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HEALTH EFFECTS DIVISION
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **December 19, 2005**

MEMORANDUM

TXR No.: **0052491**

SUBJECT: Terbacil - Update DER executive summaries

FROM: Lisa Austin, Ph.D., Toxicologist
Registration Action Branch 1
Health Effects Division (7509C)

THROUGH: Pv Shah, Ph.D., Branch Senior Scientist
Registration Action Branch 1
Health Effects Division (7509C)

TO: Daniel Rosenblatt, Product Manager
RM-# 05
Registration Division (7505C)

DP Barcode: 313756 **PC Code:** 012701

Action Requested: The Registration Division (RD) requested Health Effects Division (HED) to perform a review of existing data and to update DER executive summaries where required for a section 3 registration of Terbacil. MRIDs of updated DER executive summaries are as follows: 00050467, 00152945, 00068035, 00060850, 00060851, 00060852 and 00126770. The action was successfully completed, and the citations of the updated DER executive summaries are listed here.

DEC 28 2005

1. **CITATIONS:**

Culik, R., Wood, C.K., Kaplan, A.M., et al. (1980) Teratogeneicity study in rats with 3-tert-butyl-5-chloro-6-methyluracil: Haskel Laboratory Report No. 481-79. E.I. duPon de Nemours & Co., Wilmington, Del. MRID Number 00050467. Unpublished.

Solomon, H. (1984) Embryo-fetal toxicity and teratogenecity study of terbacil by gavage in the rabbit: Medical Research Project No. 4512-001: Haskell Report No. 528-83. E.I. du Pont de Nemours & Co., Inc.,Haskell Laboratory for Toxicology and Industrial Medicine, Central Research and Development Department, Newark, NJ, 19711. MRID No. 00150945. Unpublished.

Wazeter, F.X., Buller, R.H., Geil, R.G. (1964) Ninety-day feeding study in the rat: IRDC No. 125-004. International Research and Development Corp. E.I. du Pont de Nemours & Co., Inc., Wilmington, Del. October 28, 1964. MRID No. 00068035. Unpublished.

Wazeter, F.X.; Buller, R.H.; Geil, R.G. (1967) Two-year feeding study in the albino rat: IRDC No. 125-010. International Research and Development Corp., E.I. du Pont de Nemours & Co. Wilmington,: March 17, 1967. MRID Number 00060850. Unpublished.

Wazeter, F.X.; Buller, R.H.; Geil, R.G. (1967) Two-year feeding study in the dog: IRDC No. 125-011. International Research and Development Corp., E.I. du Pont de Nemours & Co. Wilmington, DE. March 17, 1967. MRID Number 00060851. Unpublished.

Wazeter, F.X., Buller, R.H., Gei., R.G. (1967): U-2069: Three Generation Reproduction Study in the rat: IRDC No. 125-012. E.I. du Pont de Nemours & Co., Inc., Wilmington, Del. MRID No. 00060852. Unpublished.

Goldenthal, E, Homan, S., Richter, W. (1981) 2-year Feeding Study in Mice: Terbacil: 125-027. International Research and Development Corp., E.I. du Pont de Nemours & Co. Wilmington, DE; June 19, 1981. MRID Number 00126770. Unpublished.

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Terbacil **Two Year Chronic Toxicity (§83-1[a])**

EPA Reviewer: Lisa Austin, Ph.D. Signature: Lisa Austin
Registration Action Branch 1/HED (7509C) Date: 12/20/05
EPA Secondary Reviewer: Robert Mitkus, Ph.D. Signature: Robert J. Mitkus
Registration Action Branch 1/HED (7509C) Date: 12/20/05

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 0000703 for Original DER

NOTE:
This study was previously reviewed and classified as Core Minimum data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Two Year Chronic Toxicity - rat
OPPTS Number: 870.4100 OPP Guideline Number: §83-1a

DP BARCODE: D313756
PC CODE 012701
MRID NO: 00060850

TEST MATERIAL (PURITY): Terbacil (80%)

COMPOSITION/SYNONYM(S): 2,4(1H,3H)-Pyrimidinedione, 5-chloro-3-(1,1-dimethylethyl)-6-methyl
3-tert-butyl-5-chloro-6-methyluracil

CITATION: Wazeter, F.X.; Buller, R.H.; Geil, R.G. (1967) Two-year feeding study in the albino rat: IRDC No. 125-010. International Research and Development Corp., E I. du Pont de Nemours & Co. Wilmington,: March 17, 1967. MRID Number 00060850. Unpublished.

