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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Evaluation of Studies Concerning the Effect of Dimethoate on Pregnancy of the New Zealand White Rabbit

TO: Mr. William Miller, PM Team #16
Registration Division (TS-767)

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11/7/85

Tox. Chem. File No. 358
Acc. No. 257094

Reviews of a study entitled "Effect of Dimethoate on Pregnancy of the New Zealand White Rabbit" and an accompanying dose range finding study entitled "Preliminary Investigation of Effects of Dimethoate on the New Zealand White Rabbit" are attached.

Conclusions and recommendations regarding the review of the final teratology study are found in the "Conclusions and Recommendations" section at the end of the report. The registrant has been requested to submit some additional information. Please note that two memos dated May 6, 1985 from Toxicology Branch Mission Support staff are also attached. The first memo is entitled "Transmissal of Technical Report Critiquing the Statistical Analysis of the Dimethoate Rabbit Teratology Study", by Mr. Bertram Litt, Team Leader, Mission Support Staff, and the second is entitled "Dimethoate, New Zealand White Rabbit Teratology Study: Statistical Comments" by Dr. D. Ghosh.

PRELIMINARY INVESTIGATION OF EFFECTS OF DIMETHOATE ON THE NEW ZEALAND WHITE RABBIT

HRC Report No. DTF 2/84246, April 19, 1984; Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England. EPA Reg. No. 241-75, Accession No. 257094. Pregnant preliminary study conducted from 18 January to 18 February 1983. Supplementary non-pregnant preliminary study conducted from 18 April to 11 May 1983 for Dimethoate Task Force participants.

STUDY SUMMARIES

This prelimanry investigation, conducted so that appropriate doses of Dimethoate might be selected for a subsequent study, consisted of two separate parts, a "pregnancy preliminary study" (PPS) and a "supplementary non-pregnancy study" (SNPS).

PPS. In this study, four groups of successfully mated New Zealand White rabbit females were dosed once daily by gastric intubation with either 0, 3, 10, or 30 mg/kg Dimethoate technical (97.3% purity by weight, Batch No. 611A, manufactured by I.Pi.Ci.) in a 1% methylcellulose vehicle. Animals were treated from day 7 of pregnancy through day 19 of pregnancy and were sacrificed on day 29 of pregnancy.

Five out of six mated females became pregnant in the control, low, and mid dose Dimethoate groups respectively and six out of six mated females became pregnant in the high dose group. All of the pregnant females survived the study and had viable young at the study's end. Apparently, no fetuses were aborted during the study and no fetuses were removed dead from the uterus at autopsy.

High dose group dams gained about 25% less weight during the dosing period than did controls and this may have been treatment-related. Otherwise, there were no obvious effects of Dimethoate treatment on maternal parameters.

Based on the presentation of the data by the study authors, there was no obvious effect of the test material on fetal parameters or on the incidence or pattern of fetal abnormalities (however, the only fetal abnormalities reported were malformations).

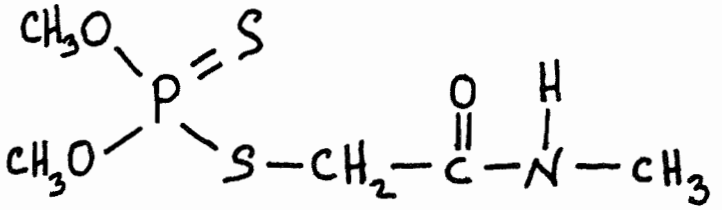
SNPS. In this study, two unmated does/group were dosed once daily by gastric intubation with either 50 or 75 mg/kg Dimethoate (as described above under PPS) for 13 consecutive days where possible. Overt reaction to treatment was observed in both groups (i.e. muscle tremors/unsteady gait, prostration/lethargy, salivation, weight loss). Both does in the 75 mg/kg dose group and one doe in the 50 mg/kg dose group had to be sacrificed prematurely due to the severity of reaction to the test material. At autopsy, both does in the 75 mg/kg group were found to have gastro-intestinal tracts with reduced contents.

EFFECT OF DIMETHOATE ON PREGNANCY OF THE NEW ZEALAND WHITE RABBIT.

