Chlorothalonil
FILE

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

CASWELL FILE

April 12, 1990

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of a Teratology Study in Rabbits with T-117-12 (Bio/dynamics Inc. Project # 87-3196)

FROM: Laurence D. Chitlik, D.A.B.T.
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Lois Rossi, Chief
Reregistration Branch
SRRD

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

Attached is a DER for the rabbit teratology study that was submitted for review. In addition, the rangefinding study was requested from the registrant and a review of this study is also included.

It is tentatively concluded that T-117-12 is a developmental toxicant and no NOAEL has been established (NOAEL < 5mg/kg/day) based upon available developmental toxicity data in both the rangefinding and definitive rabbit studies. This conclusion is based largely upon increased incidences of anomalies and possibly reduced fetal weights at all dose levels. In addition, limited rangefinding data suggested significant developmental effects at the 30 mg/kg/day dose level (statistically significant reduction in gravid uterine weights).

It also appears that an MTD was not reached in this study making assessment of a dose response relationship more difficult to interpret. Data presented in the rangefinding study did not support a reduction of dose levels from 30 to 20 mg/kg/day but actually supported the use of higher dose levels in a definitive study. Possibly the decision to lower the dose levels in the main study was erroneously based upon the incidence of premature delivery noted in the 30 mg/kg/day dose level which when compared to an equivalent incidence in the control of the definitive study, is obviously not compound related. In addition, as more data are required to complete this assessment, a determination as to core classification is not appropriate at this time.

Once the following data/information are provided by the registrant and reviewed, the above conclusion may be reassessed:

1. A diagnosis by the pathologist is requested relative to the discolored lungs noted in this study at a high frequency in all dose levels and controls but at higher incidences in Groups III and IV. The pathologist concluded that "these various discolorations of the lungs were not considered to be of toxicological significance with respect to the test article." Considering the way this opinion is caveated, are these findings associated with a disease process? Which? Are there any disease problems in rabbits at this testing facility?

2. Historical data for variations as presented on page 298 of the test report are useless in the evaluation of developmental toxicity. Incidences of individual variations need to be submitted. In addition, the investigator's contentions relative to the existence of maternal toxicity (reduced weight gain and body weight data during gestation) and whether these potential effects are biologically significant at 30 and 20 mg/kg/day, need to be supported by historical data on body weight gains in rabbits. It is also noted that the vehicle used in this study is methylcellulose and this may have potentially reduced the absorption of the test material. Metabolism/kinetic data would be useful to confirm adequacy of dose levels.

3. Since the historical data indicate that fetuses from pilot studies are always evaluated at least for external malformations (see table pg.287), it is unclear why this was not done (or was it?) in the rangefinding study for all test animals. This question is especially important considering the statistically significant effects upon gravid uterine weight observed at 30 mg/kg/day. These data must be provided if these assessments were actually performed.

4. Most, but not all, of the variation data in the report are listed only as present or not present. That is, the investigators often did not identify the incidence of delayed ossification for many anomalies (e.g., phalanges), but only listed them if the structure was absent. Considering the types of effects observed in this study, delays in ossification are especially important and a re-examination of the skeletons is necessary. This re-examination must include some level of grading for reductions in ossification.

5. In the rangefinding study, clarification is required relative to the incidence of several clinical observations including reduced feces or soft stool which the authors state were affected at the 30 and 75 mg/kg/day dose levels. However, Appendix G-4 only shows one incidence of soft stool in one low dose animal. This apparent discrepancy needs to be resolved... as the text and the data appear to be unrelated.

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If issues associated with this study cannot be resolved, a new study will be required in which an MTD dose level must be tested and a NOAEL identified. In addition, it is important to have the health status of the animals more clearly defined since the added stress of disease may potentially confound interpretation of study results.