SPONSOR: E.I. du Pont de Nemours & Co.

EXECUTIVE SUMMARY: In this chronic oral toxicity study (MRID 00060850), Herbicide 732 technical grade (terbacil, 80% wettable powder) was administered in the diet to Charles River CD male and albino female rats (36/sex/group) at nominal doses of 0, 50, 250, or 2500-10000 ppm (approximately equivalent to 0, 2.5, 12.5 or 125-500 mg/kg/day) for 104 weeks. The high dose group (2500 ppm) received an increase in Herbicide 732 at increments of 500 ppm in the diet at biweekly intervals from the 28th -36th week of the study. Thereafter, the dietary level was increased by 1000 ppm until 10000 ppm was reached in the 46th week and remained at this dose for the remainder of the study.

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There were no treatment related effects on mortality, clinical signs, urinalysis, hematology and clinical chemistry.

Body weight in high dose males was decreased by 7-25% from week 69 onward, while high-dose females exhibited body weight decreases of 20-24% by the end of the study. Body weight and body weight gain at 50 and 250 ppm in male and female rats were comparable to controls.

Mean relative liver weights were increased 23-38% and 46-53% in male and female rats, respectively, in the 2500-10000 ppm treatment group. Relative kidney weights increased by 20-58% in the 2500-10000 ppm female rats. Relative ovary weight increased by 16-28% in the 250 ppm and 41-55% in the 2500-10000 ppm females sacrificed after 2 years of treatment. The result was dose-dependent. However, the change in relative ovary weight is not considered a toxicological effect in the absence of histological findings. Relative thyroid weights were dose-dependently increased by 21-57% in females at 2500-10000 ppm. Other organ weights were comparable to controls.

Histological examination revealed an increased incidence in hepatocyte centrilobular hypertrophy at 2500-10000 ppm in males and females (5/6 vs 0/14;16/16 vs 0/27, respectively) and vacuolation in females (6/16 vs 0/27), respectively, sacrificed at 2 years when compared to controls.

The LOAEL is 2500 ppm (equivalent to 12.5 mg/kg/day) based on increased mean relative liver weights, hepatocyte centrilobular hypertrophy in males and females and vacuolation in females. The NOAEL is 250 ppm (equivalent to 2.5 mg/kg/day).

The submitted study is classified as **acceptable/guideline (§83-1[b])** and satisfies the requirements for a chronic toxicity study in rats.

COMPLIANCE: No Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Note: The study was done prior to implementation of GLP Guidelines, therefore, does not fall under purview of either GLP Guidelines or Quality Assurance requirements.

Terbacil **90-Day Oral Toxicity (§82-1[a])**

EPA Reviewer: Lisa Austin, Ph.D. Signature: [signature] Date: 12/21/05
Registration Action Branch 1/HED (7509C)
EPA Secondary Reviewer: Robert Mitkus, Ph.D. Signature: [signature] Date: 12/21/05
Registration Action Branch 1/HED (7509C)

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR Nos. 0000704 and 0000705 for Original DER

NOTE:
This study was previously reviewed and classified as Core Minimum Data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Ninety-Day Oral Toxicity- Rat
OPPTS Number: 870.3150 OPP Guideline Number: §82-1a

DP BARCODE: D313756
P.C. CODE: 012701
MRID NO: 00068035

TEST MATERIAL (PURITY): Herbicide 732 (80%)

SYNONYMS: 3-tert-butyl-5-chloro-6-methyluracil; Herbicide 732; Sinbar Weed Killer

Wazeter, F.X., Buller, R.H., Geil, R.G. (1964) Ninety-day feeding study in the rat: IRDC No. 125-004. International Research and Development Corp. E.I. du Pont de Nemours & Co., Inc., Wilmington, Del. October 28, 1964. MRID No. 00068035. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00068035) Herbicide 732 (80% wettable product) was administered to 4-5 week old albino rats 10/sex/dose in the diet at dose levels of 0, 100, 500 and 5000 ppm.(equivalent to 0, 8, 20, 200 mg/kg/day).