HRC Report No. DTF 4/84247, April 19, 1984, Huntingdon Research Centre plc, Huntingdon, Cambridgeshire, England. EPA Reg. No. 241-75, Accession No. 257094. Study conducted from July 12, 1983 to August 25, 1983 for Dimethoate Task Force participants: BASF Aktiengesellschaft-Ludwigshafen (West Germany), Celamerck GmbH Co. Kg - Ingelheim am Rhein (West Germany), A/S Cheminova-Lemvig (Denmark), Farmoplant SpA - Milan (Italy), I.PI.CI. SpA - Novate Milanese (Italy), and American Cyanamid Co. - Princeton, New Jersey (USA).

MATERIALS

Test Material: The test material used in this study was described as Dimethoate technical, a crystalline, grayish-white solid, 97.3% pure by weight, from Batch No. 611A, manufactured by I.Pi.Ci. The stability of the test material was reported to be acceptable for the duration of the study.



Structure of Dimethoate [chemical name: O,O - dimethyl - S - (N - methyl - carbamoylmethyl) phosphorodithioate], an organophosphate insecticide.

Test Animals: Sexually mature, non-pregnant, New Zealand White rabbits twelve to twenty weeks of age were obtained from several sources: Cheshire Rabbit Farms, Cheshire, Ranch Rabbits, Sussex, and Buxted Rabbit Company Limited, Sussex. No specific details regarding the male rabbits used in the study were provided in the study report.

Does were uniquely numbered with metal ear tags and allowed an acclimitization period of at least ten days prior to mating. Mated females were individually housed in metal cages and given free access to SDS Rabbit Diet SQC and tap water. For purposes of quality control, it was reported that food and water were routinely analyzed for contents and contaminants. Relative humidity and temperature in the animal quarters were generally held at levels of 19° C + 3° C and 55% + 15% respectively during the study. Both natural and artificial lighting were used to maintain a cycle of approximately 14 hours light and 10 hours dark.

PROCEDURES

Mating: Does weighing between 2.9 and 4.1 kg were mated with males of proven fertility. To promote ovulation, females were injected intraveneously with 25 i.u. of Chorulon® leutinizing hormone following successful coitus. Animals inseminated on a given day were assigned to treatment groups. In the assignment process, attempts were made to equally distribute among the groups those does which had been mated to the same buck and those does which had been supplied by the same vendor.

Dosing: Each one of four treatment groups consisted of sixteen (16) mated females. Does were dosed once daily by gastric intubation with either 10, 20, or 40 mg/kg body weight of the test substance which had been prepared as a suspension in a 1% solution of methyl cellulose. Animals in the control group were treated with 1% methyl cellulose (vehicle) alone.

Treatment preparations were administered at dose volumes of 5 ml/kg/day. Dose volumes were calculated based on individual animal body weights as determined on days 7, 9, 11, and 15 of pregnancy (the day of mating was considered to be day 0 of pregnancy). Dosing commenced on day 7 of pregnancy and continued through day 19 of pregnancy inclusive.

Assessment of Maternal Health: No animals were reported to have been unhealthy at the commencement of the study, afterwhich, all does were monitored daily for changes in health and behavior. On the 29th day of pregnancy, animals still alive were terminated, and examined post-mortem. The post-mortem examination included an examination for congenital abnormalities and macroscopic pathological changes in maternal organs as well as a detailed examination of the ovaries and uteri of the animals.

Similar post-mortem examinations were performed on does which died during the study or which were terminated for humane reasons while the study was in progress.

Examination of Fetuses: All fetuses were first examined for viability and external defects. They were then weighed, euthanized if necessary, dissected, and examined for visceral abnormalities. When it was considered appropriate, other procedures, such as micro-dissection and histopathological techniques, were used to aid in the confirmation and characterzation of suspected abnormalities.

Next, fetuses were skinned, eviscerated, and fixed. Visual inspections of fetal brains for abnormalities such as hydrocephaly and hydranencephaly were conducted after heads had been sliced through the line of the fronto-parietal suture. Lastly, fetal carcasses were stained and examined for skeletal defects.

