ATTACHMENT 2A

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

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor, PM #25
Herbicide-Fungicide Branch/RD (TS-767)

FROM: Roland A. Gessett, D.V.M.
Veterinary Medical Officer
Toxicology Branch/HED (TS-769)

11/22/83

SUBJECT: Terbacil Registration Standard. Reply from du Pont re Data Gaps. Accession #249455, 11/9/82.

In Accession 249455, received November 9, 1982, du Pont responded to the data gaps EPA declared in the EPA Registration Standard.

A data gap was stated to exist for acute oral toxicity in that the test was conducted using Terbacil 80% Wettable Powder formulation, instead of the technical chemical. At a dose of > 5000 mg a.i./kg no mortality occurred. At 7500 mg a.i./kg, mortality was 7/10 in males; 10/10 in females. Initially we had considered the data from this study to be Core Supplementary because the study was conducted using the 80% wettable powder formulation instead of the technical chemical. (The confidential statement of formula lists 85% active ingredient). Because the inactive components of the formulation consist of such toxicologically inert ingredients as [redacted] Toxicology Branch has reconsidered its position and regards the acute oral toxicity study with terbacil 80% WP formulation to adequately demonstrate the acute oral toxicity of the technical chemical. In the event a more concentrated "technical chemical" (containing 90 to 100% active ingredient) is marketed for formulation, new acute studies may be required using the chemical of such potency. The data are now considered Core Minimum and this data gap is considered filled.

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Inert ingredient information may be entitled to confidential treatment

Acute Dermal Toxicity:

Although only 3 rabbits were tested, all males, the fact that no toxicity was observed following application of the "maximum feasible" dose to the skin (5000 mg a.i./kg body weight) provides ample evidence of the lack of acute dermal toxicity of the compound. The data now are considered adequate and the data gap may be considered satisfied.

Acute Inhalation Toxicity:

The du Pont Company submitted Study Report No. 351-82 of an Acute Inhalation Toxicity Test at atmospheric concentrations in rats of terbacil of 3.0 and 4.4 mg/liter. No deaths occurred from exposure.

The study is classified Core Minimum.

Primary Eye Irritation:

The registrant submitted a copy of the laboratory notebook pages in which the eye irritation scores were recorded. However, since only 4 male rabbits were tested, 2 with powder and 2 with 10% propylene glycol suspension, the data remain Core Supplementary, and must be repeated using an acceptable protocol.

Primary Dermal Irritation:

Application of terbacil at a 15% concentration in guinea pig fat is an inadequate concentration to measure primary dermal irritation. However, since no irritation was observed in male and female rabbits in the 21-day dermal toxicity sutdy at levels to 5000 mg/kg, the requirements of the primary dermal irritation test will be considered satisfied if the complete study report for the 21-day dermal study so indicates.

Dermal Sensitization:

The dermal sensitization test was classified Core Supplementary since only a data summary was submitted and because a positive control was not utilized. du Pont are correct in stating that, while a positive control is recommended, it is not required. They also state that their guinea pigs are tested periodically with known sensitizers to demonstrate that their strains are still sensitive. However, they should submit a more complete report of their study, providing individual animal data. The study is considered incomplete without the individual animal data required for review.

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Subchronic 21-Day Dermal Toxicity:

The du Pont Laboratory is correct in stating that 5g/kg is adequate dosing in their study. However, they are required to submit a complete study report for review.

Three Generation Reproduction in the Rat:

EPA previously had classified the data as Core Supplementary due to study design (only 2 dose levels used), and also due to respiratory illness in the laboratory, necessitating antibiotic treatment (initially tetracycline, then penicillin/streptomycin).

The 1978 proposed testing Guidelines provide that at least 3 dose-level groups be used; the highest level should produce an observable toxicological or pharmacological effect in the test animal but not cause more than 10% fatalities. This level also should be higher than that expected for human exposure from use of the pesticide.

The du Pont data demonstrate that there were significant effects in body weight gain in males, but not in females at 50 and 250 ppm. There also was an increase in relative liver/body weight ratio at 250 ppm. The registrant points out that no reproductive effects are seen at 250 ppm, "a level which greatly exceeds potential human exposure".

Regarding the effect of the respiratory illness and antibiotic treatment, the registrant points out that no adverse effects on the reproductive parameters evaluated were demonstrated. We accept their rebuttals and the 250 ppm NOEL for reproductive effects.

Teratology:

Based on implantation data, Mr. Larry Chitlick, in a letter, had questioned du Pont's dosing procedure, implying that du Pont may have initiated treatment prior to day 6 of gestation. du Pont's reply cites references referring to early post-implantation death without leaving visible signs at term. They also show that the apparent dose-response in the mean number of implantation sites/dam did not occur in both breeding lots, with the conclusion that the decreased number of implantation sites/dam seen in Breeding Lot B probably was not due directly to Terbacil exposure.

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du Pont also point out that the incidence of resorptions in controls of Breeding Lot A were greatly fewer than in controls of Breeding Lot B, and also much less than historic controls for this strain in the Haskell Laboratories, or in the Charles River Breeding Laboratory. In Breeding Lot B where controls showed a "normal" incidence of resorptions, the survival rates for the terbacil groups were similar to those of the controls, indicating no adverse effect of terbacil on embryo-fetal survival. Toxicology Branch acknowledges these explanations.

In his letter to the registrant, Mr. Chaplick also noted that, while no dilation of the renal pelvis and/or hydroureter was noted in the controls, it was noted in 18 to 27% of the litters in the dosed groups, a statistically significant finding for litters. (Incidences in litters of 18%, 27%, and 18% for 250 ppm, 1250 ppm, and 5000 ppm, respectively). On a per-fetus basis the incidences were 2.3%, 4% and 2.3% for 250 ppm, 1250 ppm and 5000 ppm, respectively. The incidence did not increase with dosage. Using one-tailed Fisher's Exact Test, no statistically significant difference in the incidence of hydronephrosis occurred between any experimental group and the control group. Also, "no statistically significant difference was detected when the incidence of hydronephrosis for all groups administered terbacil were combined before comparing to the control value. Similarly, the incidence of hydroureter was not found to be significantly different between the control group and each experimental group, or when all experimental groups were combined." No dilation of renal pelvis and/or hydroureter were found in the study controls.

The historic control data for hydronephrosis and/or hydroureter from du Pont's Haskell Laboratory from 1970 through 1979 was 0% - 30.8%, on a per fetus basis. The incidence of "increased renal pelvic cavitation" for Charles River rats provided by the Charles River Breeding Laboratory is 7.89%.

Therefore, based on further consideration of the data, it is concluded that an increased incidence of hydronephrosis and/or hydroureter due to terbacil administration has not been demonstrated. This also is consistent with the initial teratology review conducted for registration of terbacil.

It also is noted that du Pont will conduct a teratogenicity study in rabbits.

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Metabolism Study:

In the registration standard for terbacil we had identified a data gap in form of a general metabolism study, preferably in the rat. In their responding submission, du Pont submitted a published study identifying terbacil metabolites in dog urine.

Although a 2-year dog feeding study was conducted, the dog metabolism study is inadequate in that only one male and one female dog were tested. The current (1982) Guidelines specify that at least 5 animals per sex per dose group should be tested. The Guidelines also specify how dosing should be conducted, recognizing that a toxic level has been difficult to demonstrate with terbacil. Using only one male and one female animal it is not possible to dose according to the proposed guidelines. Therefore, an adequate metabolism study should be conducted.

Considering that two years have elapsed since this registration standard was written, we would expect that a radio-labeled rat metabolism study and appropriate mutagenicity studies would be submitted within a short period of time. Regarding mutagenicity, sufficient information with regard to incorporation of this uracil moiety into cellular DNA requires attention by the registrant.

Roland A. Gessert

Roland A. Gessert, D.V.M.
Veterinary Medical Officer
Toxicology Branch/HED (TS-769)

TS-769:GESSERT:sll:x73710:11/9/83 card 5

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ATTACHMENT 2

DER #6

Terbacil: Developmental Toxicity Study in Rats
E.I. du Pont de Nemours & Company. 1980. MRID No. 00050467.
HED Doc. No. 003401, 003401, 007177.

REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name: Glyphosate
CASRN: 1071-83-6

Status: empty

007177

Reviewed by: Joycelyn Stewart, Ph.D. 3/21/89
Section II, Tox. Branch I IRS(H7509C)
Secondary reviewer: Marion Copley D.V.M. 3/23/89
Section II, Tox. Branch I IRS (H-7509C)

Reviewed by C. Rodriques 9/11/1981. Updated by R. Gessert 11/23/1983

DATA EVALUATION REPORT COVER

STUDY TYPE: Teratology - Rat TOX. CHEM. NO.: 821A

ACCESSION NUMBER: 249455 MRID NO.:00039001

TEST MATERIAL: Terbacil

SYNONYMS: 3-Tert-Butyl-5-Chloro-6-Methyluracil

STUDY NUMBER(S): 481-79

SPONSOR: DuPont de Nemours and Co.
Wilmington, Delaware.

TESTING FACILITY: Haskell Laboratories
Wilmington, De

TITLE OF REPORT: Rat Oral Teratology with Terbacil

AUTHOR(S):

REPORT ISSUED: 2/20/1980

CONCLUSION: The previous reviews (attached) accurately represent the results of the study. The test material was administered orally in the diet at levels of 250, 1250, and 5000 ppm from day 6 through 15 of gestation. The maternal NOEL was 250 ppm based on decreased body weight at 1250 ppm and above from day 10 to day 21. The embryofetotoxic NOEL was 250 ppm based on decreased litter size at the mid and high dose levels. The A/D ratio is 1.

$$\frac{\text{Maternal LOEL}}{\text{DEvelopmental LOEL}} = \frac{1250 \text{ ppm}}{1250 \text{ ppm}} = 1$$

Classification: Minimum.

Memo. ~~Taylor~~ Gessert to Taylor 10/1/93 Tox. Document 003401

Teratology:

Based on implantation data, Mr. Larry Chitlick, in a letter, had questioned du Pont's dosing procedure, implying that du Pont may have initiated treatment prior to day 6 of gestation. du Pont's reply cites references referring to early post-implantation death without leaving visible signs at term. They also show that the apparent dose-response in the mean number of implantation sites/dam did not occur in both breeding lots, with the conclusion that the decreased number of implantation sites/dam seen in Breeding Lot B probably was not due directly to Terbacil exposure.

du Pont also point out that the incidence of resorptions in controls of Breeding Lot A were greatly fewer than in controls of Breeding Lot B, and also much less than historic controls for this strain in the Haskell Laboratories, or in the Charles River Breeding Laboratory. In Breeding Lot B where controls showed a "normal" incidence of resorptions, the survival rates for the terbacil groups were similar to those of the controls, indicating no adverse effect of terbacil on embryo-fetal survival. Toxicology Branch acknowledges these explanations.

In his letter to the registrant, Mr. Chitlick also noted that, while no dilation of the renal pelvis and/or hydroureter was noted in the controls, it was noted in 18 to 27% of the litters in the dosed groups, a statistically significant finding for litters. (Incidences in litters of 18%, 27%, and 18% for 250 ppm, 1250 ppm, and 5000 ppm, respectively). On a per-fetus basis the incidences were 2.3%, 4% and 2.3% for 250 ppm, 1250 ppm and 5000 ppm, respectively. The incidence did not increase with dosage. Using one-tailed Fisher's Exact Test, no statistically significant difference in the incidence of hydronephrosis occurred between any experimental group and the control group. Also, "no statistically significant difference was detected when the incidence of hydronephrosis for all groups administered terbacil were combined before comparing to the control value. Similarly, the incidence of hydroureter was not found to be significantly different between the control group and each experimental group, or when all experimental groups were combined." No dilation of renal pelvis and/or hydroureter were found in the study controls.