There were no compound related effects on mortality, clinical signs, food consumption, hematology, clinical chemistry or urinalysis. Body weights were comparable across dose except for the 5000 ppm females, which showed 15% less body weight relative to controls by week 13.

Mean absolute liver weights were dose dependently increased by 22% relative to controls in males and females in the 5000 ppm group. Mean relative liver weights were significantly ($p<.001$) increased in males by 28% when compared to controls in the 5000 ppm group. Increased absolute and relative liver weights were also observed in 5000 ppm females; however, the effects were not dose-dependent. Other mean organ weights were comparable to controls.

Histopathology showed hepatocyte hypertrophy in the 5000 ppm animals (both sexes) with increased vacuolation of hepatocytes in males only. Focal necrosis, triaditis increased in incidence in a dose-dependant manner in females only (control, 2/10 vs 2, 3, 5/10 at 100, 500 and 5000 ppm, respectively).

The **LOAEL is 5000 ppm (200 mg/kg/day)**, based on the increased incidence of focal necrosis and triaditis in females, vacuolization in males and increased relative liver weight and hypertrophy of hepatocytes in both sexes. The **NOAEL is 500 ppm (20 mg/kg)**.

COMPLIANCE: No Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Note: The study was done prior to implementation of GLP Guidelines, therefore, does not fall under purview of either GLP Guidelines or Quality Assurance requirements.

TERBACIL **Two Year Chronic Toxicity (§83-1[b])**

EPA Reviewer: Lisa Austin, Ph.D. Signature: Lisa Austin
Registration Action Branch 1/HED (7509C) Date: 12/20/05
EPA Secondary Reviewer: Robert Mitkus, Ph.D. Signature: Robert J. Mitkus
Registration Action Branch 1/HED (7509C) Date: 12/20/05

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 0000703 for Original DER

NOTE:
This study was previously reviewed and classified as Core Minimum data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Two Year Chronic Toxicity - dog
OPPTS Number: 870.4100 OPP Guideline Number: §83-1b

DP BARCODE: D313756
PC CODE 012701
MRID NO: 00060851

TEST MATERIAL (PURITY): Herbicide 732 (Terbacil, 97.1%)

COMPOSITION/SYNONYM(S): 2,4(1H,3H)-Pyrimidinedione, 5-chloro-3-(1,1-dimethylethyl)-6-methyl
3-tert-butyl-5-chloro-6-methyluracil

CITATION: Wazeter, F.X.; Buller, R.H.; Geil, R.G. (1967) Two-year feeding study in the dog: IRDC No. 125-011. International Research and Development Corp., E.I. du Pont de Nemours & Co. Wilmington, DE. March 17, 1967. MRID Number 00060851. Unpublished.

SPONSOR: E.I. du Pont de Nemours & Co.

EXECUTIVE SUMMARY: In this chronic (104 weeks) oral toxicity study (MRID 00060851), Herbicide 732 (80%) was administered in the diet to beagle dogs (4/sex/group) for up to 104 weeks at nominal doses of 0, 50, 250, or 2500-10000 ppm (equivalent to ~0, 1.25, 6.25, 62.5/250 mg/kg/day). The high dose group (2500 ppm) received an increase in Herbicide 732 at increments of 500 ppm in the diet at biweekly intervals from the 28th -36th week of the study. Thereafter, dosing was increased by 1000 ppm until 10000 ppm was reached in the 46th week, and it remained at this dose for the remainder of the study

Hematological, clinical chemistry and urinalysis measurements were performed on all dogs at 0,

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1, 2, 3, 6, 12, 18 and 24 months. During the 54th week, 1 male and 1 female dog from each group were sacrificed and complete autopsies were performed. Selected organs were weighed and histopathologic examination was performed. At termination (104 weeks), all surviving dogs were sacrificed, necropsied and selected organs were weighed and histopathological examination was performed.