Testing in the rat has also been performed but after examination of the DER on the rat teratology study (R.B.Jaeger and D.L. Ritter, 5/3/84, on study # 517-STX-0011-003) this one paragraph review (attached) does not provide an adequate assessment. Even considering the limits of the review, it is pointed out that a significant increase in the number of early resorptions in the high dose group as well as post implantation losses were noted. This clearly conflicts with the DER conclusion which states, "there was no evidence of teratogenicity at any level tested." This study needs to be re-evaluated.

DATA EVALUATION RECORD

STUDY TYPE: Rabbit Developmental Toxicity

CHEMICAL: T-117-12 (assumed by laboratory to be 100% pure)
Identified as a light gray powder

STUDY IDENTIFICATION:

TITLE: "A Teratology Study in Rabbits with T-117-12"

LABORATORY: Bio/dynamics Inc.
East Millstone, New Jersey

REPORT DATE: July 28, 1988

STUDY DIRECTOR: Raymond Schroeder

MRID NUMBER: 41250503

EPA I.D.: 50534-7

CONCLUSIONS/RECOMMENDATIONS:

It is tentatively concluded that T-117-12 is a developmental toxicant and no NOAEL has been established (NOAEL < 5mg/kg/day) based upon available developmental toxicity data in both the rangefinding and definitive rabbit studies. This conclusion is based largely upon increased incidences of non-ossified phalanges and other anomalies and possibly reduced fetal weights.

In addition, it appears that an MTD was not reached in this study making assessment of dose response relationships of individual findings more difficult. In addition, this may have limited the sensitivity of the assay to detect other manifestations of developmental toxicity.

Due to the request for additional data as listed on the cover memo, a core classification of this study is not appropriate at this time.

METHODS:

A copy of the methods section of this developmental toxicity study is appended to this review.

The test material was suspended in a 0.5% (w/v) aqueous methylcellulose vehicle and administered by gastric intubation on days 7 to 19 of gestation to 20 animals per group. Dose levels used were 0, 5, 10 and 20 mg/kg/day. Dose levels were reported to be derived from a pilot study (Bio/dynamics Project No. 87-3195; Ricerca Study Reference No. 87-0059) but this report was not originally provided for review. It was requested in a telephone conversaton with Mr. Jerry Lucietta of Fermenta ASC and a copy was sent on 3/20/90. A review of this study is also attached.

Protocol deviations listed on pgs. 15 and 16 of the report due not appear to have compromised the utility of the study.

RESULTS:

Maternal Toxicity

In the controls, 2 animals delivered prematurely; in the low dose, one delivered prematurely; in the mid-dose group one animal died (likely due to intubation error) and 2 animals delivered prematurely; and in the high dose, 1 animal died and another delivered prematurely. It also appears that the high dose animal that died (#4514) may have died due to dosing error. This animal was found to have all lung lobes mottled red with scattered red foci and an abnormal trachea (dark red with thin clear fluid present.

Pregnancy rates were unaffected and were 95 to 100% in all groups.

Mean body weights for all recorded intervals at all dose levels were reported as unaffected by treatment.

The corrected body weight data did not demonstrate any significant effects and were comparable between control and treated groups.

The study authors reported a slight mean weight loss during days 7-19 of treatment and this was noted as statistically significant. The study authors also claimed that the incidence of females losing weight was increased. These incidences were respectively 2/20, 2/20, 4/20 and 9/19. However, it is this reviewer's opinion that the effects noted by the authors upon body weight during the dosing period are not biologically relevant and not compound related as rabbits are known to have large variations in body weight gain. For the author's claims that these findings represent maternal toxicity to receive any credibility, historical data providing adequate comparisons on body weight and body

weight gain in rabbits in other studies at this testing facility would need to be considered in this assessment.