The historic control data for hydronephrosis and/or hydroureter from du Pont's Haskell Laboratory from 1970 through 1979 was 0% - 30.8%, on a per fetus basis. The incidence of "increased renal pelvic cavitation" for Charles River rats provided by the Charles River Breeding Laboratory is 7.89%.

Therefore, based on further consideration of the data, it is concluded that an increased incidence of hydronephrosis and/or hydroureter due to terbacil administration has not been demonstrated. This also is consistent with the initial teratology review conducted for registration of terbacil.

It also is noted that du Pont will conduct a teratogenicity study in rabbits.

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

December 18, 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Mr. Rick Holt
Technical Development Specialist
E. I. du Pont de Nemours and Company
Biochemical Department
Brandywine Bldg.
Wilmington, Delaware

Dear Mr. Holt:

During preparation of the Toxicology Section of the Terbacil Registration Standard, some questions have surfaced relative to your rat teratology study (Haskel Laboratory, Report No. 481-79) which was recently submitted to the Agency. The following questions/issues in reference to this study would be beneficial to resolve prior to completion of the Toxicology portion of this Standard.

1. If test compound was fed to animals post-implantation days 6-15, (as per reported procedure) why is there a dose response relationship relative to the number of implantations? It is likely that the reported findings and conclusions are procedural artifact and this is not discussed in the final report. Resultant indices (i.e. - number live fetuses/litter) would also be affected as a result and this is also not reflected in your data evaluation.

2. With approximately half of the fetuses/litter examined for visceral abnormalities, not a single incidence of "dilation of renal pelvis and (or) hydroureter" was noted in the controls, while it was noted in 18 to 27% of the litters in the dosed groups. The submitted report notes that these findings are statistically significant, but at the same time dismisses the findings as due to normal incidences etc. Adequate historical data which demonstrate these conclusions should have been submitted to the Agency. The probability of finding no similar responses in the controls also creates questions. It must also be noted that at 5000 ppm, fewer fetuses per litter were available for examination and food consumption was reduced which may have a bearing on a dose response relationship.

3. The report made available to Toxicology Branch for preparation of the Registration Standard contained only summary tables and no individual animal data. Such findings as dilation of the renal pelvis and hydroureter were grouped together. Were these findings bilateral or unilateral? Was hydroureter always found in conjunction with the dilated renal pelvis or not? Were these findings graded? A more complete report would provide this type of information.

A number of other more minor questions also exist relative to reported study findings and evaluations presented which would certainly have been resolved with more comprehensive reporting. Our main concerns at this time, however, are linked to the significance of the reported hydronephrosis as a potential teratogenic response and we hope that this can be quickly resolved. The normal incidences vary considerably by strain and testing facility and the finding must therefore be carefully considered.

I would appreciate discussing any of these items with a du Pont toxicologist and can be reached at 703-557-7395.

Sincerely,

Laurence D. Chitlik

Laurence D. Chitlik, Section Head
Toxicology Branch
Hazard Evaluation Division

003457

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

MEMORANDUM

DATE: SEP 14 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Terbacil Teratology Study
CASWELL NO. 821A

FROM: Carlos A. Rodriquez Carlos A. Rodriquez 9/11/81
Review Section #1
Toxicology Branch/HED (TS-769)

TO: Robert J. Taylor, PM #25
Fungicide - Herbicide Branch
Registration Division (TS-769)

THRU: Robert B. Jaeger, Section Head RBJ 9/14/81
Review Section #1
Toxicology Branch/HED (TS-769)

Registrant: E.I. duPont de Nemours & Co.
Legal Department
Wilmington, DE 19898

PP#8F2039 with EPA Reg. No. 352-317

Action:

Establish tolerance of 0.1 ppm in or on pecans for terbacil (3-tert-butyl-5-chloro-6-methyluracil) and its metabolites 3-tert-butyl-5-chloro-6-hydroxymethyl uracil, 6-chloro-2, 3-dihydro-7-hydroxymethyl-3, 3-dimethyl-5H-oxazolo (3,2-a) pyrimidin-5-one, and 6-chloro-2,3-dihydro-3,3,7-trimethyl-5H-oxazolo-(3,2-a) pyrimidin-5-one (calculated as terbacil).

Recommendations and Conclusions:

1. The teratogic evaluation of Terbacil (IND-732) is adequate and designated Core-Minimum Data.

2. Additional data desired, but lacking:

   a) oncogenicity study in a second species

   b) teratogenicity study in a second species (rabbit)

   c) additional mutagenicity study at such time the Agency determines a suitable protocol.

Review:

Rat Oral Teratology with Terbacil (3-Tert-Butyl-5-Chloro-6-Methyluracil (IND732) (Haskell Labs; Report No. 481-79, Project No. 3143, February 20, 1980).

The test material was administered orally by gavage from days 6 through 15 of gestation to three groups of 27 female rats at levels of 250, 1250, and 5,000 ppm in the diet. Ground purina laboratory chow was provided without the test material through day 5 of gestation and for days 16 through 21. A control group received ground purina laboratory chow throughout the test period. Initial body weights ranged from 236 to 254 grams. Animals were individually housed. All animals were observed daily for clinical signs and changes in behavior. Body weights were recorded on Days 0,6,10,16, and 21. Food consumption for each rat was determined at each weighing period. On Day 21 all rats were sacrificed by chloroform inhalation. The uterus and ovaries were removed and inspected for gross changes. The uterus was then opened and the fetuses removed and examined.

The following observations and measurements were recorded: the number of corpora lutea in each ovary, number of implantation sites in each horn, number and location of all live and dead fetuses, number and location of resorptions, weight of each live fetus, crown-rump length of each live fetus, gross anomalies.

The report states that one half of the fetuses of each litter were cleared and stained, and then examined for skeletal abnormalities. The remaining fetuses were fixed and sectioned by Wilson's free hand razor technique and examined for visceral and neural anomalies. The uterus and ovaries of all animals in all groups were examined for gross changes and those of pregnant rats were preserved in Bouin's fluid for possible histologic examination.

Statistical Evaluation

The litter was considered the experimental unit of treatment and observation in this study. Maternal fetal weights and crown-rump measurements were compared to controls by analysis of variance and least significant difference tests. The Fisher exact probability test was used to evaluate the incidence of resorptions and abnormalities among litters. The number of corpora lutea, implantations and live fetuses per litter were subjected to analysis by the Wilcoxon rank sum test.

Results

Maternal body weight and food consumption

At dosages of 1,250 and 5,000 ppm - rats exhibited a dose related reduction in mean body weight during the exposure period on days 10 and 16 of gestation and 5 days following diet removal on day 21 of gestation. The 250 ppm diet did not significantly alter the mean body weight of pregnant rats. Initial and final mean group body weight are as follows:

Diet (ppm)	Day of Gestation			
	6	10	16	21
0	213 ± 12	247 ± 13	302 ± 14	374 ± 24
250	216 ± 15	247 ± 16	294 ± 18	363 ± 23
1,250	215 ± 12	236 ± 11*	279 ± 16*	351 ± 28*
5,000	214 ± 15	225 ± 12*	271 ± 13*	345 ± 19*

*$p \leq 0.05$ level of significance from control.

Average Weight Gain (gms)

Diet (ppm)	Day of Gestation		
	6 - 10	10 - 16	16 - 21
0	34 ± 4	55 ± 7	72 ± 13
250	31 ± 5	47 ± 7*	69 ± 14
1,250	21 ± 7*	43 ± 9*	72 ± 16
5,000	11 ± 7*	45 ± 8*	74 ± 14

*$p \leq 0.05$ level of significant from control.

Gross Pathology - Maternal

No gross pathological changes were observed in the ovaries, uterus, and major organs and tissues of treated females.

Pregnancy and Fetal Development

In the groups that received 1,250 and 5,000 ppm, the mean numbers of live fetuses per litter and mean final maternal body weight were signicicantly lower than those in the control group.

At 5,000 ppm the mean number of implantation per litter was also significantly lower than the mean in the control group.

	Control	250(ppm)	1250(ppm)	5,000(ppm)
Live fetuses/litter	10.9 ± 2.0	9.7 ± 3.3	9.1 ± 3.1*	8.6 ± 2.9*
Implantations/litter	11.4 ± 2.3	10.4 ± 3.3	10.0 ± 3.3	9.3 ± 3.1*

*Significantly ($p < 0.05$) lower than the control.

The decrease in the number of implantations and live fetuses per litter and final maternal body weights were dose related. The mean fetal body weight and crown-rump length were not affected by any of the dosages administered.

Fetal Anomalies and Malformations

All groups including the control group exhibited small subcutaneous and petechial hemorrhages on various part of the body. Undersized fetuses were found in all groups. An umbilical hernia was found in one undersized fetus from the control group and in one fetus from the lower group (250 ppm). Visceral anomalies occurred at a very low incidence in all groups. Dilation of the renal pelvis and ureter were found in all test groups but not in control.

Retarded ossification of pubic bones and centra, wavy ribs, and one pair of full fourteenth ribs were found only in the control group. Unossified sternebrae and rudimentary fourteenth ribs were found in all groups.

Conclusions

Terbacil is not teratogenic to rats at 5,000 ppm (highest dose tested).

Embryotoxic effects at 1250 and 5,000 ppm.

Systemic Maternal NOEL = 250 ppm

Classification: Core Minimum

TS-769:CARLOS:sll:CM#2:RM.816:X73710:9/10/81 card 1

TABLE I: REPRODUCTIVE DATA FROM TERBACIL STUDY, REANALYZED

	Groups (ppm)			
	0 (X±S.E.M.)	250 (X±S.E.M.)	1,250 (X±S.E.M.)	5,000 (X±S.E.M.)
Mean No. Corpora Lutea/Dam				
Breeding Lot A	11.4±0.45	12.6±0.48	11.7±0.60	12.3±0.45
Breeding Lot B	13.9±0.63	12.8±0.40	12.8±0.39	11.5±0.52
Group	12.5±0.38	12.7±0.30	12.3±0.36	11.9±0.34
Mean No. Implantations Sites/Dam				
Breeding Lot A	10.4±0.66	11.7±0.40	9.8±1.08	10.6±0.72
Breeding Lot B	12.6±0.68*	9.3±1.20	10.1±1.00	7.9±1.00*
Group	11.4±0.36	10.4±0.40	10.0±0.40	9.3±0.39**
Mean No. Resorptions/ Litter				
Breeding Lot A	0.1±0.2	0.8±0.3	0.8±0.3	0.9±0.2
Breeding Lot B	0.7±0.3	0.7±0.3	0.8±0.3	0.4±0.3
Group	0.4±0.2	0.7±0.3	0.8±0.3	0.7±0.2
Mean % Resorptions/ Litter				
Breeding Lot A	1.7±0.3%	7.0±0.4%	8.1±0.9%	8.4±0.6%
Breeding Lot B	5.3±0.8%	8.2±1.3%	7.1±1.0%	4.3±0.9%
Group	3.3±0.5%	7.7±0.6%	7.6±0.6%	6.8±0.6%
Mean No. Live Fetuses/Litter				
Breeding Lot A	10.3±0.47	10.9±0.42	9.1±0.58	9.7±0.49
Breeding Lot B	11.9±0.47	8.4±0.65	9.1±0.33	7.4±0.54
Group	10.9±0.34	9.7±0.40	9.1±0.36**	8.6±0.37**
Survival Rate (Mean % Live Fetuses/Litter)				
Breeding Lot A	98.3±0.6%	93.0±0.9%	91.9±0.9%	90.6±0.8%
Breeding Lot B	94.5±0.8%	91.7±1.3%	92.9±1.0%	93.6±0.9%
Group	96.4±0.5	92.4±0.7	91.9±0.7	92.1±0.6