There were no mortalities and no significant differences in body weights. Mean body weight gain at 2500-10000 ppm was decreased by 0.1 kg in females at week 104, whereas it was increased by 3.3 kg in controls. The results for food consumption were equivocal.

There were no treatment related changes in hematology. Neutropenia and lymphocytosis were observed in one female dog at 250 ppm following 1 and 24 months of treatment. Non-segmented neutrophils were increased in male (4/4) and female(3/4) dogs at 2500-10000 ppm following 1 month of treatment. These measurements returned to levels comparable to control levels for the duration of the study and were therefore considered not toxicologically significant. Clinical chemistry consisting of glucose, protein, albumin, albumin to globulin ratio, urea nitrogen, alkaline phosphatase, bromsulphalein, total cholesterol, and SGOT,were comparable to controls values for all dogs. There was a transient increase in serum glutamic pyruvic transaminase (SGPT) in 1/3 control males and 1/3 female dogs in the 2500-10000 ppm group at 18 and 12 months, respectively. No remarkable abnormalities in urinalysis were observed between the controls and treated groups.

At the 2-year sacrifice, there was a dose dependent increase in relative liver weights in males (26%; n=3) and females (49%) in the high dose group relative to controls. Since clinical chemistry measurements and microscopic changes were comparable to controls, the increase in liver weight is considered an adaptive response. Relative thyroid weights were increased by 36 and 27% in males and females, respectively, in the 250 and 2500-10000 ppm groups when compared to controls. This increase was not considered toxicologically significant in the absence of histopathological findings. Moderate involution of the thymus was observed after 2 years in 1/3 males and 1/3 females at 2500-10000 ppm.

The LOAEL is 2500 ppm (equivalent to 62.5 mg/kg/day) based on thymic involution in male and female dogs. The NOAEL is 250 ppm (equivalent to 6.25 mg/kg/day).

The submitted study is classified as **acceptable/guideline (§83-1[b])** and does satisfy the requirements for a chronic toxicity study in dogs.

Note: The study was done prior to implementation of GLP Guidelines, therefore, does not fall under purview of either GLP Guidelines or Quality Assurance requirements.

Terbacil **Developmental Study (§83-3[a])**

EPA Reviewer: Lisa Austin, Ph.D. Signature: Lisa Austin
Registration Action Branch 1/HED (7509C) Date: 12/20/05
EPA Secondary Reviewer: Robert Mitkus, Ph.D. Signature: Robert J. Mitkus
Registration Action Branch 1/HED (7509C) Date: 12/20/05

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 0007091 for Original DER

NOTE:
This study was previously reviewed and classified as Minimum. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Developmental Toxicity in Rats
OPPTS Number: 870.3700 OPP Guideline Number: §83-3a

DP BARCODE: D313756
PC CODE 012701
MRID NO: 00050467

TEST MATERIAL (PURITY): Terbacil (96.6%)

COMPOSITION/SYNONYM(S): 3-tert-butyl-5-chloro-6-methyluracil
5-chloro-3-(1,1-dimethylethyl)-6-methyl-2,4 (1M, 3M) - pyrimidinedione
Sinbar
IND-732

CITATION: Culik, R., Wood, C.K., Kaplan, A.M., et al. (1980) Teratogeneicity study in rats with 3-tert-butyl-5-chloro-6-methyluracil: Haskel Laboratory Report No. 481-79. E.I. duPon de Nemours & Co., Wilmington, Del. MRID Number 00050467. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 00050467), terbacil (96.6 % a.i., Lot#: T-811115-D) was administered to pregnant ChR-CD© rats (27/dose) at dose levels of 0, 250, 1250. or 5000 ppm (0, 24, 104, and 392 mg/kg/day) by diet on gestation days (GDs) 6 through 15. No premature deaths occurred during the study. All dams were sacrificed on GD 21.