This reviewer notes that the body weight change between the control and the high dose group constitutes .144 kg for the entire period from days 7 to 19 of dosing. Considering that the animals weigh approximately 4.1 kg at termination in all dose groups, the difference noted is extremely small and well within the normal variation of body weight gain that is commonly seen in such studies. In fact, it is this reviewers opinion that the consistency of data in the high dose as compared to controls is excellent, considering the variability in rabbit data. In addition, no rebound effect is apparent during the post dosing period (days 19-30) since the high dose and control values are nearly identical (94 vs 111). Body weight gains in this study are depicted in the following table:

Maternal Body Weight Change (in Grams) During Gestation

	Gestation days					
	0-7	7-10	10-13	13-16	16-19	19-30
Control	106	6	24	86	21	94
5 mg/kg	107	8	3	78	22	38
10 mg/kg	89	-9	22	53	6	75
20 mg/kg	101	-26	8	21	-9	111

As is to be expected in rabbit studies, the standard deviations for this type of data were quite large as noted in table D-1 of the appendix. Also note tables D-2 to D-5 which demonstrate the tremendous variation in body weight gain for animals in each dose group. For example, control animals # 1508 lost .497 kg and #1504 lost .301 kg in one three day period during the post dosing period. For all 3 day periods measured in the high dose level during the dosing period, only in one case (for animal #4504) did the weight loss exceed .3 kg and during the post-dosing period, only 2 animals (#'s 4507 and 4512) slightly exceeded a .3 kg loss.

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Food Consumption:

Appendix F tables of individual maternal food consumption and Table F-2 which presents mean values, show a slight and statistically significant effect only at one interval (day 7-8) of gestation. At other times during the dosing period, high dose values were also reduced but due to extensive spillage and high standard deviations evident in the data, no other interval reached statistical significance. Hence, it is difficult to use these data to support or refute the contention that maternal toxicity occurred at the high dose level.

Clinical Observation Data:

Examination of in-life observation data presented in Appendix I did not reveal the presence of any compound related effects at any dose level. The most prevalent finding was the incidence of AG staining which occurred without a dose response and as frequently in controls as dose groups. The only other finding that occurred with any frequency was the incidence of allopecia which occurred at a higher incidence in controls than in treated animals.

Abortions and Premature Deliveries:

No aborted pregnancies were reported.

No increase in premature deliveries was evident from the available data. Premature deliveries occurred in two controls, one low dose female, two mid-dose females and one high-dose animal. (These data also suggest that the two incidences observed in the 30 mg/kg/day dose level of the range-finding study were not associated with treatment, contrary to what was concluded by the investigators.)

Gross Necropsy Data:

As per the pathology report, numerous animals in all groups had discolored lungs (primarily red/tan/brown foci/areas) but this finding was more prevalent in groups 3 and 4. The incidences were 12, 12, 14, and 16 respectively for the control, low, mid and high (20 mg/kg/day) dose levels. The pathologist concluded that the findings were not associated with administration of the test material, however, a diagnosis was not provided. This information should be requested from the registrant as it may impact upon meaningful interpretation of data from this study. Since the prevalence of the finding was noted to increase slightly in the mid and high dose levels, and since the occurrence is not apparently associated with the test material, it is likely that the lung discolorations are associated with disease. Therefore, other study findings may also be related to a disease process

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and not necessarily to the effects of the test material.

Cesearan Section Findings:

Data in Appendix G demonstrated that numbers of corpora lutea and implantation sites were comparable in all groups. There was no dose response relationship evident in the mean pre-implantation loss data since there was an increase at the mid- but not the high dose level.

Data in all test groups and controls were comparable for mean live fetuses per litter, mean resorptions per litter, and resorptions per number of implants. There was a slight and non-significant increase in the number of litters with resorptions in the high dose and a nonstatistically significant but possibly biologically meaningful decrease in fetal weights in all the dose groups as compared with controls. The following tables depict these findings, however the copy of the table available for review was not completely readable:

	Dose levels (mg/kg/day)			
	0	5	10	20
Number of litters with viable fetuses	18	19	17	17
Resorptions	11	10	6	11
Mean	0.6	0.5	0.4	0.6
per # implants	0.054	0.049	0.031	0.067
Mean fetal wt. of viable fetuses	45.7?	43.38	43.32	42.91
males	46.9?	43.19	43.34	43.89
females	44.93	43.34	41.99	41.9?