* Lot B significantly different from Lot A, $p \leq 0.05$ (two-tailed Mann-Whitney U test)
** Different from control group, $p \leq 0.05$ (R. Quick's statistical test used)

TABLE [redacted] REPRODUCTIVE DATA FROM BUSSEY LABORATORY

Crl:CD®BR, Control Rats

Study		Dams (N)	Impl (N)	Live Fetus (N)	Dead Fetus (N)	Resorp (N)	Mean Implantation/Dam ($\bar{X}$ #Impl/♀)	Mean Resorptions/Dam ($\bar{X}$ #r/♀)	Mean % Resorptions/Implantation ($\bar{X}$ %r/Impl)
1970	a	21	195	185		10	9.3	0.48	5.1
	b_1	28	270	257	1	12	9.6	0.43	4.4
	b_2	24	230	212		18	10.0	0.78	7.8
1971	a	22	233	220		13	10.6	0.59	5.6
	b	25	245	232		13	9.8	0.52	5.3
	c	23	245	238		7	10.6	0.30	2.8
1973	a	23	212	199	3	10	9.2	0.43	4.7
	b	9	93	89		4	10.3	0.44	4.3
	c	24	226	214		12	9.4	0.50	5.3
1974	a	23	239	221		18	10.4	0.78	7.5
	b	24	246	229		17	10.2	0.71	6.9
	c_1	21	190	178		12	9.0	0.57	6.3
	c_2	11	117	107		5	10.2	0.45	4.5
	d	3	38	36		2	12.7	0.67	5.3
1975	a	21	200	192		8	9.5	0.38	4.0
	b	20	184	164		20	9.2	1.00	10.9
	c	27	283	262		21	10.5	0.78	7.4
1976 1979 not available									
1979	a	33	327	307		20	9.9	0.60	6.1
1980	a	50	520	495		25	9.9	1.39	4.8
							10.0♀ 0.2 (SEM)	0.62♀ 0.10 (SEM)	5.7%♀ 0.3 (SEM)

TABLE III: BACKGROUND DATA OBTAINED FROM CHARLES RIVER BREEDING LABORATORY

Mean No. Implantations/Dam	Dams	$\bar{X}$ No. Implantations/Dams
Charles River 1964-1969	3,233	10.9
Mean No. Live Fetuses/Litter		
Charles River 1964-1969	3,233	10.2
Mean No. Resorptions/Litter		
Charles River 1964-1969	3,233	0.6
Mean % Resorptions/Litter		
Charles River 1964-1969	3,233	6.0%

TABLE IV. [illegible]: TERATOGENIC POTENTIAL IN THE RAT, INCIDENCE OF ALTERATIONS OF THE KIDNEY AND URETER

Group (fetuses examined)	"Hydronephrosis" (dilated renal pelvis) No. affected fetuses	Side	Hydroureter No. affected fetuses	Side
Control (97)				
Lot A	0	-	0	-
Lot B	0	-	0	-
Group total	0		0	
Terbacil 250 ppm (101)				
Lot A				
Dam 239670	1	right	1	right
239680	1	right	0	-
Lot B				
Dam 239722	0	-	2	bilateral
Group total	2		3	
Terbacil [illegible] ppm (96)				
Lot A				
Dam 239703	1	right	0	-
239714	0		1	
Lot B				
Dam 239733	1	unilateral	1	bilateral
239745	0		1	bilateral
239756	0		1	bilateral
Group total	2		4	
Terbacil 5000 ppm (88)				
Lot A				
Dam 239677	1	right	1	bilateral
239712	0	-	1	left
239725	0	-	1	unilateral
Lot B				
Dam 239767	0	-	1	right
Group total	1		4	

TABLE V: HISTORIC CONTROL DATA FOR "HYDRONEPHROSIS AND/OR HYDROURETER" FROM HASKELL LABORATORY (DU PONT CO.)

Experiment	Total No. Fetuses Affected	Total No. Fetuses Examined	% Fetuses Affected
1970 a	0	51	0.0
b	14	88	15.9
c	18	74	24.3
1971 a	8	73	11.0
b	3	83	3.6
c	15	82	18.3
1972 a	0	69	0.0
b	0	30	0.0
c	15	76	19.7
1973 a	11	75	14.7
b	14	82	17.1
c	4	58	6.9
d	3	34	8.8
e	4	13	30.8
1975 a	9	66	13.6
b	10	61	16.4
c	11	123	8.9
1976 a			
b			
c			
d	Recorded as number of		
e	affected/litters only		
1977 a			
b			

TABLE V (CONT)

Experiment		Total No. Fetuses Affected	Total No. Fetuses Examined	% Fetuses Affected	
1978	a	0	83	0.0	
	b	2	107	1.9	
	c	3	93	3.2	
	d	2 1	100	3.0	+2.0 hydronephrosis +1.0 hydroureter
	e	6	120	5.0	
1979	a	7	97	7.2	
	b[1]	0	90	0.0	
	b[2]	1	105	1.0	
	c	2 1	112	2.7	+1.8 hydronephrosis +0.9 hydroureter
	d	1	105	1.0	
Terbacil study	e	0	97	0.0	
	f	11 6	145	11.7	+7.6 hydronephrosis +4.1 hydroureter
Charles River 1964 - 1969	"Increased renal pelvic cavitation"	235	2979	7.89	

REFERENCES:

Gebhardt, D. O. E., The effects of starvation or of treatment with cytotoxic agents on pregnancy in mice. J. Reprod. Fert., 19:519-526.

Hoar, R. M., and T. J. King. Further observations on resorption in guinea pigs following injections of trypan blue. Anat. Rec., 157:617-620.

Staples, R. E., Blastocyst transplantation in the rabbit. Methods in Mammalian Embryology, W. H. Freeman & Co., San Francisco, 1971, pp. 209-304.

Woo, D. C., and R. M. Hoar. "Apparent hydronephrosis" as a normal aspect of renal development in late gestation of rats: the effect of methyl salicylate. Teratology, 6:191-196.

Response to Question 1

The original report stated that "A dose-dependent decrease in the number of implantations and live fetuses per litter was suggestive of an IND-732-related embryotoxic effect." Dr. Chitlik questioned the likelihood of an adverse effect of Terbacil on implantation since implantation occurred before the dosing period.

It has been demonstrated that early post-implantation death can occur without leaving visible signs at term (Hoar and King '67; Gebhardt '69; Staples '71). The data presented in the original report evolved from two "runs" (Breeding Lots A & B). When each "run" was analyzed independently (Table I) it was found that the apparent dose-response in the mean number of implantation sites/dam did not occur in both runs. In fact, in the high dose and control groups the incidence differed significantly between runs. Hence, the decreased number of implantation sites dam observed in Breeding Lot B was probably not due to the direct result of Terbacil exposure.

After implantation the incidence of embryo-fetal mortality was comparable among groups given Terbacil (Table I). However, it should be noted that the incidence of resorptions for the control group in Lot A was considerably less than the 0.6 resorptions/litter (5.7% resorptions/litter) found historically for the Crl:CD® strain used at Haskell Laboratory (Table II) and Charles River Breeding Laboratory (Table III). The "Survival Rate" for the groups given Terbacil in Lot B was similar to that for the concurrent control group (Table I); hence, no adverse effect of Terbacil administration on embryo-fetal survival was demonstrated during this period of gestation.

Response to Questions 2 and 3

Data concerning kidney alterations were retabulated and re-analyzed to respond to Questions 2 and 3 (Table IV). The types of alterations observed were "hydronephrosis" (dilated renal pelvis), and hydroureter. These data were reanalyzed separately using a one-tailed Fisher's exact test.

No statistically significant difference in the incidence of hydronephrosis occurred between any experimental group and the control group, and the incidence did not increase with increased dosage (Table IV). In fact, no statistically significant difference was detected when the incidence of hydronephrosis for all groups administered Terbacil were combined before comparing to the control value. Similarly, the incidence of hydroureter was not found to be significantly different between the control group and each experimental group, or when all experimental groups were combined.

The fact that no kidney alterations were noted in the control group for the Terbacil study was not unusual in view of the sporadic frequency of this alteration historically; similar results were obtained in 5/31 studies conducted at Haskell Laboratory between 1970-1979 (Table V).

Hydronephrosis and hydroureter occurred on the same side of the fetus once each in the 250 ppm and the 1250 ppm Terbacil groups. In the remaining three fetuses exhibiting hydronephrosis, hydroureter was not present. Since fetal identification within litters was not practiced at the time this study was conducted it is not possible to determine whether the kidney alterations tended to occur in the smallest fetuses. Kidney alterations of the type described are known to result from developmental delay (Woo and Hoar, '72).

Please let us know if this response does not meet your need.

ATTACHMENT 3

DER #7

Terbacil: Developmental Toxicity Study in Rabbits
E.I. du Pont de Nemours & Company. 1984. MRID No. 00150945.
HED Doc. No. 004443, 007177.

007177

Reviewed by: Joycelyn Stewart, Ph.D. 3/21/89
Section II, Tox. Branch I (IRS)(H7509C)
Secondary reviewer: Marion Copley,D.V.M. MC 3/23/89
Section II, Tox. Branch I (IRS) (H7509C)

Review date: 5/10/1985 R. Gessert.

DATA EVALUATION REPORT COVER

STUDY TYPE: Teratology-Rabbit TOX. CHEM. NO.: 821A

ACCESSION NUMBER: 255763 MRID NO.: 00150945

TEST MATERIAL: 3-tert-butyl-5-chloro-6 methyluracil 80%

SYNONYMS: Herbicide 732

STUDY NUMBER(S): 528-83

SPONSOR: E.I. duPont de Nemours and Co.
Wilmington, Delaware

TESTING FACILITY: Haskell Laboratory

TITLE OF REPORT: Embryo-Fetal Toxicity and Teratogenicity Study of Terbacil by Gavage in the Rabbit.

AUTHOR(S): Solomon, H.M.

REPORT ISSUED: 2/21/1984

Classification: Mimimum

CONCLUSION: The previous review (attached) accurately represents the results of the study. This reviewer concurs with the evaluation of the study in the review by R. Gessert, 5/10/1985, Toxicology Branch document 004443.

83-3

004443

MRID 00150945

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY OF TERBACIL BY GAVAGE IN THE RABBIT. Haskell Laboratory Report Number 528-83. By Howard M. Solomon, et al. February 21, 1984.

MATERIAL TESTED: Terbacil, IND-732-53. 96.1% pure.

VEHICLE: 0.5% aqueous suspension of methyl cellulose 1500 centipoise, supplied by Callahan Chemical Company, Palmyra, New Jersey.