Structural deviations were grouped into three categories described by the study authors as follows:

Malformations - rare and/or probably lethal defects;

Anomalies - minor differences from 'normal' that are detected relatively frequently either at initial examination or at skeletal examination;

Variants - alternative structures (either permanent or transient) occuring regularly in the control population.

Parameters Reported: Maternal body weights were measured on days 1, 7, 9, 11, 15, 20, 24, and 29 of gestation. Based on these measurements, maternal body weight changes for various time intervals were calculated. Food consumption was determined for the following time intervals: gestation days 1 to 6, 7 to 8, 9 to 10, 11 to 14, 15 to 19, 20 to 23, and 24 to 28. Clinical signs and behavioral changes were noted as they were observed and post-mortem findings were reported.

For each rabbit in the treatment group, the number of corpora lutea, the number of implantations, the number of early and late embryonic deaths, and the number of aborted fetuses were determined. An early embryonic death was characterized by the visible presence of placental tissue only while a late embryonic death was characterized by the visible presence of both placental and embryonic tissue. If only an implantation site scar was visible at termination of the dam, the embryonic death was classified as an abortion. The number, sex, viability, and abnormalities of fetuses in each litter as well as litter weights were also recorded.

Calculations: Pregnancy rates for each treatment group were calculated by the study authors and expressed as a percentage as follows:

$$\frac{\text{number of pregnant females surviving the study}}{\text{number of pregnant and non-pregnant survivors*}} \times 100$$

Group means of maternal food consumption, body weight, and body weight changes were calculated as simple averages.** Group means of the number of fetuses/doe, number of embryonic deaths/doe, number of implantations/doe, number of corpora lutea/doe, and litter weights (each litter weight was calculated by summing the individual weights of the fetuses composing it) were similarly determined.

However, the study authors calculated fetal weight group means by first dividing the total weight of each litter in a group by the corresponding number of fetuses to get a mean fetal weight for each litter. Then, the the mean fetal weights determined for each litter in a particular treatment group were averaged to get the group mean. The study authors calculated the group mean incidences of pre- and post-implantation losses, the numbers of fetuses of a particular sex, and fetal abnormalities by first calculating the percent incidence of a parameter in each litter of a treatment group and then averaging the percents.

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*Excluded from the calculation were animals with uni- or bi-lateral interrupted uteri (1 non-pregnant female in the control group and 1 pregnant female in the 40 mg/kg Dimethoate-treated group).

** Data obtained from n individual pregnant animals for a given parameter were summed and the sum then divided by n.

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All group means were calculated based on data obtained from pregnant females which survived the study. However, data obtained from certain pregnant survivors were omitted from these calculations by the study authors (see Table I, this report) for reasons which the authors stated did not involve the animals' exposure to the test material. The following formulae were used to calculate the per cent pre- and post-implantation losses:

$$\% \text{ pre-implantation loss} = \frac{\# \text{ corpora lutea} - \# \text{ implantations}}{\# \text{ corpora lutea}} \times 100$$

$$\% \text{ post-implantation loss} = \frac{\# \text{ implantations} - \# \text{ live young}}{\# \text{ implantations}} \times 100$$

Statistical Methods: It was reported that litter data (pregnancy rate, # live young, embryonic deaths, # implants, # corpora lutea, % pre-implantation and post-implantation losses, litter weights, fetal weights, and fetal sex ratios) as well as incidences of skeletal anomalies and skeletal variants were statistically evaluated by means of the Jonckheere and Kruskal-Wallis tests for non-parametric data. The litter was used as the basic sample unit. There was no indication given that maternal body weight and food consumption data and fetal malformations and external/visceral anomalies (determined as a result of gross autopsy of fetuses) were analyzed statistically.

RESULTS

Pregnancy Rates: Pregnancy rates in the control and 10, 20, and 40 mg/kg Dimethoate-treated groups were 93.3, 100, 100, and 84.6% respectively and were considered to be acceptable.