Note: ? reflects non-readable numbers in the table

Sex ratios appear unaffected by treatment.

Fetal External Examinations:

No external malformations were noted at the mid- or high dose levels. One fetus, from low-dose female #2516, was found to have a single external nare and this finding has no association with treatment with the test material.

Fetal Visceral Examinations:

There is no increase in the incidence of any soft tissue malformation or variation. Very few findings were noted in all groups.

Eighteen fetuses from a total of 7 dams (2 per dose level except at the high dose level where only one dam was affected) failed to have the cranium sectioned and therefore, brain tissue was not evaluated from these animals.

Fetal Skeletal Examinations:

The following table lists findings which appear to increase with dose:

	Dose Levels (mg/kg/day)			
	0	5	10	20
Litters evaluated	18	19	17	17
Fetuses evaluated	173	169	156	158
Anterior Fontanel enlarged				
fetal incidence	1(0.6%)	0	0	7 (4.4%)
litter incidence	1(5.6%)	0	0	2(11.8%)
Parietal -Incompl. ossified				
fetal incidence	0	0	0	3 (1.9%)
litter incidence	0	0	0	3(17.6%)
6th sternebra not ossified or incomplete				
fetal incidence	11(6.4%)	12(7.1%)	16(10.3%)	21(13.3%)
6th sternebra not ossified				
fetal incidence	6(3.5%)	5(3.0%)	7(4.5%)	14 (8.9%)
litter incidence	4(22.2%)	2(10.5%)	3(17.6%)	6(35.3%)
6th sternebra incompl. ossif.				
Fetal incidence	5(2.9%)	7(4.1%)	9(5.9%)	7 (4.4%)
litter incidence	3(16.7%)	4(21.1%)	4(23.5%)	5 (29.4%)
6th sternebra Split				
fetal incidence	1(0.6%)	2(1.2%)	2(1.3%)	6 (3.8%)
litter incidence	1(5.6%)	2(10.5%)	2(11.8%)	5(29.4%)

Dose Levels mg/kg/day

	0	5	10	20
2nd sternebra incompl. ossif.				
fetal incidence	0	0	1(0.6%)	2(1.3%)
litter incidence	0	0	1(5.9%)	2(11.3%)
Forelimb(s): mid-phalanges not ossified				
fetal incidence	3(1.7%)	4(2.4%)	8(5.1%)	8(5.1%)
litter incidence	2(11.1%)	2(10.5%)	2(11.8%)	4(23.5%)
Forelimb(s): Proximal phalang. Not ossified				
fetal incidence	0	0	0	2(1.3%)
litter incidence	0	0	0	2(11.8%)
Tarsals -Not Ossif.				
fetal incidence	0	1(0.6%)	3(1.9%)	3(1.9%)
litter incidence	0	1(5.3%)	2(11.8%)	1(5.9%)
Hindlimb(s): mid-phalanges not ossified				
fetal incidence	0	0	2(1.3%)	2(1.3%)
litter incidence	0	0	1(5.9%)	1(5.9%)
Pubis-not ossified				
fetal incidence	0	0	0	2(1.3%)
litter incidence	0	0	0	1(5.9%)

The above data support the conclusion that developmental toxicity was observed in this study and possibly at all dose levels. However, reduced levels of ossification were not assessed for numerous ossification sites (findings were often noted only when no ossification was observed). These data are necessary as per the Agency's Risk Assessment Guidelines for Developmental Toxicity and would allow for determination of a more meaningful NOAEL.

On page 29 of the test report, the authors discussed the incidence of fused sternebrae. The incidence of this finding was increased but not to a meaningful extent. Several malformations of the cranial bones including misshapen nasals and fused frontals were also discussed by the authors but there was no increase with increasing dose.

