose in water)	27
50 mg/kg	27
250 mg/kg	27
400 mg/kg	38

These doses were selected based on a dose range-finding study. The synopsis of this study (from the original report) is found in Appendix I. During the initial phase of this full phase of the teratology study, however, excessive toxicity (mortality) was noted at the high dose (see Appendix II). Therefore, the high dose was lowered from 575 mg/kg/day to 400 mg/kg/day, and new animals were mated to replace those previously exposed to higher levels of metalaxyl. There was no explanation as to why the animals in the second, full phase of this study displayed greater signs of toxicity than those in the first, range-finding phase of this study. Mated females were administered metalaxyl by gavage to yield dose levels of 50, 250 or 400 mg/kg/day on days 6 thru 15 of gestation; the control group received vehicle only. The test material was prepared so that the dosage volume was constant for all groups, including controls, at 10 ml/kg. Individual dosages were determined from individual body weights on gestation days 6, 9 and 12.

The following regimen was observed during the study:

- Maternal appearence and behavior	Twice daily prior to treatment
- Maternal mortality	Twice daily, days 6-15 of gestation
- Maternal clincal signs	Once daily during days 6-15 of gestation
- Maternal body weights	Recorded on gestation days 0, 6, 9, 12, 16 & 20
- Maternal food consumption	Daily, gestation days 0-19

7

On gestation day 20 all surviving females were sacrificed by carbon dioxide inhalation and Caesarean sections performed. The following data were collected:

- number and location of viable and non-viable fetuses
- number of early and late resorptions
- total number of implantations
- total number of corpora lutea
- gross examinations of maternal abdominal and thoracic cavities and organs.

Maternal tissues, including uteri of non-gravid females (for detection of implantations) were preserved for examination as deemed necessary.

Fetuses were removed, and the following data collected:

- individual fetal weights
- fetal sex
- gross external malformations and variations
- approximately one-half of the fetuses were placed in Bouins solution for subsequent soft tissue examination using the Wilson razor-blade sectioning technique.
- approximately one-half of the fetuses were eviscerated and prepared for subsequent sheletal examinations by a method similar to that described by Dawson.

Various statistical analyses were performed as summarized below:

- Chi-Square and/or Fisher's exact tests	male to female sex ratios and proportions of litters with malformations
- Mann - Whitney U-test	proportions of resorbed and dead fetuses and post-implantation losses
- Analysis of variance/Bartlett's test and/or appropriate t-test	Mean numbers of corpora lutea, total number of implantations, live fetuses and mean fetal body weights

8

Results:

1) Maternal Effects:

Maternal toxic effects were observed at the two highest doses of 250 and 400 mg/kg/day. These effects consisted of mortality (32%; all deaths on gestation days 6-8) at the highest dose and numerous clinical signs at both 250 and 400 mkd, e.g., convulsions, ataxia, decreased motor activity and, reduced/loss of righting reflex. These clinical signs were more pronounced at 400 mkd than at 250 mkd (see Table 1; reproduced intact from the original report). In addition, although all animals gained weight during gestation; the high dose animals gained somewhat less than controls during dosing days 6 to 15 (32 $\pm$ 11.4 g vs 38 $\pm$ 8.7 g). The summary of maternal body weights and body weight changes are shown in Table 2 (reproduced in-tact from original report). There were no apparent differences in food consumption between any of the groups during gestation (Table 3; reproduced from original report). No remarkable observations were noted in the dams of any dose at necropsy (Table 4; reproduced intact from the original report). This lack of effects at necropsy at the high dose is somewhat unusual in light of the high degree (32%) of mortality at this dose.

Based on the apparence of clinical observations in dams, i.e., convulsions and ataxia, the NOEL for maternal toxicity in this study is 50 mkd (LDT); LEL = 250 mkd.

2) Reproductive and Embryotoxic Effects:

Pregnancy rates were comparable in all groups (86 - 92%) and resulted in 22-25 pregnant dams being examined at C-section, all with viable fetuses. None of the non-gravid dams (2-4) had resorptions only. There were no remarkable reproductive or embryotoxic effects at any dose (Table 5; reproduced intact from original report). Therefore, the reproductive and embryotoxic NOEL = 400 mkd (HDT); LEL not established.