ANIMALS: 5-month old nulliparous female New Zealand White rabbits obtained from Hazleton-Dutchland Laboratories; Denver, PA. Males of same strain from same supplier.

PROCEDURE: 21 days after arrival the does were given 25 USP units HCG/kg body weight IV and inseminated 1 to 3 hours later. Day of insemination was designated day 0 of gestation. Only healthy does were placed on study, and dose groups were randomized by body weight. Eighteen inseminated does were assigned to each dose group.

Dose groups received 0, 30, 200, or 600 mg/kg body weight by gavage on days 7-19 of gestation in a volume of 2 ml/kg body weight 0.5% methyl cellulose suspension in distilled water.

OBSERVATIONS:

Body weights of the does were taken upon arrival, before breeding, and on the mornings of Days 0, 6, 7, 10, 13, 16, 19, 20, 24, and 29 of gestation. Individual does were observed for clinical signs upon arrival, twice during quarantine, each morning on gestation days 0 through 29, and each afternoon during the dosing period. Food consumption was determined visually, and a doe was considered anorectic when she ate less than 1/4 of her daily ration.

After sacrifice by cervical dislocation each doe was examined grossly. The liver was removed and weighed, and the corpora lutea were counted under magnification.

The number and position of all live, dead, and resorbed fetuses were recorded. The uterus of each apparently non-pregnant doe was stained with ammonium sulfide to determine very early resorptions.

All fetuses were weighed and live fetuses were examined for external alterations & visceral alterations, and sex of each fetus was determined. "Hydrocephaly was detected by making a transverse section between parietal and frontal bones through the unfixed fetal head. . . . eyes were examined visually to detect microphthalmia," and if bilateral microphthalmia was suspected, measurements were made for comparison.

"After evisceration, all fetuses were fixed in 70% ethanol, macerated in 1% aqueous potassium hydroxide solution, and stained with alizarin red S to examine skeletons for alterations. Data from fetuses classified as dead were excluded from statistical analyses and data summaries." Appropriate statistical analyses of the data were conducted.

2

00443

RESULTS: See table on next page.

CONCENTRATION OF TEST SUSPENSIONS: Nominal dose levels were 0, 30, 200, and 600 mg terbacil/kg body weight. Actual mean dose levels administered were 0, 33, 208, and 680 mg terbacil/kg body weight.

MATERNAL MORTALITY: One control doe and 5 high dose does died during the study. An additional 2 high dose does were sacrificed in extremis.

CLINICAL SIGNS:

Besides maternal mortality, the chief highly significant dose related clinical sign was anorexia. In addition, a discharge on the cageboard was seen in the high dose group.

MATERNAL BODY WEIGHT:

Anorexia in the high dose does was reflected in body weight loss, particularly during the treatment period.

POST MORTEM FINDINGS IN DOES:

Hairballs completely filled the stomachs of all does on the high dose. A lower incidence of hairballs was found in the controls and other dose groups, but these were not dose related. No other significant maternal post mortem findings were noted.

REPRODUCTION:

There were no significant differences between groups in corpora lutea, implantations, resorptions, or live and dead fetuses. The mean live fetal weight was significantly less in the high dose group.

FETAL MALFORMATIONS:

The average percent of malformed fetuses per litter was higher in the high dose (600 mg) group than in the controls or other treatment groups, but the difference is not statistically significant or dose related. (5.8%, 9.0%, 6.0%, and 16.5% for the controls, low, mid, and high dose groups, respectively).

In general, there was no significant increase in malformed fetuses between the control and treatment groups.

FETAL VARIATIONS:

At the high dose, there was a significant increase in the incidence of extra ribs, partially or unossified phalanges, and partially or unossified pubes. These all occurred in only 3 litters, and cannot be considered a significant dose-related effect. Because they occurred at a dose that was overtly toxic to the dams, they may be considered to result from maternal toxicity.

3

004443

	DOSE (mg/kg/day)							
	0		30		200		600	
Pregnancies	14/18	77.8%	17/18	94.4%	14/18	77.8%	15/18	83.3%
Abortions	3/14	21.4%	0	0	0	0	4/15	26.7%
Deaths	1		0		0		5 + 2	
Fetal Visceral Malformations	1/1		4/?		1/1		2/1	
Hypoplastic thyroid	1/1							
Hypoplastic pancreas			3/1					
Cleft palate							1/1	
Microphthalmia			3/2					
Hydrocephaly			1/1		1/1		2/1	
Distended sinus			1/1					
Skeletal Malformations	4/3		11/8		2/2		5/3	
Malformed vertebra	1/1		1/1		1/1		1/1	
Absent vertebra			2/1				1/1	
Angular hyoid cornu	1/1		2/1		1/1			
Fused sternebra	2/2		5/5				3/2	
Fused ribs			1/1				2/2	
Total Malformed (fetuses/litters)	4/3		12/8		3/3		7/3	
(Fetuses/total fetuses)	4/70		12/136		3/80		7/29	
Visceral Variations	3/2		4/3		4/3		1/1	
Bifurcated gall bladder			1/1					
Left carotid artery branches off innominate artery	3/2		3/2		4/3		1/1	
Skeletal Variations	56/10		100/17		53/12		23/3	
Skull: hole in parietal bone					1/1			
Misaligned sternebra	2/2		3/2		2/2			
Bipartite sternebra	1/1						1/1	
Ribs: extra ossification center	41/9		74/15		38/11		16/3	
rudimentary ribs	21/10		27/13		17/9		4/2	
extra ribs	17/9		43/13		24/9		18/3	
thickened ribs					1/1			
Total with skeletal variations due to retarded development	40/10		88/17		47/11		18/3	
Average % fetuses with variations due to retarded development	53.5%		66.1%		54.8%		69.0%	
Total fetuses with variations	64/10		123/17		73/13		23/3	
Average % fetuses with variations	90.6%		90.4%		87.4%		87.2%	

4

It is noted that fertility of the controls was 14/18; fertility of the high dose (600 mg/kg) rabbits was 15/18. The proposed guidelines suggest 12 (pregnant) rabbits per group. Of the 14 pregnant does in the control group, 3 aborted and 1 died. These 4 does all had hair balls in their stomachs.

In this study and in other rabbit studies where dosing is by gavage I have noted a high incidence of trichobezoars, or gastric "hair balls", with resulting anorexia, abortions, and death. Apparently the hair consumption is a sequel to the stresses of dosing and handling procedure or chemical toxicity. In one laboratory where very few trichobezoars were encountered I noted that a very large breed of rabbits were used with apparently less physical resistance of the dosing procedure.

So in this study, while there were only 10 litters from 18 control does, there were 14/18 pregnancies. At the low and mid dose levels there was good fertility (17/18 and 14/18) with no abortions or deaths, and the mid-dose level (200 mg/kg) can be considered a NOEL for maternal and embryotoxicity, so in a sense the low and mid dose groups can be considered with the controls. Obvious toxicity is seen at the 600 mg/kg (high dose) level.

The treatment levels are relatively high. So even though there are only few litters from the high dose (600 mg/kg) to evaluate because of maternal toxicity, the relatively high NOEL level (200 mg/kg) indicates a large margin of safety.

CONCLUSIONS:

1. Terbacil is not teratogenic in the rabbit.
2. The NOEL for maternal toxicity and embryotoxicity was 200 mg/kg.
3. The data meet Core Minimum requirements.

5

16

TABLE 2

MR-4512
HH-14673

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY
IN RABBITS GIVEN TERBACIL
BY GAVAGE ON DAYS 7-19 OF GESTATION

PREGNANCY, ABORTION AND MATERNAL MORTALITY RATES

DOSE LEVEL (MG/KG)	INSEMINATED FEMALES	PREGNANCIES TOTAL	PREGNANCIES %	ABORTIONS TOTAL	ABORTIONS %	DEATHS†† SPONTANEOUS	DEATHS†† SACRIFICED IN EXTREMIS	DEATHS†† TOTAL
0	18	14	77.8	3	21.4	1	0	1
30	18	17	94.4	0	0	0	0	C
200	18	14[a]	77.8	0	0	0	0	0
600	18	15	83.3	4	26.7	5	2[b]	7*

[a] One detected by ammonium sulfide staining.
[b] One not pregnant.
†† Significant dose-related response, $p \leq 0.01$.
* Significantly different from control value, $p \leq 0.05$.

TABLE 4

MR-4512
HN-14673

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY
IN RABBITS GIVEN TERBACIL
BY GAVAGE ON DAYS 7-19 OF GESTATION

MEAN MATERNAL BODY WEIGHT CHANGES[a] (KG)

DOSE LEVEL (MG/KG)	DAYS OF GESTATION 1-6	7-9†	10-12	13-15	16-19	7-19†	20-29
0	0.16	0.01	0.04	0.08	-0.06	0.06	0.08
30	0.13	0.01	0.05	0.04	0.03	0.13	0.09
200	0.15	0.00	-0.04	0.04	0.03	0.04	0.11
600	0.18	-0.24*	0.04	-0.03	0.05	-0.19*	0.22

[a] Data from rabbits that aborted, died or had total resorptions were omitted from calculations of means.
† Significant dose-related response, $p \leq 0.01$.
* Significantly different from control value, $p \leq 0.05$.

TABLE 5

MR-4512
HN-14673

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY
IN RABBITS GIVEN TERBACIL
BY GAVAGE ON DAYS 7-19 OF GESTATION

SUMMARY OF REPRODUCTIVE DATA

DOSE LEVEL (MG/KG)	CORPORA LUTEA	IMPLANTATIONS	RESORPTIONS	FETUSES LIVE	FETUSES DEAD	MEAN LIVE FETAL WEIGHT (G)
0	10.4	8.1	1.1	6.9	0.1	44.2
30	10.2	8.5	0.5	8.0	0.1	43.2
200	9.5	6.8	0.6	6.2	0.0	44.1
600	10.4	8.4	2.4	5.8	0.2	36.9*

* Significantly different from control value, $p \leq 0.05$.

TABLE 6

MR-4512
HN-14673

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY
IN RABBITS GIVEN TERBACIL
BY GAVAGE ON DAYS 7-19 OF GESTATION

INCIDENCE OF FETAL MALFORMATIONS

	DOSE LEVELS (MG/KG)			
	0	30	200	600
NO. EXAMINED (FETUSES/LITTERS)	70/10	136/17	80/13	29/4
External				
No. affected (fetuses/litters)	0/0	0/0	0/0	2/1
Tail short	...	...	...	2/1[a]
Visceral				
No. affected (fetuses/litters)	1/1	4/2	1/1	2/1
Thyroid - hypoplastic	1/1[b]	...	...	...
Pancreas - hypoplastic	...	3/1[c,d]	...	...
Cleft palate	...	...	...	1/1[e]
Microphthalmia	...	3/2[c,d]	...	...
Hydrocephaly	...	1/1[c]	1/1	2/1[e]
Distended superior sagittal sinus	...	1/1[c]	...	...
Skeletal				
No. affected (fetuses/litters)	4/3	11/8	2/2	5/3
Vertebra: malformed	1/1[b]	1/1	1/1	1/1[a]
absent	...	2/1	...	1/1[a]
Hyoid, cornu angular	1/1	2/1	1/1	...
Sternebra fused	2/2	5/5	...	3/2[a]
Ribs: fused†	...	1/1	...	2/2[a]
TOTAL AFFECTED (FETUSES/LITTERS)	4/3	12/8	3/3	7/3
AVG. % MALFORMED FETUSES/LITTER (±S.E.M.)	5.8 (±3.20)	9.0 (±2.84)	6.0 (±3.95)	16.5 (±8.30)

† Significant dose-related response, $p \geq 0.05$.
a-e Each letter represents a fetus that has multiple malformations.