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Chlorothalonil

Page_____ is not included in this copy.

Pages 11 through 25 are not included.

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STUDY TYPE: Range-finding Rabbit Developmental Toxicity
TITLE: A Teratology Dose Range-finding Study in Rabbits with T-117-12

LABORATORY: Bio/dynamics Inc.
East Millstone, New Jersey

STUDY NUMBER: 87-3195

REPORT DATE: March 11, 1988

EPA I.D.: Not available

MRID Number: Not available

STUDY AUTHOR: Raymond E. Schroeder

CHEMICAL: T-117-12, light gray powder, assumed to be 100% pure The test material was identified inadequately since no lot number was provided to identify the test material which was provided to Bio/dynamics.

An ancillary evaluation by Ricerca, Inc. was attached to the test report which reported the test material to be 98.2% pure 2,4,5,6,-tetrachloroisophthalonitrile. This was stated to be technical chlorothalonil. Analyses of dose suspensions provided confirmation that dosing was adequate.

VEHICLE: 0.5% methylcellulose
Lot number 57F-0199

DOSE LEVELS/ROUTE:
Dose volume: 2 ml/kg
Dose levels: 5,15,30, and 75 mg/kg/day; 7 females/group
Route: oral gavage

TEST ANIMAL: New Zealand White [Hra; (NZW)SPF]
supplied by Hazelton Research Products, Inc.
Denver, Pennsylvania
Range of Body weight 2794-3829gm 4-5 months of age

Three additional animals were added which were outside this body weight range due to a dosing error. These animals weighed less than 3.0 kg (# 2526,4524, and 5524)

Materials and Methods: A copy of the "Materials and Methods" section from the test report is appended.

Apparently due to technician error, on the first day of treatment 2 animals in each group received half of their required dose volume and were sacrificed and replaced by other mated females.

Results:

Maternal Toxicity:
Mortality:

No test animals died in dose groups I-IV (up to 30 mg/kg). One female at 5 mg/kg (group II) and 2 females at 30 mg/kg delivered slightly prematurely. These animals were sacrificed and received a postmortem exam. The pathologist concluded that postmortem findings were not considered to be related to the administration of the test material. Group IV premature delivery animal # 4524 (on study 27 days) had originally been excluded from the study (due to low body weight?), but was added back in due to the dosing error which resulted in a shortage of animals, and was not reported to have any gross lesions. The other animal (# 4525) in this group which delivered prematurely also did not have any reported gross lesions.

At the high dose level, 75 mg/kg, animal # 5521 had numerous findings noted at necropsy which included a distended and discolored colon but was reported to be autolyzed. Animal # 5522 was reported to have all lung lobes red and discolored which could be associated with a dosing error. Animal # 5523 which aborted was found to have a hair ball. Animals # 5524 (aborted), 5525 (aborted), and 5526 (died) had no lesions reported at necropsy. As noted above, the pathologist concluded that the none of the gross pathology findings were considered related to administration of the test material at any dose level in this study.

Hence, mortality data only at the 75 mg/kg dose level may be indicative of a compound related effects, but this is was not confirmed by necropsy findings.

Maternal Body Weight:

Mean body weight and gains do not appear affected in the 5 and 15 mg/kg/day dose groups. At the 30 mg/kg dose level, slight but persistent weight reductions were suggested during the dosing period and persisted post dosing up to day 24. Only during two time periods measured, days 19 and 24, was the difference noted as statistically significant. The loss appeared to be only 200-300 grams, which is less than 10 % of the body weight of these animals. At the high dose level, reductions were more apparent and reached 500 grams by day 13.