3) Fetotoxic Effects:

There was no effect on the number of fetuses/dam, fetal body weights or fetal sex distributions in any group (Table 5). However, the data presented in Table 6 (reproduced intact from the original report)

show evidence of fetotoxicity, relating primarily to problems with ossification in sternebrae # 5 and/or #6, at 250 and 400 mkd vs control (56 fetuses in 20 litters, 66 in 19 and 36 in 17, respectively). In addition, the high dose (group (400 mkd) also showed fewer than normal ribs (12 fetuses in 8 litters vs 2 in 2 for control), reduced ossification in the skull (9 fetuses in 5 litters vs 3 in 3) and pubic bones unossified (5 fetuses in 3 litters vs 1 in 1).

Although there was a dose related increase in the absolute number of fetuses with sternebrae # 5 and/or #6 being unossified (see below), there was not an increase in the number of litters with this effect.

	Dose Group (mg/kg/day)			
Sternebrae #5 and/or #6 unossified	0	50	250	400
Number of fetuses / number of fetuses examined skeletally	36/150	46/151	56/135	66/139
Number of litters affected / Number of litters examined	17/24	18/25	20/22	19/22
% of fetuses affected	24%	30%	41%	47%
% of litters affected	71%	72%	91%	86%

The historical controls included in the report showed that this effect was common in this strain and ranged from 10-15% (fetuses) in 13-88% (litters) of control groups. Therefore, based on all of the above information, the fetotoxic NOEL = 50 mkd, LEL = 250 mkd based on unossified sternebrae # 5 and/or #6.

4) Teratogenic Effects:

There were only 2 major fetal malformations noted in this study (see Table 7; reproduced intact from the original report), i.e., 1 incidence of anascaca (generalized fetal edema) in the high dose and 1 incidence of acephaly at the low dose. No other fetal malformations were reported. The historical controls presented with this study also showed a low spontaneous incidence of malformations in this strain. Therefore, under the conditions of this study, metalaxyl was not teratogenic at doses up to 400 mkd (NOEL).

Discussion:

This study was an adequate test for the embryotoxic, fetotoxic and teratogenic effects of metalaxyl in rats. Maternal toxic effects were present at the 2 highest doses, as evidenced by clincial signs (convulsions and ataxia). The maternal toxic NOEL = 50 mkd, LEL = 250 mkd. Fetotoxic effects (unossified sternebrae # 5 and/or # 6) were observed at doses as low as 250 mkd (LEL); NOEL = 50 mkd. There was a high background incidence of this effect in the control and low dose group, as well as the historical controls presented with this study. However, the increase in this effect seen at 250 mkd and 400 mkd were judged to be compound related and evidence of the fetoxicity of metalaxyl in rats. No embryotoxic or teratogenic effects were noted, even in the presence of maternal toxicity at 400 mkd, the highest dose tested.

There was a low incidence of major malformations in this study, i.e., there were only 2 malformations observed in all of the futuses examined - 1 acephaly in the low dose and 1 anasarca in the high dose. This was supported by historical control data included in the report for this strain of rat. Therefore, it may be concluded that under the conditions of this study metalaxyl is not teratogenic in rats.

As noted earlier, and in Appendix II, the dams in the full phase of the teratology study showed greater signs of toxicity at the same doses used in the preliminary range finding study. These differences are unexplained. If the metalaxyl had been unstable and degraded, the toxic signs would have been decreased (not enhanced), unless the parent compound had degraded to a more toxic compound. Although no information was provided on the purity or composition of the test article, it is assumed that these enhanced signs of toxicity were not due to changes in metalaxyl, since it was shown to be stable in methylcellulose for up to one week.

Although no information was provided on the "stock males" used for breeding, the fertility rates in this study were adequate (86-92%).

Finally, the lack of significant gross necropsy findings in 34 of 38 high dose females examined *in extremis* or at C-section is somewhat unusual. This lack of findings was reported despite the fact that 12 dams in this dose group died or were sacrificed *in extremis* prior to C-section on gestation day 20. Furthermore, the frequency of clinical signs (Table I) in both the mid and high dose group would suggest that at least some gross necropy findings would have been anticipated. The lack of gross findings is therefore unexplained.

METALAXYL

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DATA EVALUATION REPORT

Compound: Metalaxyl

Citation: Range - finding and Definitive Teratology studies conducted in Rabbits, M.F. Kend; International Research and Development Corporation, Studies No. 382-097/382-098; Nov. 28 and Dec. 4, 1984 Accession No. 255939.

Report Numbers: 382-097 and 382-098.

Reviewed by:

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Chad B. Sandusky
4/17/85

Secondary Review by:

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Acting Head, Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/25/85

CORE Classification: Minimum.

The following deficiencies were noted in this study.

1) No information was provided on compound purity, stability or composition.

2) No information was provided on "proven males" used for artificial insemination, e.g., age, or number and frequency of semen donations.