There were no effects of treatment on mortality, clinical signs or gross pathology.

A significant ($p<0.05$) decrease in average body weight gain was observed in the mid (38%)and high (68%) dose groups on GD 6-10, and in all treatment groups on GD 10-16 (15%, 21%, 18% at 250, 1250 and 5000 ppm, respectively). This was accompanied by a dose-dependent decrease in mean body weight that reached significant levels ($p\leq 0.05$) at 1250 (5%, 8%, 6 %) and 5000 ppm (10%, 10%, 8 %) on GD 10, 16, and 21, respectively, relative to controls. Food consumption was significantly decreased relative to controls in the mid (21%, 34%) and high (13%, 14%) dose groups on GD 6-10 and 10-16, respectively.

The maternal Lowest Observed Adverse Effect Level (LOAEL) was 250 ppm (24 mg/kg/day) based on decreased body weight gain. The maternal No Observed Adverse Effect Level (NOAEL) was not observed.

There was no significant difference between the control and treated groups in pregnancy rate or number of abortions, resorptions, or dead fetuses.

The mean number of implantations per litter was significantly lower ($p<0.05$) relative to controls (11.4 ± 2.3) at 5000 ppm (9.3 ± 3.1) and the effect was dose-dependent. The mean number of live fetuses per litter decreased in a dose-dependent manner and was significant ($p<0.05$) at 1250 (9.1 ± 3.2) and 5000 ppm (8.6 ± 2.9) relative to controls (10.9 ± 2.0). A dose-dependent increase relative to controls in litters with early resorption (24%, 24% and 48%) and litters partially resorbed (19%, 19%, and 29%) was observed at 250, 1250 and 5000 ppm, respectively. However, the differences were not statistically significant and the mean number of resorptions/litter and resorptions was similar across treatment group. There was a significant increase of fetuses with dilation of the renal pelvis and/or hydroureter observed in all treated groups (4/22, 6/22, 4/22) relative to control (0/19); these effects were not dose dependent. Additionally, the recorded incidences were within range of historical control values as reported by DuPont in a response to concerns regarding the increase in dilation of the renal pelvis and/or hydrourteter during the 1982 Registration Standard. The response was accepted (Tox. Doc. No. 003401). No statistically or biologically significant increases in gross and skeletal malformations were detected.

The developmental LOAEL is 1250 ppm (104 mg/kg) based on decreased number of live fetuses/litter. The developmental NOAEL is 250 ppm (24 mg/kg).

The developmental toxicity study in rats is classified **Acceptable/Non-guideline (§83-3[a])**, and **does not** satisfy the guideline requirements for a developmental toxicity study in the rat because of the following deficiencies: treatment occurred during GD 6-15 instead of GD 6-21, individual data on fetal sex and body weight, gravid uterine weight, body weight adjusted for gravid uterine weight. However, this study is adequate to evaluate the teratogenic susceptibility of rats to terbacil.

Terbacil **Developmental Study (§83-3[b])**

EPA Reviewer: Lisa Austin, Ph.D. Signature: Lisa Austin
Registration Action Branch 1/HED (7509C) Date: 12/20/05
EPA Secondary Reviewer: Robert Mitkus, Ph.D. Signature: Robert J. Mitkus
Registration Action Branch 1/HED (7509C) Date: 12/20/05

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 0004443 for Original DER

NOTE:
This study was previously reviewed and classified as Core Minimum Data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Developmental Toxicity Study [Rabbit]
OPPTS Number: 870.3700 OPP Guideline Number: §83-3b
DP BARCODE: D313756
P.C. CODE: 012701
MRID NO: 00150945

TEST MATERIAL (PURITY): Terbacil (80%)

SYNONYMS: 2,4(1H,3H)-Pyrimidinedione, 5-chloro-3-(1,1-dimethylethyl)-6-methyl
3-tert-butyl-5-chloro-6-methyluracil

CITATION: Solomon, H. (1984) Embryo-fetal toxicity and teratogenecity study of terbacil* by gavage in the rabbit: Medical Research Project No. 4512-001: Haskell Report No. 528-83. E.I. du Pont de Nemours & Co., Inc.,Haskell Laboratory for Toxicology and Industrial Medicine, Central Research and Development Department, Newark, NJ, 19711. MRID No. 00150945. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company