MR-4512
EM-14673

TABLE 7

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY IN RABBITS GIVEN TERBACIL BY GAVAGE ON DAYS 7-19 OF GESTATION

INCIDENCE OF FETAL VARIATIONS

	DOSE LEVELS (MG/KG)			
	0	30	200	600
NO. EXAMINED (FETUSES/LITTERS)	70/10	136/17	80/13	27/3[a]
DEVELOPMENTAL VARIATIONS				
External				
No. affected (fetuses/litters)	16/7	16/10	14/6	8/3
Subcutaneous hemorrhage	16/7	16/10	14/6	8/3
Visceral				
No. affected (fetuses/litters)	3/2	4/3	4/3	1/1
Gall bladder - bifurcated	...	1/1	...	...
Left carotid artery branches off of the innominate artery	3/2	3/2	4/3	1/1
Skeletal				
No. affected (fetuses/litters)	56/10	100/17	53/12	23/3
Skull - hole in parietal bone	...	...	1/1	...
Sternebra - misaligned	2/2	3/2	2/2	...
- bipartite	1/1	...	...	1/1
Rib - extra ossification center	41/9	74/15	38/11	16/3
- rudimentary	21/10	27/13	17/9	4/2
- extra	17/9	43/13	24/9	18/3**
- thickened	...	...	1/1	...
TOTAL FETUSES WITH DEVELOPMENTAL VARIATIONS	59/10	106/17	58/12	23/3
AVG. % AFFECTED FETUSES/LITTER (±S.E.M.)	88.0 (±3.54)	78.2 (±4.41)	67.9 (±8.19)	87.2 (±7.93)

TABLE 7 (CONT.)

MR-4512
HN-14673

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY
IN RABBITS GIVEN TERBACIL
BY GAVAGE ON DAYS 7-19 OF GESTATION

INCIDENCE OF FETAL VARIATIONS

VARIATIONS DUE TO RETARDED DEVELOPMENT	DOSE LEVELS (MG/KG) 0	30	200	600
External				
No. affected (fetuses/litters)	0	0	0	0
Visceral				
No. affected (fetuses/litters)	1/1	1/1	1/1	2/2
Lung - intermediate lung lobe absent	1/1	1/1	1/1	2/2
- lobes partially separated	...	1/1	...	...
Skeletal				
No. affected (fetuses/litters)	39/10	87/17	47/11	18/3
Centrum - hemi	...	...	...	1/1
Sternebra - partial or no ossification	32/8	52/16	37/10	9/3
- hemi	...	3/2	...	...
Vertebral Arch - partial or no ossification	1/1	1/1	1/1	...
Metcarpal - partial or no ossification	2/1	12/4	...	...
Phalanges - partial or no ossification†	2/1	4/2	1/1	3/3*
Tarsal - partial or no ossification	...	...	...	1/1
Pubis - partial or no ossification	13/4	35/8	22/7	13/3*
Hyoid - partially ossified	11/5	30/10	6/4	4/2
TOTAL WITH VARIATIONS DUE TO RETARDED DEVELOPMENT	40/10	88/17	47/11	18/3
AVG. % FETUSES WITH VARIATIONS DUE TO RETARDED DEVELOPMENT (±S.E.M.)	53.5 (±11.95)	66.1 (±6.74)	54.8 (±8.86)	69.0 (±9.08)
TOTAL WITH VARIATIONS	64/10	123/17	73/13	23/3
AVG. % FETUSES WITH VARIATIONS (±S.E.M.)	90.6 (±3.40)	90.4 (±2.78)	87.4 (±5.08)	87.2 (±7.93)

TABLE 7 (CONT.)

MR-4512
HN-14673

EMBRYO-FETAL TOXICITY AND TERATOGENICITY STUDY
IN RABBITS GIVEN TERBACIL
BY GAVAGE ON DAYS 7-19 OF GESTATION

INCIDENCE OF FETAL VARIATIONS

[a] Variations in malformed fetuses are not tabulated. Thus the litter of doe 18122 was excluded from calculations since it contained malformed fetuses only.
† Significant dose-related response, $p \leq 0.05$.
* Significantly different from control value, $p \leq 0.05$.
** Significantly different from control value, $p \leq 0.01$.

DER #5

ATTACHMENT 4

Terbacil: 3-Generation Reproduction Study in Rats
E.I. du Pont de Nemours & Company. 1967. MRID No. 00060852.
HED Doc. No. 000706, 003401, 007177.

83-4 007177

Reviewed by: Joycelyn Stewert, Ph.D.
Section II, Tox. Branch I (IRS)(H7509C)
Secondary reviewer: Marion Copley, D.V.M.
Section II, Tox. Branch I (IRS) (H7509C)

Review dates: 9/7/1967 C. Berry, DHEW; 12/20/1973 D. Ritter, Tox. Branch

DATA EVALUATION REPORT COVER

STUDY TYPE: Reproduction-Rat TOX. CHEM. NO.:821A

ACCESSION NUMBER: N/A MRID NO.: 00039003
00060852

TEST MATERIAL: 3-tert-butyl-5-chloro-6 methyluracil 80%

SYNONYMS: Herbicide 732

STUDY NUMBER(S): 125-012

SPONSOR: E.I. duPont de Nemours and Co.
Wilmington, Delaware

TESTING FACILITY: IRDC
Mattawan, Michigan

TITLE OF REPORT: Three Generation Reproduction Study in Rats

AUTHOR(S): Buller, R.H. and Geil, R.G.

REPORT ISSUED: 3/23/1967

Classification: Mimimum

CONCLUSION: The previous reviews (attached) accurately represent the results of the study. This reviewer concurs with the evaluation of the study in the review by D. Ritter, 12/20/1973, Toxicology Branch document 000706. Body weight gain was decreased in male rats at both dosage levels studied. The NOEL for reproductive toxicity was 250 ppm (HDT). The study is deficient by current standards. However, considering the study design, and the lack of reproductive toxicity shown in the study, it has been decided to accept this three generation study in place of the two generation study which is required under Subdivision F Guidelines.

The study showed the following deficiencies:

1. Only ten male rats/group were used in the study. However the study was carried out for three generations instead of two.

2. Histopathology was limited to the F_{3b} generation. However, the reproductive organs showed no compound related toxicity.

In accepting this study, data was also considered from the ~~mouse~~ mouse chronic/oncogenic study in which terbacil 97.8% was admin-

istered at doses up to 7500 ppm for two years, and in which no adverse reproductive effects were seen (MRID 00126770).

Three Generation Rat Reproduction Study (125-012)

Methods:

Terbacil was fed through three generations, two litters per generation, to Charles River CD rats at 0, 50 and 250 ppm. 10 males and 20 females per group were used. Rats from the second litter of each generation served as parents for the succeeding generation. All animals were maintained on diet for 100 days prior to mating, then 2 females were placed with one male for three weeks. Three weeks later all litters were weaned and studied. Five days following weaning of the first litter, females were again bred to different males and a second litter was thus produced.

All animals were observed for appearance and behavior and body weight and food consumption was recorded at weekly intervals.

The first litters in each generation were examined grossly and destroyed. Rats from second litters served as parents for the next generation and were placed on diet for 100 days prior to mating, as before.

Special observations on all offspring were made and included: fertility, embryo development, abortion, casting of litters, live births, litter size, viability and pup survival (see Table I).

All pups were examined for possible teratogenic effect.

At weaning, 10 male and 10 female pups from each control and treated group from the F_{3b} litter were sacrificed with chloroform and subjected to necropsy examination. Major organs were weighed and representative tissues from each rat were collected into 10 per cent neutral buffered formalin for subsequent histologic processing and microscopic examination.

Microscopic Examination:

The following tissues from each of 10 male and 10 female rats from the control and each treated group were paraffin embedded, sectioned, stained with hematoxylin and eosin and examined microscopically (*organ weights obtained):

brain*	heart*	pancreas
spinal cord	spleen*	liver*
peripheral nerve	thymus*	kidney*
pituitary*	bone marrow	urinary bladder
thyroid*	stomach	testis or ovary*
adrenal*	small intestine	skeletal muscle
lung*	large intestine	bone

Results:

No abnormalities that could be attributed to treatment were seen in any of the parameters measured. Table I summarizes the Indices of Reproduction. A decrease in the Fertility Index (Pregnancies/matings) was noted for the females bearing the 250 ppm F_{2b} litter. There was a decrease in the rate of body weight gain in the males servicing these dams. Other indices of reproduction were not appreciably altered by treatment.

Histological examination of representative tissues failed to reveal compound-related effects.

Conclusions:

Although there was a significant reduction of Fertility Index in the females casting the F_{2b} litter, this could be attributed to a secondary effect on the servicing males, since these failed to thrive as evidenced by failure of normal body weight gain. Unfortunately, daily vaginal smears of mating females were not taken; thus there is no direct evidence that mating in fact occured, although all the other groups demonstrated satisfactory fertility indices. Therefore, since the aberrent values are confined to the one group, we conclude that they do not represent a compound effect, and we thus find that the NEL for this study is 250 ppm.

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TABLE I

INDICES OF REPRODUCTION IN THE RAT

TERBACIL

Litter	Diet ppm	Fertility (a)	Gestation (b)	Viability (c)	Lactation (d)	Litter size
F_{1a}	0	85%	100%	95%	95%	11.8
	50	90%	100%	96%	89%	10.9
	250	90%	100%	92%	87%	13.4
F_{1b}	0	85%	100%	94%	82%	12.5
	50	61%	100%	94%	63%	10.2
	250	80%	100%	93%	71%	12.1
F_{2a}	0	70%	93%	95%	99%	11.9
	50	90%	100%	97%	96%	10.2
	250	60%	100%	92%	99%	10.0
F_{2b}	0	70%	100%	98%	89%	10.1
	50	85%	100%	96%	93%	11.1
	250	45%	100%	89%	91%	11.6
F_{3a}	0	90%	100%	98%	96%	11.1
	50	90%	100%	100%	96%	11.9
	250	90%	100%	97%	95%	11.7
F_{3b}	0	76%	100%	96%	92%	10.4
	50	72%	100%	97%	91%	12.1
	250	100%	95%	93%	84%	12.2

(a) Pregnancies/Matings (b) Litters born/Pregnancies (c) Pups surviving 4 days/pups born
(d) Pups weaned/Pups at 4 days

ACBERRY:mtw
September 7, 1967

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Three Generation Rat Reproduction Study Method

30 male and 60 female albino rats were used for this study. The rats were divided into one control and two test groups of ten males and twenty females each and were selected and grouped in such a manner that the average group body weights were similar for each sex. Herbicide 732 was incorportated into the standard powdered laboratory diet of Purina Laboratory chow at concentrations of 50 or 250 ppm of the active ingredient. The control group of rats received the same powdered diet of Purina Laboratory chow but without Herbicide 732. After an initial 100 days period of feeding all the control and test rats were mated for 21 days by housing two females with one male throughout the study. After the three week mating period the rats were separated again and individually housed. Three weeks were allowed for gestation and an additional three weeks for nursing prior to weaning. Following the five day period of rest after weaning the parental rats were again mated as above except that a different male was paired with two females within each respective group. As in the first breeding cycle three weeks were allowed for mating, three weeks gestation, and three weeks for nursing the pups prior to weaning. The pups from the first mating (F_{1a}) were examined for abnormalities and sacrificed. Representative pups were necropsied and examined for gross signs of pathology. After weaning the pups from the second litter (F_{1b}) the parental (P_1) rats were sacrificed and discarded. Selections

were made of 20 females and 10 male rats from each respected group of the F_{1b} litter to serve as the second (P_2) generation parental rats. The remaining pups in each group were examined for abnormalities and discarded. Selective pups were necropsied and examined grossly for signs of pathology.

