UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDOM

Subject: TERBACIL, Toxicology Chapter of the Registration Standard Tox Chem No 821A

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Attached is the Toxicology Chapter of the Final Registration Standard (FRSTR) for Terbacil. This document has been constructed by taking those parts of the 1982 Terbacil standard that refer to studies which are still valid, deleting those portions that refer to data gaps that have been filled and adding new information on new data that have been received since 1982. The DER's attached are for old studies that have been re-reviewed, and new studies received since 1982.

The following portions of this chapter are available on Lexitron disk. You may obtain a copy from this reviewer.

A. Toxicology Summary
B. Toxicology Profile
C. Data Gaps
D. ADI Reassessment
E. Toxicological Issues
F. Toxicology Summary Tables
H. One Liners

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Toxicology Chapter

of the

TERBACIL

Registration Standard

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A. Toxicology Summary

Terbacil is a substituted uracil herbicide whose mechanism of action is photosynthesis inhibition. Chemically, it is 5-chloro-3[1,1-dimethyl]-6-methyl-2,4[1H,3H]-pyrimidinedione. It is used as a herbicide for controlling perennial grasses and annual weeds. It is registered for use on apples, peaches, alfalfa, mint (spearmint and peppermint) sugarcane, strawberries, pecans, blueberries, caneberries, and citrus.

Technical terbacil is classified as a manufacturing-use product, intended to be used only for re-formulation into end-use pesticides. It is supplied as an 80% active ingredient wettable powder.

Terbacil 80% WP has an acute oral LD_{50} of > 5000 mg/kg (Toxicity Category IV), and an acute dermal LD_{50} of > 5000 mg/kg (Toxicity Category III). The acute inhalation LC_{50} is > 4.4mg/L, placing Terbacil in Toxicity Category III. The compound is a mild eye irritant (Toxicity Category III). Terbacil is not a primary dermal irritant, nor a dermal sensitizing agent. There is no evidence at present of any neurotoxicological problem.

Data are available to assess the subchronic oral toxicity of terbacil in rodents. A NOEL of 500 ppm was established in a 90 day feeding study based on increased absolute and relative liver weight at 5000 ppm (HDT). Adequate data are not available to assess the subchronic oral toxicity in a non-rodent. However, the data requirement is satisfied by a two year feeding study in dogs. In subchronic dermal toxicity, no systemic dermal toxicity was observed in rabbits at 5000 mg/kg (only level tested).

Terbacil demonstrated a NOEL of 5000 ppm (HDT) in rats and a NOEL of > 600 mg/kg (HDT) in rabbits when tested for teratogenic effects. Terbacil did not produce reproductive toxicity when administered to rats at 250 mg/kg (HDT) for three generations.

Data are available to determine the chronic toxicity of terbacil in non-rodent species, demonstrating a NOEL of 50 ppm (LDT) based on increased relative thyroid weight, increased absolute liver weight, and elevated alkaline phosphatase at 250 ppm. Data are inadequate to assess the chronic oral toxicity of terbacil in a rodent species. Data are inadequate to assess the oncogenic potential of terbacil.

There are no data on the mutagenic potential, or the metabolism of terbacil.

Terbacil is registered for several tolerances on Raw Agricultural Commodities (RAC's). An ADI of 0.013 mg/kg was determined from a two year dog feeding study.

B. Toxicology Profile

81 Series Acute toxicity and Irritation Studies

81-1 Acute Oral

A data gap was stated to exist for acute oral toxicity in the 1982 registration standard, because the study had been performed on the 80% wettable powder formulation (Acc. No. 114693). Data (Acc. No. 24955) was later accepted by Toxicology Branch which placed Terbacil in Toxicity Category IV for acute oral toxicity, since the 80% formulation was also used as the Technical (Tox Doc 003401).

No further data are required.

81-2 Acute Dermal

A data gap was determined to exist for acute dermal toxicity in the 1982 registration standard (Acc. No. 114693). Data later presented to Toxicology Branch (Acc. No.24955) demonstrated that the data was adequate to place Terbacil in Toxicology Category III for dermal toxicity. The requirement for acute dermal toxicity has been satisfied.

No further studies are required.

81-3 Acute Inhalation

An acute inhalation study in rats was submitted in response to the Data Call-In for terbacil. The LC_{50} was > 4.4 mg/L., placing Terbacil Technical 97.8% in Toxicity Category III (MRID 00125700).

No additional data are required.

81-4 Primary Eye Irritation

A primary eye irritation study in rabbits was submitted in response to the Data Call-In for terbacil. Nineteen mg of Terbacil 96.1% a.i was placed in the conjunctival sac of each rabbit. The eyes of six rabbits were washed, while three remained unwashed. Slight conjunctival irritation was observed which was reversed within 72 hours in animals with unwashed eyes and within 24 hours in animals with washed eyes. The data place Terbacil in Toxicity Category III for primary eye irritation (MRID 157-179).