EXECUTIVE SUMMARY: In a developmental toxicity study [MRID 00150945], Terbacil [96.1% a.i. in 0.5% methyl cellulose vehicle]was administered to 18 artificially inseminated New Zealand White female rabbits/group via gavage at dose levels of 0 (0.5% methyl cellulose vehicle), 30, 200, and 600 mg/kg body weight/day from days 7 through 19 of gestation. Surviving does were sacrificed on GD 29 and their fetuses were removed by cesarean and

examined.

Maternal mortality was significantly ($p \leq 0.05$) increased among does in the 600 mg/kg group. 4/18 does died and 1/18 was sacrificed in extremis during the treatment period. During post-treatment 1/18 doe died and 1/18 was sacrificed in extremis. There was a significant ($p \leq 0.05$) decrease in body weight gain in the high dose group (-0.19 kg vs 0.06 kg in controls). There were also significant incidences of anorexia (15/18) and semi-solid and watery yellow (7/18), orange or red discharges (from GD day 19). Trichobezoars filled the stomachs completely in 11/18 does at dose levels of 600 mg/kg versus 5/18 in the control group. Mild gastric lesions were observed microscopically in the control and high dose groups but were considered secondary to the formation of trichobezoars. The incidences of these lesions were not significantly different between the two groups.

The maternal toxicity LOAEL is 600 mg/kg/day based on mortality, clinical finding (anorexia, discharge) and decreased bodyweight gain. The maternal NOAEL was 200 mg/kg/day.

There was no significant difference between the control and treated groups in pregnancy rate or in the number of nidation, abortions, resorptions, live and dead fetuses. Fetal toxicity at 600 mg/kg was demonstrated by a significant decrease in fetal body weight (17%). There was a 184% increase relative to controls, in the percentage of malformed fetuses/litter and a significantly higher incidence of fused ribs in the 600 mg/kg group relative to controls (7% pups in 50% litters vs 0% in controls). Also, a significant increase in the frequencies of extra ribs (2.8X controls) and partially ossified or unossified phalanges (30% vs 3%) and pubes (48% vs 18%) was observed relative to controls.

The developmental toxicity LOAEL is 600 mg/kg/day based on decreased body weight, increased incidence of skeletal malformations (fused ribs) and an increased frequency of skeletal variations (extra ribs and partially ossified or unossified phalanges and pubes). The developmental NOAEL was 200 mg/kg/day.

The developmental toxicity study in the rabbit is classified **Acceptable/Non-guideline**. This study does not satisfy the guideline requirement for a developmental toxicity study [OPPTS 870.3700; §83-3(b)] in the rabbit, because of inadequate study duration. Other, deficiencies noted included no measurement of food consumption, gravid uterine weights, body weights adjusted for gravid uterine weights, and no historical control data. In addition, dead fetuses were not examined for external or visceral anomalies. However, this study is considered adequate to evaluate the teratogenic potential of terbacil in developing rabbits during the period of organogenesis.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging Statements were provided.

Terbacil | **Two Year Chronic Toxicity (§83-1[a])**

EPA Reviewer: Lisa Austin, Ph.D.
Registration Action Branch 1/HED (7509C)
EPA Secondary Reviewer: Robert Mitkus, Ph.D.
Registration Action Branch 1/HED (7509C)

Signature: Lisa Austin
Date: 12/20/05
Signature: Robert J. Mitkus
Date: 12/20/05

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 0003251 for Original DER

NOTE:
This study was previously reviewed and classified as Core Minimum data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Two Year Chronic Toxicity - mice
OPPTS Number: 870.4100 OPP Guideline Number: §83-1a

DP BARCODE: D313756
PC CODE 012701
MRID NO: 00126770

TEST MATERIAL (PURITY): Terbacil (80%)

COMPOSITION/SYNONYM(S): 2,4(1H,3H)-Pyrimidinedione, 5-chloro-3-(1,1-dimethylethyl)-6-methyl
3-tert-butyl-5-chloro-6-methyluracil

CITATION: Goldenthal, E, Homan, S., Richter, W. (1981) 2-year Feeding Study in Mice: Terbacil: 125-027. International Research and Development Corp., E.I. du Pont de Nemours & Co. Wilmington, DE; June 19, 1981. MRID Number 00126770. Unpublished.