Changes in mean body weight were also presented in appendix D, page 97. These data support the contention that there were effects at both the 30 and the 75 mg/kg/day dose levels. However, at the 30 mg/kg level, there was no indication of a rebound effect during the post-dosing period when compared to the controls or lower dose groups. In addition, the loss during any 3 day measuring period was very small ranging from a loss of 83 grams from days 7 to 10, to 32 grams

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during the interval from days 16 to 19. During the entire dosing period, animals in the 30 mg/kg/day group only lost 218 grams. At the 75 mg/kg/day dose level, no animals survived to day 30 so weight gain during the post-dosing period was not provided. During the entire dosing period, animals lost 685 grams at the 75 mg/kg dose level which appears to confirm toxicity was observed at this dose level.

In attempting to reach any firm conclusions on maternal toxicity based on these data, it is important to realize that rabbit body weight data are in general an unreliable indicator of toxicity. Even within the control group, there was about a 900 gram difference between the weights of animals at day 30. In addition, only seven animals were utilized per dose level. Hence, it appears likely that the reduced weights and weight gain observed at 75 mg/kg/day, is associated with administration of the test material but decreases at 30 mg/kg are not as obvious but may also suggest compound related maternal toxicity. However, this conclusion is weakened when corrected body weight data were assessed and it was determined that there were no effects at 30 mg/kg/day or at lower dose levels. Comparisons to historical control maternal weight gain data may have proven useful in making a determination, but such data were not submitted.

Of note in these data was the statistically significant decrease in uterine weight at the 30 mg/kg/day level. Such an effect would have been consistent with significant developmental toxicity at this dose level, but fetal exams were apparently not performed in this rangefinding study. The study protocol stated that the presence or absence of implantation sites were to be noted and when no uterine implants were grossly apparent, the uterus was to be stained with ammonium sulfide. Only pregnancy status was reported in the test report.

Food Consumption:

In the 30 mg/kg/day group level, there was some suggestion of a reduction in food consumption during the dosing period only. At days 10-11 and 16-17, this difference reached statistical significance. Except for the initial measurement period, these were the two other time intervals when none of the more consistent spillers were excluded.

Food consumption was clearly reduced at the high dose level.

Physical Observations:

The high dose level showed an increase in the incidence of Ag staining, matted fur in the A-G area and red vaginal discharge. In addition, isolated incidences of other findings were also noted at this level including pale gums, red nasal discharge,

and excess lacrimation. At the 30 mg/kg/day level, an increase in the level of alopecia was noted. Scabs were also noted in this dose group. Alopecia was not noted to increase at the high dose level. At one interval on day 24, 4 animals were noted to have alopecia at the 30 mg/kg level but at the high dose level only one animal was affected. It is therefore likely that this finding may not be associated with administration of the test material (possible infestation). Further, two of these four animals (#'s 4522 and 4524 had decreased food consumption and # 4524 also delivered early.

On pages 20 and 21 of the test report, the authors state that reduced feces or soft stool was noted to increase in the 30 and 75 mg/kg dose levels. However, appendix G-4 shows only one incidence of soft stool in one low dose animal and appendix G-5 notes that this happened only on day 16 in animal number 1521. This apparent discrepancy requires explanation from the registrant.

Abortion and Premature delivery:

As noted previously, 3 females in the 75 mg/kg/day group aborted. This is likely a compound related effect. Premature delivery was noted in one low dose female on day 28, in no litters at the next highest dose level (15 mg/kg/day) and two 30 mg/kg/day females. One female in the 30 mg/kg group partially delivered on day 26 and the other on day 27. In both cases at sacrifice, except for the 1-2 pups which were delivered, the remainder of the fetuses were found live. The authors concluded that the incidence at 30 mg/kg/day (only two litters) was "increased" and concluded that it may be indicative of a treatment related effect. However, it appears to this reviewer that this conclusion would also need to be supported by adequate historical control data and the equivalent incidence in the controls of the primary study does not support their conclusion.

Study Deficiencies:

Uterus exam data should have been included for all females on study. The protocol does not appear to be especially clear on this issue. Regardless, when the differences in the gravid uterine weights were noted at the 30 mg/kg/day, more thorough exams should have been performed rather than just for determination of pregnancy status. Discrepancies in the incidence of clinical observations in the text versus in the tables need to be resolved.