3) There was only a marginal demonstration of maternal toxicity. Higher doses, i.e., >300 mkd, may have been used to more clearly demonstrate a maternal toxic effect.

Toxicity Category: N/A

Conclusion:

Dutch belted rabbits (18/group) were artifically inseminated, ovulation induced, and gavaged with technical metalaxyl on gestation days 7-19 at 0, 30, 150 or 300 mg/kg/day. Methylcellulose (1%) served as vehicle control. Slight maternal toxicity was noted at 300 mkd, as evidenced by a small decrease in mean body weight (2.3%) during the 13 day treatment period. The results of a preliminary dose range finding study supported this observation of maternal toxicity, i.e., 500 mkd produced greater maternal weight loss (7.4%) and 1000 mkd produced maternal mortality (100%). Therefore, the maternal toxic NOEL = 150 mkd; LEL = 300 mkd.

Under the conditions of this study, metalaxyl was not embryotoxic, fetototxic or teratogenic. The NOEL for these parameters = 300 mkd, LEL not established.

Materials:

1) Metalaxyl, technical (FL840049), described as light brown chucky solid. Assays of target concentrations used for gavage (6, 30 or 60 mg/ml) were 97-105% of desired levels. No other information on sample purity or stability was given.

2) Methylcellulose (1%) was used to suspend metalaxyl for gavage and as vehicle control. No other information was provided.

3) Virgin female Dutch Belted rabbits were obtained from Longshaw Farms, Augusta, Michigan for use in this study. Rabbits were 4-5 months old upon receipt and weighed 3098± 284g (mid dose group) to 3238 ± 314g (low dose group) on gestation day 0.

Methods:

Eighty-six female rabbits were acclimated 28-days in individual cages. During this period, animals were observed for changes in appearance and behavior. Throughout the study, animals were housed individually in an environmentally controlled room and provided food and water ad libitum.

Approximately 3 weeks prior to insemination, the does were superovulated by an injection of 50 U.S.P. units of A.P.L. (chorionic ganadotropin; Ayerst Laboratories) via a marginal ear vein.

The procedures for the organization of test groups and selection of animals for inclusion in the study were followed as stated below:

"At the end of the acclimation period, all animals were weighed and subjected to a detailed physical examination. Animals considered suitable for study were randomly assigned to one control group and three treatment groups of 18 rabbits each by the following computer-generated system. Animal numbers and corresponding body weights were entered onto magnetic tape which was used as the data source for the randomization procedure. The mean

body weight and standard deviation were calculated and a computer-generated edit developed a listing of those animals whose body weights were within ± 2.9 standard deviations of the mean. From qualifying animals, the randomization procedure selected and assigned the required number of animals. Bartlett's test for homogeneity of variances was applied to the groups."

No further criteria were given as to what parameters made a doe "qualified" or "suitable" for inclusion in the study.

The test groups and the number of animals assigned to each group were as follows:

Dose (mg/kg)	Number of Rabbits
0	18
30	18
150	18
300	18

These doses were selected on the basis of maternal toxicity produced in a dose-range finding study conducted prior to the initation of the definitive study (see Appendix I, "Synopsis of Dose Range Finding Study", reproduced in-tact from the original report).

Does were artificially inseminated with semen (>60% motility) from one of nine proven male rabbits, of the same strain (no other information provided). Semen from 1 male was used to inseminate an equal number of females in each group. Immediately after insemination, ovulation was incduced by an injection of 100 U.S.P. units of A.P.L. (chrionic gonadatropin, Ayerst Laboratories) into a marginal ear vein.

The day of insemination was designated as day 0 of gestation.

The test article, suspended in 1% methylcellulose, was prepared fresh daily and administered by gavage at a constant dosage volumne of 5.0 ml/kg on days 7-19 of gestation.

The following schedule of maternal observations was used:

- mortality	twice daily during entire study
- clinical signs	twice daily prior to and after treatment; once daily on days of treatment
- body weights	recorded on days 0, 7, 13, 20, 24 and 28
- food consumption	daily during gestation

Dose not surviving to scheduled sacrifice were necropsied and fetuses externally examined. On day 28 surviving does were sacrificed by injection of sodium pentobartital. The uterus and ovaries were exposed and the following data recorded:

- number and location of viable fetuses
- number and location of non-viable fetuses
- early and late resorptions
- number of total implantations
- gross necropsy observations of does

All maternal tissues including uteri of non gravid females were preserved in 10% formalin for histopathology as deemed necessary.

All fetuses were removed and the following data recorded:

- body weight
- external malformations/variations
- sex
- internal visceral malformations/variations
- skeletal malformations/variations (according to method of Dawson).