SPONSOR: E.I. du Pont de Nemours & Co.

EXECUTIVE SUMMARY: In this chronic oral toxicity study (MRID 00126770), Herbicide 732 technical grade (terbacil, 97.8%) was administered in the diet to Charles River CD strain male and female mice (80/sex/group) at nominal doses of 0, 50, 1250, or 5000/7500 ppm (equivalent to 0/0, 6.5/8.0, 162/199 or 746/895 mg/kg/day) for 104 weeks. The highest dose was increased to 7500 ppm at week 54.

An increase in mortality was observed in all groups but was statistically significant in the 5000/7500 ppm males (29%). However, the incidence after 24 months fell within historical

control range. Body weights were comparable to control values at study termination. There were no treatment related effects on clinical signs and hematology. Clinical chemistry measurements were not reported.

Mean absolute and relative liver weights were increased by 35 and 32%, respectively, in high dose males when compared to controls. Kidney mean absolute and relative weights were significantly reduced in high dose males (by 8 and 11%, respectively) and mean absolute weights were reduced in high dose females (12%). Relative pituitary weights were decreased by 23 % and 22 % at 1250 ppm and 5000/7500 ppm in males, respectively; however, the toxicological significance of this effect is unknown.

Histological examination revealed a dose dependent increase in the incidence of hyperplastic nodules (9/80, 12/80, 20/80 vs 10/79 controls) and hypertrophy of the centrilobular hepatocytes (0/80, 6/80, 47/80 vs 0/79 controls) in males at 50, 1250, and 5000/7500 ppm, respectively. An increase in the incidence of hepatocyte vacuolation (5/80 vs 0/79 controls) and necrosis (13/80 vs 1/80 controls) was also observed in high dose males. In high dose females, there was an increased incidence of hypertrophy of the centrilobular hepatocytes (4/80 vs 0/80 controls) and foam cell foci/areas in the lungs (7/80 vs 0/80 controls). An increase in the incidence of perivascular mononuclear infiltrate (11/76 vs 4/80 controls) was observed in the lung in mid dose females; however, the effect was not dose-dependent.

There was no treatment related increase in the incidence of neoplastic lesions. An increased incidence of lung adenomas was observed in low and high dose males (24/80 and 27/80, respectively, vs 0/80)and spleen hemagiosarcomas in mid dose females (4/79 vs 0/79). However, due to the lack of a dose response the increase in these neoplastic lesions was not considered toxicologically significant.

The LOAEL is 5000 ppm (equivalent to 746 mg/kg/day) based on mortality, increased liver weights and histopathological changes (hyperplastic nodules, necrosis, vacuolation) in the liver in males. The NOAEL is 1250 ppm (equivalent to 162/199 mg/kg/day).

The submitted study is classified as **Acceptable/Guideline (§83-1[b])** and satisfies the requirements for a chronic toxicity study in mice.

COMPLIANCE: No Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Note: The study was done prior to implementation of GLP Guidelines, therefore, does not fall under purview of either GLP Guidelines or Quality Assurance requirements.

Terbacil **Reproduction Study (§83-4[a])**

EPA Reviewer: Lisa Austin, Ph.D. Signature: Lisa Austin
Registration Action Branch 1/HED (7509C) Date: 12/20/05
EPA Secondary Reviewer: Robert Mitkus, Ph.D. Signature: Robert J. Mitkus
Registration Action Branch 1/HED (7509C) Date: 12/20/05

TXR No.: 0052491

DATA EVALUATION RECORD- SUPPLEMENTAL
See TXR N0. 0000703 for Original DER

NOTE:
This study was previously reviewed and classified as Core Minimum Data. However, the format for the executive summary and the first page of the **DER** were different from the current format. This is to update the format and, at the same time, to add needed data to the **DER** for the ease of evaluating this study.