Core Classification:

This is only a rangefinding study and is classified as Core-Supplementary Data.

Conclusions/Recommendations:

This study supports a high dose level in a definitive study of

greater than 30 mg/kg/day and less than 75 mg/kg/day. Historical data on maternal weight gains and premature delivery would have been useful in the dose selection process for the definitive study.

The discrepancy between the incidence of reported clinical observations in the individual data versus the text discussion requires explanation.

It is worthwhile to note that in the definitive study, premature delivery occurred in two litters of the controls. Hence, it appears that conclusions to set dose levels based upon this finding are not supported by available data. This rangefinding study would also have provided much more useful information had it included the addition of a more complete in utero exam on all dams.

Review of 1st Study

83-3
Mat 003797

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MRID 00130733

MEMORANDUM:

TO: Henry Jacoby, PM # 21
Herbicides/Fungicides Branch
Registration Division TS-767C

THRU: R. Bruce Jaeger, Section Head
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

FROM: David L. Ritter, Toxicologist
Rev. Sec. # 1/Toxicology Branch
Hazard Evaluation Division TS-769C

Subject: EPA Reg. # 677-313 - Review of miscellaneous Toxicity Data.

Caswell #: 215B

Sponsor: SDS Biotech. (Formerly Diamond Shamrock Corp., Cleveland, OH.)

This Rat Teratology Study, # 517-STX-0011-003, is reviewed under the attached DER.

We find that the study is acceptable for regulatory purposes.

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DATA EVALUATION REPORT

003797

STUDY: Teratology Study in Rats

EPA # 677-313

LABORATORY: WIL Research Laboratories

MRID 00130733

DATE: 5/13/83

STUDY NUMBER: # 517-5TX-0011-003

ACCESSION NUMBER: 250855

MATERIAL TESTED: Technical Chlorothalonil

ANIMALS: Sprague-Dawley gravid female rats

METHODS:

"Groups of Sprague-Dawley rats (25 females/group) were administered chlorothalonil orally, via gavage, doses of 0, 25, 100 and 400 mg/kg/day from day 6 through 15 of gestation. Surviving females were necropsied on day 20 and fetuses delivered by hysterotomy. The number and position of viable/nonviable fetuses, early/later resorptions, mean number of corpora lutea and total number of implantations were recorded. External, internal and skeletal examinations of fetuses were performed for evidence of abnormalities and anomalies. Half of the fetuses were evaluated for soft tissue anomalies and the other half for skeletal effects.

[RESULTS]:

There was no dose related mortality in the 25 and 100 mg/kg/day groups. However, three dams in the 400 mg/kg which died during treatment were considered related to compound ingestion. There were no abortions in any group. General appearance and behavior were unremarkable except for evidence of cathartic action at 400 mg/kg (e.g. loose feces, matting of urogenital fur). Mean maternal body weights were significantly different (less) than control at the high dose. Food consumption was significantly reduced in all treatment groups initially (days 6-9), and in the high dose group throughout the dosing period (days 6-15). There were no differences compared to control for mean number of viable fetuses, implantation sites, corpora lutea or fetal weights. There was a significant increase in the number of early resorptions in the high dose group, as well as post implantation losses, when compared to controls. There were no reported effects on number or percentage of fetuses/litters with external, internal or skeletal malformations or developmental variations at any dose level administered.

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[CONCLUSION]:

Chlorothalonil was considered maternally toxic to rats at 400 mg/kg but there was no evidence of teratogenicity at any level tested (Rodwell et al., 1983)."

CORE RATING:

Guideline.

REFERENCE

Jaeger, R.B. "The Toxicity of Chlorothalonil". Report to the Joint Committee on Pesticide Residues. FAO/WHO. Geneva. 1983. (Draft).

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Chlorothalonil

Page_____ is not included in this copy.

Pages 34 through 47 are not included.

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____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

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____ Identity of the source of product ingredients.

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