Maternal Body Weight:

10 mg/kg Dimethoate group. When maternal body weight change group means for gestation days 7-20 (an interval just encompassing the dosing period) were determined and compared, the group mean for those animals receiving 10 mg/kg Dimethoate was found to be 154% of the control value. Over the subsequent post-dosing time interval (gestation days 20-29), the change in the maternal body weight group mean for the animals in this low dose group remained steady at about 145% of the control value. Thus, the somewhat greater gain in maternal body weights noted for the 10 mg/kg treatment group relative to the control group appears to have been due to biological variation in sample groups rather than to the administration of the test material. The relative increase noted could not be obviously accounted for by the difference in mean litter weights between the control and low dose groups.

20 and 40 mg/kg Dimethoate groups. During the dosing period, the body weight change group means for those animals receiving 20 and 40 mg/kg Dimethoate were determined to be only about 67% and 22% respectively of the control value. These smaller increases in body weight gain in the mid- and top-dose group relative to controls are judged by Toxicology Branch (TB) to be related to the administration of the test material and appear to be indications of maternal toxicity. The decreases noted were not obviously accounted for by differences between the respective mean

litter weights of the mid- and high-dose groups and the control group.

Food Consumption: Estimation of food consumption was hampered by the excessive wastage of food by the test animals, particularly those in the high dose group. The study authors indicated that mean food consumption was reduced in the high dose group between days 15 to 23 of pregnancy.

Maternal Health:

Excluded animals. Although 16 animals were assigned to each treatment group, data from some of these animals were not considered when group means were calculated. Animals were excluded from various groups by the study authors for reasons listed in Table 1 below. The final number of animals/group from which data were obtained and used to calculate group means is also given:

Table I. Animals Excluded From Group Mean Value Calculations*

Treatment	# Animals Excluded	Autopsy Findings	Ammended # Animals/Group
Control (Vehicle)	1	Killed day 15 - suspected pulmonary disorder	14
	1	Not pregnant - bilateral interrupted uterus	
Dimethoate (mg/kg/day)			
10	1	Suspected uterine infection	13
	2	Suspected pulmonary disorder	
20	0		16
40	1	Unilateral interrupted uterus	11
	1	Killed Day 26 - Suspected pulmonary and uterine infection	
	1	Killed Day 16 - Apparent infection at ear tag site	
	2	Not pregnant	

* Animals other than those culled and replaced early in treatment period. This table was prepared from data submitted by the study authors.

Post-mortem findings. There was no evidence presented that the post-mortem findings reported for animals excluded from group mean calculations were associated with the administration of the test material. As presented in the study report, there was nothing remarkable about the post-mortem findings reported for dams included in group mean calculations.

Clinical signs. Dose- and apparently treatment-unrelated fur loss was noted in at most four animals per treatment group. The extent of fur loss was not mentioned. A number of dams were observed to have "cold ears after dosing on five or more occasions". The data presented provided evidence for a dose-response relationship between test material administration and cold ears in that 0% of the animals in the control group were observed to have cold ears on five or more occasions while approximately 15%, 19%, and 55% of the animals in the 10, 20, and 40 mg/kg Dimethoate-treatment groups respectively had at least five occurances of cold ears post-dosing. No mention was made of the method used to detect or measure the intensity of each "cold ear" episode nor were the onset time and duration of each incidence reported.

"Muscle tremors/unsteady gait post-dosing during Days 14 to 19" noted in three of the high-dose Dimethoate group does was attributed by TB to the administration of the test material. Five high-dose group animals were observed to have "abnormal feces on five or more occasions"*. Since the number of animals with abnormal feces in the high-dose group was greater than in the other treatment groups, it is the opinion of TB that the increase noted could be associated with Dimethoate treatment. (Muscle tremors/unsteady gait were not observed in any other test group and five or more incidences of abnormal feces were seen in one animal in both the control and 10 mg/kg group and in no animals in the 20 mg/kg treatment group). Four of the dams gavaged with 40 mg/kg Dimethoate were observed to have at least two of the three clinical signs which appear to be associated with ingestion of test material in that dose group and three of the dams were observed to have all three of these clinical signs (i.e. abnormal feces, cold ears, muscle tremors/unsteady gait).

Other Maternal Parameters: Pre- and post-implantation losses in all Dimethoate-treated groups were less than those of the respective controls.