STUDY TYPE: Three-generation Reproduction Study - Rat
OPPTS Number: 870.3800 OPP Guideline Number: §83-4a

DP BARCODE: D313756
P.C. CODE: 012701
MRID NO: 00060852

TEST MATERIAL (PURITY): Terbacil (80%)

SYNONYMS: 3-tert-butyl-5-chloro-6-methyluracil; Herbicide 732; Sinbar Weed Killer

Wazeter, F.X., Buller, R.H., Gei., R.G. (1967): U-2069: Three Generation Reproduction Study in the rat: IRDC No. 125-012. E.I. du Pont de Nemours & Co., Inc., Wilmington, Del. MRID No. 00060852. Unpublished.

SPONSOR: E.I. du Pont de Nemours and Company

EXECUTIVE SUMMARY: In a 3-generation reproduction study (MRID 00060852), Herbicide 732, Terbacil technical (Batch # 1, 80%) was administered in the diet continuously to 3 generations of albino CD rats (10 males/20 females/dose) at dose levels of 0, 50 and 250 ppm (0, 2.0 and 10 mg/kg/day). Parental animals from every generation underwent 2 breeding cycles. Two females were mated with one male; each cycle with a different male. Pups from the 1st litter (1st breeding cycle) of all matings were examined for abnormalities and sacrificed. Representative pups (10 males/20 females/dose) from the 2nd litter (2nd breeding cycle) of all

matings were selected as parental rats for the succeeding generation. Observations were recorded for 10 mice/sex/dose of the 2nd breeding cycle in each generation.

There were no treatment related clinical signs or mortalities. Mean body weight was decreased relative to controls, in a dose-dependent manner after 26-33 weeks in P_1 (9%, 10%), P_2 (4%, 17%), and P_3 (5%, 9%) males and P_2 females (8%, 10%) at 50 and 250 ppm. Weekly mean food consumption per rat was increased in P_1 males (3%, 14%) and decreased in P_2 males (4%, 4%) and females (8%, 13%) and P_3 males (9%, 10%) at 50 and 250 ppm, respectively, relative to controls. P_3 males exhibited a 10-13% decrease in body weight gain in the last 12 weeks of treatment.

There was a dose-dependent increase in relative adrenal weights in P_3 females (15%, 21%) relative to controls at 50 and 250 ppm, respectively. Relative and/or absolute weights were increased in various organs in females at both doses. However, in the absence of histopathological changes, changes in organ weights were not regarded as toxicologically significant.

The fertility index for F_{2B} females decreased to 45% at 250 ppm; however, this effect was not dose-dependent and fell within the historical control range (14-90%). The number of litters per group, total number of stillbirths, live births, percent survival, mean body weight at weaning and the reproductive capabilities of rats fed terbacil in the diet were comparable to those of control rats in each generation.

The Lowest Observed Adverse Level (LOAEL) for systemic parental toxicity was 250 ppm (equivalent to 10 mg/kg/day) based on decreased body weight in both sexes. The No Observed Adverse Effect Level (NOAEL) was 50 ppm (equivalent to 2.0 mg/kg/day).

The LOAEL for systemic offspring toxicity was not established. The Offspring NOAEL is 250 ppm (equivalent to 10 mg/kg/day).

The LOAEL for reproductive toxicity was not established. The reproductive NOAEL is 250 ppm (equivalent to 10 mg/kg/day).

The study was done prior to implementation of GLP Guidelines, therefore, does not fall under the purview of either GLP Guidelines or Quality Assurance requirements. It 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. The study was upgraded to core-Minimum (Tox. Doc. 003401) after the registrant addressed concerns (Acc. No. 249455) regarding unavailable necropsy records for the first litters and incomplete breeding records. The study is classified as **Acceptable/Non-guideline** and **satisfies** the regulatory requirements (**§83-4[a]**) for a multigenerational reproductive toxicity study in rats.

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Chemical: Terbacil

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