Second Generation (P_2)

After weaning the F_{1b} pups which were selected for the P_2 generation were continued on a diet for 100 days and then mated in the same manner described above for the P_1 generation. The pups from this mating (F_{2a}) were examined for abnormalities and sacrificed. Representative pups were necropsied and examined for gross signs of pathology. After a five day rest period the rats were again mated as described above. The F_{2b} offspring were nursed for 21 day and then weaned. The P_2 parental rats were sacrificed and discarded. Selections were made of 20 females and 10 males from each respected group of the F_{2b} litter to serve as the third (P_3) generation parents. Remaining pups in the F_{2b} litter were examined for abnormalities, sacrificed and discarded. Representative pups were necropsied and examined grossly for signs of pathology.

Third Generation (P_3)

After a 100 days of feeding the test diet the F_{2b} control and test groups of rats were mated and two litters raised in identical fashion in that described above. The first litter (F_{3a}) was sacrificed and discarded.

Representative pups in the F_{3a} litters were necropsied and examined for gross pathology. After weaning the F_{3b} litter one female and male pup from each of ten litters from the control and test groups were sacrificed, necropsied and representative tissues selected for histopathologic examination. The usual observations were made on a daily and weekly basis and in addition specific observations were made during and after each breeding cycle for abnormalities in reproduction and teratogenesis.

Results

General behavior and appearance--No unusual alterations and behavior in appearance were observed in any of the three generations of parental rats in the study. Both sexes of all three generations exhibited an occasional oral ocular and/or nasal porphyrin discharge and respiratory congestion. In addition, an occasional animal in the control and test groups exhibited an odd formed mass at various sites on the body surface. Also seen was an occasional incidence of alopecia. No signs however, were seen which could be related to the feeding of Herbicides 732 in the diet.

Body weights P_1 generation rats--The gain in body weight of the male rats in both of the test groups in the P_1 generation was slower than the control male rats. Differences in group body weight between control and test groups did not exceed 15%. There was no apparent dose relationship.

Female rats in the test group of the P_1 generation compared favorably with the control rat group throughout this portion of the study.

P_2 Generation Parental Rats--the gains in body weight exhibited by the female rats in both test groups and the male rats at the 50 ppm dietary level of Herbicide 732 was slightly less than the control rat. The difference did not exceed 10% of any point in this period of the study. The male rat group at the 250 ppm dietary level of Herbicide 732 exhibited a significant difference in body weight in the control rat group from the 41st week of the study onward. This difference obtained a maximum of 17.2% in the 67th week.

P_3 Generation Parental Rats--male rats in the 50 ppm test group and female rats in both test groups exhibited weight gains during the third generation which compared favorably to their respective control rat groups. Male rats at the 250 ppm dietary level exhibited a 10% inhibition in body weight gain as comparison to the P_3 control male rat group in the 82nd week of the study. This difference increased to 15% in 87th week with a plan to work for the remainder of this phase of the study.

Survival

In the P_1 generation two control rats, one male rat at the 50 ppm level and two male rats at the 250 ppm dietary level did not survive this study. One control female rat and three female rats of the 50 ppm dietary level also did not survive on the P_1 generation. All female rats at the 250 ppm dietary level survived this study.

In the P_2 generation only one male control rat did not survive the study. One male rat at the 50 ppm dietary level and three control female rats in the P_3 generationd did not survive the study.

Food Consumption

Male parental rats at the 250 ppm dietary level appeared to eat slightly less food in grams per rat per week, but not in grams/kg/day in all generations in this study. No meaningful differences in food consumption were found between control and test male rats at the 50 ppm dietary level, or between the control and either test group of female rats in any of the three generations of parents.

Breeding Cycle

Reproduction -- Data obtained from both breeding cycles of all three generations did not reveal abnormalities relative to fertility of the parental male and female rats, development of the embryo and fetus, abortion, delivery, live births, size of the litters, viability of the newborn, survival of the pups to weaning or growth of the pups during the nursing period.

The fertility index of the female rats at the 250 ppm dietary level during the F_{2B} mating was found to be lower than the control female rats; however, the index for this group of test rats is well within the range which has been obtained from control female rats in the second litter mating from many similar studies in this laboratory.

Teratogenesis

Gross examination of those pups surviving at weaning from both litters of all three generations did not reveal any evidence of abnormalities.

Terminal Pathological Studies

F_{3B} litter--Extensive gross and microscopic examinations revealed the following, gross pathology in organ weight; no compound related gross pathologic leisons were observed at necropsy and pups from either treated group. Because of the wide variations in weights of individual pups from both the control and treated groups no significance was attached to slight variations in relative mean organ weights between these groups. Although some of the relative organ weights expressed as per cent body weights seemed to increase with increase in dose it must be recalled that the body weights, especially at 250 ppm, had decreased and this would falsely elevate the per cent body weight organ weights.

Gross Pathology

No compound related histopathologic leisons were observed in any tissues examined from any pups from either treated group, however, in the control at 50 ppm group there was slight hepatocyte vacuolation and/or hematopoesis noted in the liver. In the 250 ppm, in addition to slight hepatocyte vacuolation and hematopoesis there are two recorded incidences of slight portal lymphocytic infiltration. One of the recorded cases of hepatocyte vacuolation was treated as moderate in one of the B_1 female rats. The changes in the 50 and 250 ppm groups are probably not any more striking than the changes in the control group.

Herbicide 732: Three-Generation Reproduction Study in the Rat.

TABLE 14. Summary of Reproduction and Lactation Data - P_1 Generation, First Litter (F_{1A}).

Reproduction Cycle/Group	Fertility		Reproduction Data at Birth					Gestation		Viability		Lactation		Pup Data at Weaning	
	Pregnancies/ Matings	Index (%)	Av. No. Pups/ Litter	Total Born M	Total Born F	Total Born U*	Av. Pup Wgt. Gms.	Litters Born/ Pregnancies	Index (%)	Pups Surv. at 4 Days/ Pups Born	Index (%)	Pups Weaned/ Pups at 4 Days	Index (%)	No. Weaned	Av. Wt.
Control P_1 Generation, 1st Litter Mating (F_{1A})	17/20	85	11.8	99	101	0	6.7	17/17	100	190/200	95	181/190	95	181	44.2
50 ppm. P_1 Generation, 1st. Litter Mating (F_{1A})	18/20	90	10.9	95	100	1	6.6	18/18	100	188/196	96	167/188	89	167	44.7
250 ppm. P_1 Generation, 1st Litter Mating (F_{1A})	18/20	90	13.4	136	102	3	6.4	18/18	100	222/241	92	194/222	87	194	45.3

*Sex Undetermined.

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Herbicide 732: Three-Generation Reproduction Study in the Rat.

TABLE 15 Summary of Reproduction and Lactation Data - P_1 Generation, Second Litter (F_{1B}).

Reproduction Cycle/Group	Fertility: Pregnancies/ Matings	Fertility: Index (%)	Reproduction Data at Birth: Av. No. Pups/ Litter	Total Born: M	Total Born: F	Total Born: U*	Av. Pup Wgt. Gms.	Gestation: Litters Born/ Pregnancies	Gestation: Index (%)	Viability: Pups Surv. at 4 Days/ Pups Born	Viability: Index (%)	Lactation: Pups Weaned/ Pups at 4 Days	Lactation: Index (%)	Pup Data at Weaning: No. Weaned	Pup Data at Weaning: Av Wgt.
Control P_1 Generation, 2nd Litter Mating (F_{1A})	17/20	85	12.5	99	99	2	6.6	16/17**	94	187/200	94	154/187	82	154	43.2
50 ppm. P_1 Generation, 2nd Litter Mating (F_{1A})	11/18	61	10.2	60	50	2	6.7	11/11	100	105/112	94	66/105	63	66	44.1
250 ppm. P_1 Generation, 2nd Litter Mating (F_{1A})	16/20	80	12.1	103	88	2	6.4	16/16	100	180/193	93	127/180	71	127	43.4

*Sex Undetermined. **One pregnant female succumbed prior to delivery.

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Herbicide [illegible] — Three-Generation Reproduction Study in the Rat.

[illegible] — Summary of Reproduction and Lactation Data - F_1 Generation, First Litter (F_{2A})

Reproduction Cycle Group	Fertility: Pregnancies/Matings	Fertility: Index (%)	Reproduction Data at Birth: Av. No. Pups/Litter	Total Born: M	Total Born: F	Total Born: U[*]	Av. Pup Wgt. Gms.	Gestation: Litters Born/Pregnancies	Gestation: Index (%)	Viability: Pups Surv. at 4 Days/Pups Born	Viability: Index (%)	Lactation: Pups Weaned/Pups at 4 Days	Lactation: Index (%)	Pup Data at Weaning: No. Weaned	Pup Data at Weaning: Av. Wgt.
Control F_2 Generation, 1st Litter Mating (F_{2A})	14/20	70	11.9	66	87	2	6.6	13/14[a]	93	148/155	95	146/148	99	146	43.8
50 ppm. F_2 Generation, 1st Litter Mating (F_{2A})	18/20	90	10.2	86	98	0	6.8	18/18	100	179/184	97	172/179	96	172	46.0
250 ppm. F_2 Generation, 1st Litter Mating (F_{2A})	12/20	60	10.0	65	55	0	[illegible].0	12/12	100	10/120	92	109/110	99	109	48.3

[*] Sex Undetermined. [a] One treated parental female, apparently pregnant, failed to deliver.

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Herbicide 732: Three-Generation Reproduction Study in the Rat.

TABLE 38. Summary of Reproduction and Lactation Data - F_2 Generation, Second Litter (F_{2B}).

Reproduction Cycle/Group	Fertility		Reproduction Data at Birth					Gestation		Viability		Lactation		Pup Data at Weaning	
	Pregnancies/ Matings	Index (%)	Av. No. Pups/ Litter	Total Born M	Total Born F	Total Born U[A]	Av. Pup Wgt. gms.	Litters Born/ Pregnancies	Index (%)	Pups Surv. at 4 Days/ Pups Born	Index (%)	Pups Weaned/ Pups at 4 Days	Index (%)	No. Weaned	Av. Wgt.
Control F_2 Generation, 2nd Litter Mating (F_{2B})	14/20	70	10.1	0	75	1	6.8	14/14	100	139/142	98	124/139	89	124	47.9
50 ppm. F_2 Generation, 2nd Litter Mating (F_{2B})	17/20	85	11.1	102	86	0	6.6	17/17	100	180/188	96	167/180	93	167	45.7
250 ppm. F_2 Generation, 2nd Litter Mating (F_{2B})	9/20	45	11.6	60	43	1	6.6	9/9	100	93/104	89	85/93	91	85	42.7

[A] Sex Undetermined.

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Herbicide 732: Three-Generation Reproduction Study in the Rat.