On day 26 of gestation, one dam in the 40 mg/kg Dimethoate-treatment group aborted her entire litter. However, the dam was later sacrificed on that same day due to a pulmonary disorder not associated with administration of the test chemical. Data from this dam were excluded from group mean calculations by the study authors.

Early and late embryonic deaths were reportedly found in all treatment groups. When the total number of early intra-uterine deaths per number of litters in each treatment group were compared, a slight increase of about 13% was noted in the 40 mg/kg Dimethoate group compared to the control value. The study authors indicated that the increase was not statistically significant. In addition, autopsy findings for one of the dams in the high dose group which had four of the eight reported early intrauterine deaths, was found at autopsy to have an additional liver lobe which may have stressed the developing litter in utero. The percent pre-implantation loss (46.7%) for this particular animal was much higher than the group mean of 12.8%. The total number of late intra-uterine deaths per number of litters in each Dimethoate treatment group were all less than that of the control.

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* Definition of "abnormal" not provided by study authors.

Fetal Parameters: No dead fetuses were reported to be found in utero in any study group on Day 29 of gestation. While the average litter size of the animals given 20 mg/kg Dimethoate (8.9 fetuses) was similar to that of the control group (9.1 fetuses), the average litter sizes of the animals treated with 10 or 40 mg/kg Dimethoate were somewhat larger with 9.9 fetuses each.

Litter weight group means were calculated but the usefulness of these means for intergroup comparisons was diminished by the group-to-group variation in the ranges of individual litter weight values from which the group means were calculated.

Compared to the control group mean of 45.0 g, fetal weight group means were lower in the 10 and 20 mg/kg Dimethoate treatment groups with values of 43.9 g and 42.2 g respectively, although the decreases were not found to be statistically significant by the statistical methods used. However, the comparative decrease in the fetal weight group mean (mean = 40.9 g) observed in the 40 mg/kg (highest dose tested) Dimethoate treatment group was statistically significant by methods of analysis used by the study authors. Having reviewed the statistical methods used by the study authors to analyze these data, the TB statistical team felt a statistical reevaluation of fetal body weight data should be performed (see "Discussion" section - this report). Therefore, no opinion on the biological significance of the fetal body weight data will be presented at this point.

Fetal crown/rump length measurements (not provided) would have been useful in evaluating the effects of test chemical administration on fetal size.

Dimethoate treatment had no apparent effect on the sex ratio of male to female fetuses.

Fetal Abnormalities: When controls were compared with Dimethoate-treated groups, no statistically significant differences were reported by the study authors in the incidences of fetal malformations, skeletal anomalies, or skeletal variations when the litter was used as the basic sample unit. However, this reviewer felt it necessary to prepare an independent tabulation of the data (see Tables II and III below) since it was possible to analyze the data in a more precise fashion than in the manner in which it was presented in the study report.

It can be seen from Tables II and III that occurances of at least one fetal malformation or anomaly per total fetuses per group or per total number of litters per group fell below control occurances at all dose levels of Dimethoate tested. When fetal anomalies were separated into external/visceral and skeletal categories (not shown in Tables II or III), there was some increase above control values in the number of fetuses per total fetuses per group and the number of litters per total litters per group with at least one external/visceral anomaly in the 10 and 20 mg/kg Dimethoate treatment groups. However, these increases did not appear to be associated with the administration of the test material since the occurances of external/visceral abnormalities in the 40 mg/kg Dimethoate dose group were equal to or less those of the controls.

Table II. Fetal Malformations, Anomalies, or Skeletal Variations Per Total Fetuses Examined in a Treatment Group[a]

	Dimethoate (mg/kg/day)			
	0	10	20	40
(1) # fetuses with at least one malformation[b]	4/128 (3)[c]	1/129 (0.8)	3/142 (2)	2/109 (2)
(2) # fetuses with at least one anomaly	22/124 (18)	17/128 (13)	19/139 (14)	11/107 (10)
(3) # fetuses with 13 ribs[d]	41/124 (33)	41/128 (32)	54/139 (39)	41/107 (38)
(4) # fetuses with variant sternebra(e)[d]	40/124 (32)	25/128 (20)	28/139 (20)	18/107 (17)

a Based on data submitted by petitioner
b Fetuses with at least one malformation were excluded by study authors from totals in anomaly and variant categories
c Ratio expressed as a percent
d Skeletal variants