The following statistical analyses were performed.

male/female sex ratios	-	Chi Square and/or Fisher's exact
proportious of litters with malformations	-	Chi Square and/or Fisher's exact
proportions of resorbed and dead fetuses	-	Mann-Whitney U-test
post implantation losses	-	Mann-Whitney U-test
mean numbers of corpora lutea, total implantations, live fetuses, mean fetal body weights	-	Analysis of variance, Bartlett's test for homogeneity of variance, T-test

Results:

1) Maternal Effects:

The data in Table I (reproduced in-tact from the orignial report) summarize the antemortem and necropsy observations of the does. Only 1 animal died (at the HDT) and the antemortem and necropsy the observations were unremarkable. The only apparant difference was that 7 does (38.9%) in the high dose (300 mkd) had a "small amount of stool" vs. 2-3 does (11.1% -16.7%) in the control, low (30 mkd) and mid dose (150 mkd) groups. There were no other dose related effects reported on these parameters. However, the does in the HDT did lose weight (75± 114 g) an gestation days 7 to 19, i.e., during the 13-day treatment interval (see Table II, reproduced in tact from the original report). This loss represented only 2.3% of the mean body weight for this group. On the other hand, does in all other groups continued to gain weight during the treatment period. This weight gain ranged from 97 ± 102 g (2.9%) in the low dose group to 39 ± 140 g (1.2%) in the control group. All does consumed comparable amount of food during the entire experiment (Table 3; reproduced in-tact from the original report)

While these signs of maternal toxicity at the high dose are minimal, the data from the range finding study (Appendix I, reproduced from the original report) indicate that they may be compound related. The maternal body weight in the range finding study decreased 246 g (7.4%) on gestation days 7 to 13 at 500 mkd and maternal mortality was observed at 1000 mkd (see Table 4, reproduced in-tact from the original report). Based on the results of the range finding study, as well as the small decreased body weight loss at 300 mkd, the maternal toxic NOEL = 150 mkd; LEL = 300 mkd.

2) Embryo and Fetal Effects:

These were 16 (control, mid and high dose groups) to 17 (low dose group) gravid females examined at C-section on day 28 of gestation (see Table 5; reproduced in-tact from original report) there were no dose-related effects observed on any of the embryo on fetal parameters reported (Table 5). There was a statistically significant decrease in the number of corpora lutea/doe in the low dose (10.1 $\pm$ 2.25) vs the control (12.3 $\pm$ 2.08) group. In addition there was an apparent increase in group mean pre-implantation loss in the mid-dose (32.1%) vs the control (28.6%) group. All other paramerters were comparable.

It should be noted that the data in Table 5 exclude fetal parameters from doe # 24949 which had excessive (26) numbers of corpora lutea. No further justification was given for excluding this doe. However, these data would not change the interpretation of the results.

The data in Table 6 (reproduced in-tact from the original report) summarize the fetal developmental variations observed. There were no dose-related effects observed at any dose.

Based on all of the above observations, the embroytoxic and fetotoxic NOEL = 300 mkd; LEL not established.

3) Teratogenic Effects:

The data in Table 7 (reproduced from the original report) summarize the incidence of the fetal malformations observed in this study. Some of malformations noted only at the high dose included 2 vertebral aromalies in 2 litters, 1 acephaly in 1 litter, 1 tail anomaly in 1 litter and 1 malformed clavicle in 1 litter. All of these effects were in only 3 fetues in 2 litters. It may be concluded that there were no dose-related effects observed on the incidence of fetal malformations. Therefore, based on these data, metalaxyl was not teratogenic in rabbits at doses up to 300 mkd, even in the presence of slight maternal toxicity.

Discussion:

This study was an adequate test for the embryotoxic fetotoxic and teratogenic effects of metalaxyl in rabbits. The demonstration of clear cut maternal toxicity was, however, at best, marginal. There was only a small decrease in mean maternal body weights (2.3%) on days 7-19, i.e., during the 13 day treatment period, at the high dose (300 mkd). All other group gained weight during treatment. In a preliminary dose range-finding study, however, does lost more body weight (7.4%) at 500 mkd and at 1000 mkd, maternal mortaily was observed. Therefore, the small decrease in maternal body weight observed in the complete study at 300 mkd is probaby compound related and may serve as an indication of maternal toxicity. Higher doses may have been used to produce a more prominent maternal toxic effect.

There were nc embryotoxic, fetotoxic or teratogenic effects observed at any dose in this study. Therefore the NOEL for these parameters was 300 mkd; LEL not established.

MATALAXL

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