TABLE 9[illegible]. Summary of Reproduction and Lactation Data - P_3 Generation, First Litter (F_{3A})

Reproduction Cycle/Group	Fertility		Reproduction Data at Birth					Gestation		Viability		Lactation		Pup Data at Weaning	
	Pregnancies/ Matings	Index (%)	Av. No. Pups/ Litter	Total Born M	Total Born F	Total Born U*	Av. Pup Wgt. Gms.	Litters Born/ Pregnancies	Index (%)	Pups Surv. at 4 Days/ Pups Born	Index (%)	Pups Weaned/ Pups at 4 Days	Index (%)	No. Weaned	Av. Wgt.
Control P_3 Generation, 1st Litter Mating (F_{3A})	18/20	90	11.1	97	104	0	6.9	18/18	100	197/201	98	190/197	96	190	44.0
50 ppm P_3 Generation, 1st Litter Mating (F_{3A})	18/20	90	11.9	101	114	0	6.7	18/18	100	215/215	100	207/215	96	207	42.5
250 ppm P_3 Generation, 1st Litter Mating (F_{3A})	20/20	100	11.7	118	115	1	[illegible]	20/20	100	226/234	97	214/226	95	214	43.1

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Herbicide 732: Three-Generation Reproduction Study in the Rat.

TABLE 45. Summary of Reproduction and Lactation Data - P_3 Generation, Second Litter (F_{3B})

Reproduction Cycle/Group	Fertility		Reproduction Data at Birth					Gestation		Viability		Lactation		Pup Data at Weaning	
	Pregnancies/ Matings	Index (%)	Av. No. Pups/ Litter	Total Born M	F	U*	Av. Pup Wgt. Gms.	Litters Born/ Pregnancies	Index (%)	Pups Surv. at 4 Days/ Pups Born	Index (%)	Pups Weaned/ Pups at 4 Days	Index (%)	No. Weaned	Av. Wgt.
Control P_3 Generation, 2nd Litter Mating (F_{3B})	13/17	76	10.4	64	71	0	7.2	13/13	100	130/135	96	124/135	92	124	44.9
50 ppm P_3 Generation, 2nd Litter Mating (F_{3B})	13/18	72	12.1	78	79	0	6.4	13/13	100	153/157	97	139/153	91	139	43.5
250 ppm P_3 Generation, 2nd Litter Mating (F_{3B})	20/20	100	12.2	128	101	3	7.4	19/20	95	214/231	93	179/214	84	179	45.5

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Deborah Nelson Raven 7/30/81

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Historical Control

Herbicide 732: Three-Generation Reproduction Study in the Rat

TABLE 46. Summary of Rat Reproduction Data[1]

No. of Individual Studies	Reproduction Cycle/Group	Fertility Index		Reproduction Data at Birth					Gestation Index		Viability Index		Lactation Index		Pup Data at Weaning	
		Pregnancies/ Matings	Index	Av. No Pups/ Litter	Total Born M	Total Born F	Total Born U[2]	Av. Pup Wgt. Gms.	Litters Born/ Pregnancies	Index	Pups Surv. at 4 Days/ Pups Born	Index	Pups Weaned/ Pups at 4 Days	Index	No. Weaned	Average Weight
17	1st Litter	267/372	72	11.7	1553	1527	35	6.4	266/267	99.5	2920/3115	94	2421/2920	88	2521	42.1
	Range[3]		37-93	9.9-12.9				5.9-6.7		92-100		81-100		56-99		33.9-47.8
15	2nd Litter	201/326	64	11.3	1090	1097	61	6.4	194/201	96	2049/2187	91	1717/2049	83	1717	43.6
	Range[3]		14-90	8.5-13.2				5.[illegible]-6.9		80-100		76-99		38-100		39.2-50.1
3	3rd Litter	32/47	56	11.3	178	159	26	6.3	32/32	100	317/361	88	232/317	73	232	40.1
	Range[3]		53-61	10.9-11.7				5.9-[illegible]		100-100		79-97		51-86		36.9-45.4

NOTE: 1 - Data obtained from 17 separate reproduction studies conducted at the International Research and Development Corporation.

2 - Sex not determined because of mutilation.

3 - Range of means from individual studies.

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ATTACHMENT 5
Caswell
821A

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

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: 1/29/97

SUBJECT: ID#97VA0001 and 97MD0001 SECTION 18 EXEMPTION FOR USE OF **TERBACIL** ON **WATERMELONS** IN THE STATES OF **VIRGINIA AND MARYLAND**

DP Barcodes: D231995 and D231994 Caswell: 821A
Trade Name: Sinbar 80 WP Chem#: 012701
Reg#: 352-317 Class:Herbicide
40 CFR: 180.209
PRAT Case # 288197, 288227

TO: Pat Cimino/Robert Forrest, PM Team #41
ERMUS/RSB/RD (7505W)

FROM: G. Jeffrey Herndon
William Dykstra
William Cutchin
Pilot Interdisciplinary Risk Assessment Team
RCAB/HED (7509C)

THRU: Michael S. Metzger, Acting Chief
RCAB/HED (7509C)

INTRODUCTION

The Virginia Department of Agriculture and Consumer Services and the Maryland Department of Agriculture are proposing specific exemption for the use of terbacil (SINBAR 80WP) on watermelons for control of morningglory and other broadleaf weeds. A similar Section 18 use was previously granted in 1996. The proposed program will entail application of about 550 lbs.ai. on about 3000 acres (in each State), during the period from mid-April to mid-June, 1997.

RECOMMENDATION

Aggregate risk estimates do not exceed HED's level of concern. This Section 18 exemption should not pose an unacceptable aggregate risk to infants and children. Therefore, HED has no objection to the issuance of this Section 18 exemption for the use of terbacil on watermelons in the States of Maryland and Virginia. A time-limited tolerance at 0.4 ppm should be established to support this Section 18 specific exemption.

of Reregistration and tolerance reassessment, and when methodologies for determining common mode of toxicity and for performing cumulative risk assessment are finalized.

Determination of Safety for Infants and Children

The pre- and post-natal toxicology data base for terbacil is complete with respect to current toxicological data requirements.

In the rat developmental study, the NOEL and LOEL for developmental and maternal effects occurred at the same levels (12.5 and 62.5 mg/kg/day, respectively). PIRAT notes that the effects seen at the LOEL were more severe in the pups than the maternal effects. This indicates a potential special, pre-natal sensitivity. (*)

The results of the rabbit developmental study demonstrated that there were no developmental effects up to 600 mg/kg/day [highest dose tested].

There was no evidence of post-natal toxicity to infants and children, since the pup NOEL was 12.5 mg/kg/day [highest dose tested] in the 2-generation rat reproduction study.

The acute dietary MOE for females 13+ years was 2,500. This MOE is considered sufficient to protect infants and children against a pre- and post-natal toxicity from aggregate exposure to terbacil.

ATTACHMENT 6.

CASWELL FILE

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

MAY 30 1996

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RED Chapter for Terbacil: Toxicology

Tox. Chem. No.: 012701
Caswell No.: 821A
DP Barcode No.: D220526

TO: Paula Deschamps
RCAB

FROM: Melba S. Morrow, D.V.M. MSM 5/14/96
Review Section II, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Joycelyn E. Stewart, Ph.D. JS 5/23/96 KB 5/29/96
Section Head, Review Section II
Toxicology Branch I
Health Effects Division (H7509C)

Attached is the Toxicology Chapter for the Registration Eligibiligy Document (RED) for Terbacil. The compound is intended for use as a herbicide for selective weed control in food crops.

Human Health Assessment

1. Toxicology Assessment

The toxicology data base for Terbacil is adequate and will support the reregistration eligibility of this chemical.

a. Acute and Subchronic Toxicity

Terbacil 80% WP has been tested in acute oral toxicity studies with rats (Acc. Nos. 114693 and 24955) and has an acute oral LD50 of > 5,000 mg/kg (Toxicity Category IV). In an acute dermal toxicity study in rabbits, the LD50 was > 5,000 mg/kg (Toxicity Category IV), with no toxic signs noted (Acc. Nos. 114693 and 24955). Technical Terbacil (97.8%) was tested in an acute inhalation study in rats (MRID 00125700), which indicated that the LC50 was > 4.4 mg/L (Toxicity Category III). Technical Terbacil (96.1%) was tested in rabbits' eyes and produced only mild conjunctival effects, which cleared within 72 hours (Toxicity Category III). Although a primary dermal irritation study is not available on technical Terbacil, Toxicology Branch had indicated to the Registrant that if no dermal irritation was observed in a 21-day subchronic dermal study, then the requirements for the primary dermal irritation study would be satisfied (Tox. Doc. 003401). No dermal irritation was reported in that study (MRID 00125785). Terbacil is not a dermal sensitizing agent in guinea pigs (MRID 157-180).

The table below summarizes the values and toxicity categories for the various acute toxicity routes.

ACUTE TOXICITY DATA FOR TERBACIL

TEST	RESULT	CATEGORY
Oral LD_{50}	> 5000 mg/kg	IV
Inhalation LC_{50}	> 4.4 mg/L	III
Dermal LD_{50}	> 5000 mg/kg	IV
Eye Irritation	Mild conjunctival irritant up to 72 hours	III
Dermal Irritation	Not a skin irritant	IV
Dermal Sensitization	Not a dermal sensitizer	

Subchronic oral toxicity was tested in a 90-day feeding study in rats (MRIDs 00039009 and 00068035). A NOEL of 100 ppm (equivalent to 5 mg/kg) and LOEL of 500 ppm, equivalent to 5 mg/kg (HDT) were established, based on increased absolute and relative liver weights, vacuolization and hypertrophy of hepatocytes. The data requirement for subchronic oral toxicity in a nonrodent was

satisfied by a 2-year feeding study in beagle dogs (MRID 00060851), in which a NOEL of 50 ppm (equivalent to 1.25 mg/kg) and LOEL of 250 ppm (equivalent to 7.2 mg/kg) were established, based on increased thyroid to body weight ratios, slight increase in liver weights, and elevated alkaline phosphatase levels.

Subchronic dermal toxicity was tested in a 21-day study in rabbits (MRID 00125785). Terbacil was applied to prepared skin of male and female rabbits at 5,000 mg/kg, 5 hours/day, 5 days/week. No systemic toxicity was observed; mild scaling and staining was reported at the test sites.

b. Chronic Feeding Toxicity

Terbacil 80% a.i. was administered to beagle dogs (4/sex/group) in the diet for 2 years, at doses of 50, 250, or 2,500/10,000 ppm, equivalent to 1.2, 7.0, 70/250 mg/kg (MRID 00060851). The NOEL was 50 ppm (1.2 mg/kg), and the LOEL was 250 ppm equivalent to 7.2 mg/kg, based on increased thyroid to body weight ratios, slight increase in liver weights, and elevated alkaline phosphatase levels. Relative liver weights were also increased at 2,500 and 10,000 ppm in dogs sacrificed at 1 year and 2 years.