Table III. Fetal Malformations, Anomalies, or Skeletal Variations Per Total Litters in a Treatment Group[a]

	Dimethoate (mg/kg/day)			
	0	10	20	40
(1) # litters with at least one malformation[b]	4/14 (29)[c]	1/13 (8)	3/16 (19)	1/11 (9)
(2) # litters with at least one anomaly	11/14 (79)	9/13 (69)	10/16 (63)	7/11 (64)
(3) # litters with at least one 13-ribbed fetus[d]	10/14 (71)	10/13 (77)	8/16 (50)	10/11 (91)
(4) # litters with at least one fetus with variant sternebra(e)[d]	9/14 (64)	8/13 (62)	8/16 (50)	9/11 (82)

a Based on data submitted by petitioner
b Fetuses with at least one malformation were excluded from totals in anomaly and variant categories
c Ratio expressed as a percent
d Skeletal variants

When number of non-lethal skeletal variations (13-ribs, variant sternebra(e)) in each test group were compared (see Tables II and III), deviations from control values noteworthy to TB occurred in the 40 mg/kg Dimethoate-treatment group. When comparisons were made based on the number of skeletal variations per total litters per treatment group, the number of litters in the high dose group containing at least one 13-ribbed fetus or at least one fetus with variant sternebra(e) was increased by about 20% above control values (Table III). The increases noted could have been related to test material administration since high dose group fetuses, during their development in utero, may have been subjected to environmental stress associated with the apparent effects of test material administration on high doses group dams (see "Maternal Health - Clinical signs" and "Maternal Body Weight - 20 and 40 mg/kg Dimethoate groups", this report).

There was no discernable pattern in the specific types of either fetal malformations or anomalies reported for any treatment group. The following malformations were reported: Four control fetuses each had one of the following malformations respectively - scoliosis, spina bifida occulta/un-ossified parietal, absent interparietal*, and distortion of the sternum with fused sternebrae. One fetus in the 10 mg/kg Dimethoate group had additional liver lobes** and an umbilical hernia. In the 20 mg/kg group, one fetus had an absent interparietal, one had a number of skeletal irregularities, and one had malrotated limbs and forelimb flexure. In the high dose Diemthoate group, one fetus had a lumbar sacral meningocele and one was found with scoliosis. The most common anomalies found were sutural bones* (4, 3, 6, 5, incidences in the control and 10, 20, and 40 mg/kg Dimethoate groups respectively), connected sternabrae at various locations, extra sternabrae centers, and extra liver lobes** (0, 1, 2, 2 incidences in the control and 10, 20, and 40 mg/kg Dimethoate groups respectively).

DISCUSSION

Effects of Treatment - Maternal:

1. High-Dose Group. Only dams in the high dose group were observed to have muscle tremor/unsteady gait. Dams in this group gained on the average only 22% of the control group mean weight over the dosing period. These findings were considered by TB to be toxicological effects of the test material. Reduced food intake in this group was also noted during the dosing period. In addition, 5/13 animals in this group had abnormal feces on five or more occasions compared to only at most one animal per group in the other test groups. This increase in the high dose group appeared to be treatment related (details regarding the actual number of observations and severity of the occurances were not reported for any group). Fifty-five percent of the high dose group animals had cold ears post-dosing on five or more occasions. No control animals had cold ears on five or more occasions (however, it was not reported if any control animals(s) had less than five occurances) while within the low and mid dose groups, 15% and 19% respectively of the animals manifested this sign which was apparently

* Vague terminology used to describe abnormality.
** May have genetic basis.

treatment related. Unfortunately, the study authors provided no details about the duration, severity or actual total numbers of these occurances. While the circulatory system hemodynamics of an animal manifesting cold ears appears to have been altered in some way as a result of dosing, the pharmacological and/or toxicological significance of the finding is unclear.

The study authors acknowledged the effects of treatment mentioned above but did not clearly indicate whether the effects were toxicologically significant.

2. Mid-Dose Group. The study authors stated that in this group they found "no overt signs of reaction to treatment and only a slight reduction in mean weight gain". As a group, mid-dose dams gained 33% less weight over the dosing period than did controls. Because of food wastage by animals in this group it was difficult to quantify their food intake, however, food consumption was as low as 78% of controls during the dosing period. It is this reviewer's opinion that the relatively lower weight gains in this group suggests toxicity due to the test material. Cold ears (a clinical sign discussed in (1) above) were observed in 19% of the animals in this group.

3. Low-Dose Group. Other than "cold ears" (see discussion in (1) above) in 15% of the animals in this group, there was no other indication of test material effects or toxicity. In the absence of other signs, "cold ears" did not appear to be an adverse effect in dams in this group.

Effects of Treatment on Fetal Parameters: The study authors reported that there were no obvious adverse effects of treatment on incidences of malformations, visceral and skeletal anomalies or skeletal variants. However, TB made independent tabulations (see Tables II and III) of these data because (1) the study authors evaluated these parameters on the basis of the number of fetuses per group and it was desirable to have an evaluation of the data on the basis of the litter as well; and (2) the study authors calculated the group mean incidences of certain parameters in this study (including certain fetal parameters) in a manner that this reviewer thought somewhat imprecise (i.e. the study authors determined group mean incidences of fetal abnormalities by first calculating the percent incidence of an abnormality in each litter of a group and then averaging the individual litter values).

TB found that there was no discernable pattern in the specific types of either fetal malformations or anomalies reported for any treatment group. However, vague terminology was used to describe some of abnormalities (i.e. absent interparietal and sutural bones) and clearer descriptions of these should be provided to TB. In addition, increases of about 20% in non-lethal skeletal variants, as determined by the number of litters with at least one 13-ribbed fetus and number of litters with at least one fetus with variant sternebra(e), were noted in the high-dose group. The increases may have been related to test material administration since high dose group group fetuses, during their development in utero, may have been subjected to environmental stress associated with the apparent effects of test material administration on high dose group dams.

Compared to controls, decreases in mean fetal weight were noted with increases in the dose of Dimethoate. The study authors found only the decrease in the high-dose group to be statistically significant but, because of the way mean fetal weights were determined by the study authors (see "Calculations" - this report) and the potential that some effects (direct or indirect) of the test chemical on fetal weight might be masked as a result, this reviewer requested the TB Statistical team to review the statistical methods used in evaluating this parameter. The statistical team was of the opinion that certain data should be reevaluated (see attached memo by Dr. D. Ghosh and accompanying cover letter by Mr. Bertram Litt, Team Leader, Mission Support Staff, dated May 6, 1985). At this point, this reviewer is mainly concerned with the reevaluation of the litter weight and group mean fetal weight data, since other parameters have been examined independently.

As a further measure of the possible effects of the test material on fetal weight/size, this reviewer is also requesting that crown/rump length data for each fetus be submitted.

CONCLUSIONS AND RECOMMENDATIONS

Before TB can conclude its evaluation of this study, the registrant must submit the following additional information. The rationale for these requests appears in the "Discussion" section of this report:

1. submit statistical reevaluation of litter and fetal body weight data as indicated in accompanying memo and cover letter from TB statistical team;

2. submit crown/rump length data for each fetus and provide proper statistical evaluation of this data;

3. provide clear definitions of the fetal abnormalities described as "absent interparietal" and "sutural bones" in the study report.

Based on the data evaluated thus far, the No Observable Effect Level (NOEL) and Lowest Observable Effect Level (LEL) for maternal toxicty and teratogenicity would appear to be as follows:

Maternal Toxicity	LEL	20 mg/kg/day
	NOEL	10 mg/kg/day
Teratogenicity	NOEL	40 mg/kg/day (highest dose tested)

However, these values are subject to change pending the study sponsor's response to the points listed above. Comment on the fetal toxicity/embryotoxicity NOEL and LEL will not be made until the study sponsor addresses the points listed above.

Core Classification: Supplementary. However, depending on the study sponsor's response to the points listed in the "Comments and Recommendations" section of this report, Toxicology Branch will consider upgrading the classification of this study.