A 2-year rat study (MRID 429876-01) was supplied to the Agency in response to the Registration Standard Data Call-In notice. In this study, Terbacil 97.4% a.i. was administered to male and female Sprague-Dawley Crl:CD BR rats at dietary levels of 0, 25, 1500, or 7500 ppm (approximate doses for males of 0, 0.9, 58, and 308 mg/kg/day and for females of 0, 1.4, 83, and 484 mg/kg/day). Ten animals/sex/dose were sacrificed by study design at 12 months. Excessive mortality was observed in the control and low dose groups, and the study was terminaated at 23 months. No clinical signs relating to dosing were reported. Body weight was significantaly reduced in males receiving 7500 ppm and in females receiving 1500 and 7500 ppm throughout most of the study. At 51 weeks, body weight gain in males receiving 7500 ppm was 13% lower than controls and in females receiving 1500 ppm and 7500 ppm gains were 18% and 39% lower than in controls. No toxicologically significant changes in hematology parameters were observed. Serum cholesterol was significantly increased in high dose females at all reporting periods. A marginal increase was observed in mid dose females. A slight increase was observed in 7500 ppm males at 18 and 24 months but only the increase at 18 months was significant compared to controls. At 1500 ppm, a significant increase in the mean liver to body weight ratio was observed in females at 12 months (16%) and at study termination (21%). At termination, the liver weight increase was accompanied by a marginally increased incidence of centrilobular hepatocyte hypertrophy (minimal) and a 20% decrease in mean body weight. At 7500 ppm, significant increases in liver to body weight ratios were seen in both sexes at 12 and 23 months and mean liver weight in males was 20% increased

compared to controls at study termination. Centrilobular hypertrophy as well as fatty changes were seen in both sexes at the high dose and an increase in biliary hyperplasia was observed in high dose females. Eosinophilic foci of cellular alteration in the liver were increased in incidence in dosed groups of male and females with a significant trend. However, this is of equivocal importance because it was not accompanied by hypertrophic or hyperplastic changes or hepatocellular tumors. The systemic NOEL is 25 ppm (0.9 mg/kg for males and 1.4 mg/kg for females) and the LOEL is 1500 ppm (56 mg/kg for males and 83 mg/kg for females) based on the liver effects and decreased body gain in females. The study was conducted at adequate dosages as demonstrated by the decrement in body weight gain in both sexes. There was no evidence of increased tumor incidence in the treated animals when compared to the controls.

c. Carcinogenicity

Terbacil has been tested in a chronic 2-year feeding/ oncogenicity study in mice (MRID 00126770,) at doses of 0, 50, 1250, or 5000/7500 ppm (equivalent to 7, 179, 714/1071 mg/kg) The increase in dose occurred after week 54. Body weight and survival were decreased in the high-dose males, and liver weight was increased in the high-dose mice of both sexes. Mid- and high-dose males exhibited mild hypertrophy of the centrilobular hepatocytes, and decreased pituitary weights. Pituitary weight was also decreased in high-dose females. There was an increased incidence of lung neoplasms (adenomas and adenocarcinomas) in all treated male mice, which was not dose-related; in addition, these tumors were within the range of similar tumors observed in historical control mice. Additional information (MRID 42031601), provided by the registrant demonstrated that, under the conditions of this study, administration of terbacil did not significantly increase the incidence of any proliferative hepatocellular carcinoma, single/multiple adenomas, or foci of cellular alteration, or combined hepatocellular adenomas and carcinomas, in either sex. Toxicology Branch I determined that the Guideline requirements 83-2 were satisfied by this information (Tox. Doc. 009441).

Terbacil was also tested in the rat (MRID 429876-01, described under chronic feeding toxicity studies, above). Under the study conditions, terbacil did not induce any increase in tumor incidence in the treated animals.

d. Developmental Toxicity

Terbacil has been tested in rats and rabbits for its potential to produce developmental toxicity. Rats (MRID 0003900010) were fed 0, 250, 1,250 or 5,000 ppm (equivalent to 0, 12.5, 62.5 or 250 mg/kg) of Terbacil in the diet from days 6 through 15 of gestation. The study was graded core-Supplementary, because of concerns raised about an increased number of post-implantation losses and increased

pre-

Developmental NOEL = 250ppm (LOEL = 250ppm based on dtg. ↓ mean no. of implantations and live fetuses, apparently due to fetal loss occurring before or near the time of implantation

hydronephrosis in fetuses from the treated dams. The concerns were addressed by duPont in a response to the 1982 Registration Standard, and the response was accepted (Tox. Doc. No. 0030401). The NOEL for teratogenicity was > 5,000 ppm (250 mg/kg); maternal NOEL was 250 ppm 12.5 mg/kg), based on decreased body weight at 1,250 ppm (62.5 mg/kg).

Rabbits were given doses of Terbacil of 0, 30, 200, or 600 mg/kg by gavage, on gestation days 7 through 19 (MRID 001509450). Maternal and fetotoxic NOEL was 200 mg/kg, based on maternal deaths (5 died and 2 were sacrificed in extremis) and decreased live fetal weights in the high dose group. The NOEL for teratogenicity was > 600 mg/kg.

e. Reproductive Toxicity

Terbacil was tested in male and female rats at dietary levels of 50 or 250 ppm (equivalent to 2.5 or 12.5 mg/kg), over three generations. The first litter of each generation was discarded, and the second litter bred to produce the next generation. The study was reviewed for the 1982 Registration Standard, and graded core-Supplementary, based on testing only 2 dose levels and the use of antibiotics on the test animals during the study. In addition, necropsy records were not available for the first litters, and the breeding records were incomplete. After addressing these concerns (Acc. No. 249455), the study was upgraded to core-Minimum (Tox. Doc. 003401), with a systemic NOEL of < 50 ppm (2.5 mg/kg) based on the reduction of body weight gain in males. The NOEL for reproductive toxicity was > 250 ppm (12.5 mg/kg).

f. Mutagenicity

Terbacil technical (96.1%) was tested and found negative for clastogenicity in a chromosomal aberration study in rat bone marrow cells, at doses up to 500 mg/kg (MRID 00157181). It was also negative in a CHO (HGPRT) gene mutation assay (MRID 260460) when tested up to cytotoxic levels, with and without S-9 activation (cytotoxicity > 3.0 mM without activation; > 2.75 mM with activation). Terbacil technical was also negative for unscheduled DNA synthesis when tested up to cytotoxic levels (5 mM) in the rat.

g. Metabolism

Terbacil was tested in rats (MRID 40104702) in single doses of 6.5 or 500 mg/kg; 97 to 103% of radioactivity was recovered within 5 days: 70-86% in urine, and 28% in feces. The major metabolites were glucuronide, sulfate, and N-acetylcysteine conjugates. The primary metabolic pathway is hydroxylation of the 6-methyl group to form the alcohol, which is conjugated to form the glucuronide (35%

of the dose) and the sulfate derivatives (11%). Terbacil is also metabolized to the 5-hydroxy intermediate, which is further conjugated to form a sulfate derivative (17%).

h. Carcinogencity Classification

Terbacil was classified as E (no evidence of carcinogenicity in animal studies) with respect to its carcinogenic potential

i. Reference Dose

The reference dose (RfD) for systemic toxicity was determined for Terbacil as 0.013 mg/kg/day, by the HED RfD Committee in May, 1986. This was verified by the Agency Review Committee in June, 1986. The RfD was calculated from a two-year feeding study in dogs (MRID 00060851) in which the NOEL was 1.25 mg/kg/day (based on increased relative liver weights and increased serum alkaline phosphatase), and an uncertainty factor of 100. The RfD of 0.013 mg/kg/day was reaffirmed by the HED RfD Committee on September 1, 1994.

j. Other Toxicological Considerations

The developmental toxicity study in Sprague Dawley rats was used to establish the acute dietary endpoint and dose for risk assessment. The endpoint was established in a dietary study administered at doses of 0, 250, 1250, or 5000 ppm (12.5, 62.5, or 250 mg/kg/day) on gestation days 6 through 15. The NOEL for developmental toxicity was greater than 250 mg/kg (highest dose tested); however, embryotoxicity was reported at 62.5 mg/kg and consisted of decreases in the number of implants and live fetuses. The NOEL for embryotoxicity was 12.5 mg/kg. Although the compound was administered for a period that exceeded one day, the study was selected for determination of acute dietary risk because it could not be ascertained whether the embryotoxicity resulted from a single exposure or from cumulative exposures during the 10 day period that corresponded to organogenesis.

No short term occupational or residential risk estimate is required because the results of a 21 day dermal toxicity study conducted in rabbits demonstrated that at doses as high as 5000 mg/kg, there were no toxic signs or histopathological lesions that could be associated with administration of terbacil.

ATTACHMENT 7.

TOXICOLOGY ENDPOINT SELECTION DOCUMENT

TO: Elizabeth Doyle, DRES
Larry Dorsey, OREB
Debra Edwards, CCB
Caswell File
, CBTS
Edward Zager, CBRS
William Burnam, SAB
George Ghali, RfD Secretary

Chemical Name: Terbacil
Caswell No. 821A
PC Code: 5902-51-2

Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: _____ Date: _____

Branch Chief: _____ Date: _____

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Dermal Absorption Data (If available)

Dermal absorption data were not available for this chemical. It was assumed by the LTL committee that there would be 100% absorption.

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Acute Dietary Endpoint (One Day)

Study Selected - Guideline No.: 83-3a

MRID No.: 249455

Summary: In female Crl:CDBR (Sprague Dawley rats, terbacil was administered at dietary doses of 250, 1250 or 5000 ppm (12.5, 62.5 or 250 mg/kg) on gestation day 6 thru 15. The developmental NOEL was greater than 250 mg/kg (highest dose tested); however, embryotoxicity was reported at 62.5 mg/kg and consisted of a decrease in the number of implants and a decrease in the number of live fetuses. The NOEL for embryotoxicity was 12.5 mg/kg.

Endpoint and dose for use in risk assessment.
Embryotoxicity was the endpoint selected for risk assessment.

Comments about study and/or endpoint:

Although the compound was administered for a period that exceeded one day, the study was selected for the determination of acute dietary risk because it uncertain whether the observed embryotoxicity resulted from exposure on the first day of dosing or resulted from cumulative exposure during the 10 day period that corresponded to organogenesis.

This risk assessment is required.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

This risk assessment is not required.

The results of a 3 week dermal study conducted in rabbits demonstrated that at doses as high as 5000 mg/kg, there were no toxic signs or histopathological lesions that could be associated with the administration of the test material. Furthermore, in a 90 day feeding study in rats (doses tested: 100, 500 and 5000 ppm) there appeared to be low toxicity associated with the administration of the compound based on the observation of adaptive hepatic alterations of increased liver weight and hepatic vacuolation and hypertrophy at 500 ppm (25 mg/kg).

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Intermediate Term Occupational or Residential (1 Week to Several Months)

This risk assessment is not required for reasons stated under the short term occupational or residential section.

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Cancer Classification and Basis: This chemical was classified as an E with regard to its carcinogenic potential.

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R_fD and basis:

The RfD was 1.3 x 10-2 mg/kg-day, as determined by the HED RfD Committee.

The RfD was based on the results of a 2 year dog study in which the NOEL was 50 ppm (1.25 mg/kg). An uncertainty factor of 100 was used to account for inter and intra-species differences. In this study the effects were observed at 250 ppm (6.25 mg/kg) and included increased thyroid:body weight ratio, slight increase in liver weight and elevated alkaline phosphatase.

Study Type - Guideline No.: Chronic non-rodent 83-1(b)

MRID: 00060851

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Chemical:	**Terbacil**
PC Code:	**012701**
HED File Code	**13100 Other Tox Documents**
Memo Date:	**11/22/83**
File ID:	**TX003401**
Accession Number:	**412-03-0116**

HED Records Reference Center
06/30/2003