No further data are required.

81-5 Primary Dermal Irritation

No data are available on the primary dermal irritation properities of Terbacil. However, Toxicology Branch indicated to the registrant that if no dermal irritation was observed in the 21 day subchronic dermal study, the data gap would be considered filled (Tox.Doc.003401). No dermal irritation was reported in this study; therefore no further data are required for primary dermal irritation (MRID 00125785). See Subchronic Studies 82-2)

81-6 Dermal Sensitization

A dermal sensitization study in guinea pigs was submitted in response to the Data Call-In for terbacil(MRID 157-180). No dermal sensitization was demonstrated when Terbacil 96.1% was tested in guinea pigs as a 3% and 30% solution.

No further studies are required.

81-7 Acute Delayed Neurotoxicity

No data are available on the acute neurotoxic effects of Terbacil. This test is required only for compounds which are organophosphate inhibitors of cholinesterase, or related to such inhibitors or metabolites of such inhibitors. Terbacil is not an organophosphate, therefore, a study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

Sufficient data (core-Minimum) have previously been submitted in the 1982 initial registration standard to satisfy the requirement for subchronic testing in the rodent. (MRID # 00039009, 00068035). The NOEL was 500 ppm based on increased liver weights and hypertrophy of parenchymal liver cells in males and females administered 5000 ppm (HDT).

No further testing is required in the rodent.

Studies are not required in the nonrodent because an acceptable two year dog study is available (MRID 00060851).

82-2 Subchronic Dermal (21-day)

A 21 day subchronic dermal toxicity in rabbits was submitted in response to the Data Call-In for Terbacil. Terbacil was applied to prepared skin sites of 5 male and 5 female rats at 5000 mg/kg, 5 hours/day, 5 days/week. No subchronic toxicity in the form of body weight differences, organ weight changes, or gross or micro-

scopic lesions was observed in any of the test animals. Mild scaliness and staining were reported at the test sites (MRID 00125785).

No additional studies are required.

82-3 Subchronic Dermal (90-day)

No data are available on the 90-day subchronic dermal toxicity of Terbacil. A study is not required under the use pattern.

82-4 Subchronic Inhalation

No data are available on the subchronic inhalation toxicity of Terbacil. A study is not required under the use pattern.

82-5 Subchronic Neurotoxicity

No data are available on the subchronic neurotoxicity of Terbacil. Since an acute neurotoxicity study is not required and there is no evidence of neurotoxicity in mammalian species, this study is not required.

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

A two year rat study was accepted in support of the registration of Terbacil in the 1982 registration standard. Terbacil was administered in the diet to 36 per sex Charles River CD rats at doses of 0, 50, 250, and 2500/10000ppm a.i. for two years. The 2500 ppm group received increments of 500 ppm or 1000 ppm every two weeks until a level of 10000 ppm was achieved in Week 46 of the study.

The study was re-reviewed for the FRSTR and was found to be inadequate to satisfy the requirement for chronic or oncogenic testing in a rodent species for the following reasons:(a) an insufficient number of animals was used at study start(36/sex/dose) (b) an intercurrent infection was present in the animal colony,(c) an insufficient number of animals survived the study(the highest survival rate was 16 in the high dose females,(d) only terminally sacrificed control and high dose animals were examined microscopically, (e) biochemical determinations were incomplete and were done on only six animals/sex/dose (MRID 00060850).

A new study is required.

Sufficient data (core-Minimum) have previously been submitted in the 1982 registration standard to satisfy the requirement for chronic testing in a nonrodent species (MRID 00060851).

Terbacil 80% a.i. was administered in the diet to 4/sex/group beagle dogs at levels of 50, 250, and 2500/10000 ppm for two years. One/sex of each dose level were sacrificed at one year. No adverse effects of the test compound were observed with respect to biochemical parameters, food consumption, body weight, or gross or microscopic changes. The NOEL was 50 ppm based on increased thyroid weight in dogs administered 250 ppm and above. Relative liver weights were also increased at 2500/ 10000 ppm in dogs sacrificed at 1 year and at two years.

No further testing is required.

83-2 Oncogenicity

A chronic toxicity/oncogenicity study in the mouse study was submitted in response to the DCI(MRID 00126770). Terbacil was administered in the diet to 80/sex of CD-1 mice at doses of 0, 50, 1250, and 5000/7500 ppm for two years (the 5000 ppm level was increased to 7500 ppm at week 54). Clinical laboratory tests were conducted on 10/sex/group at 1, 3, 6, 12, 18 and 24 months of the study.

Survival was significantly decreased ($p < 0.05$) in high dose males. Body weight was significantly lower in high dose males in the initial phase of the study. Liver weight was significantly increased ($p < 0.01$) in high dose male and female mice compared to the controls, and mild hypertrophy of centrilobular hepatocytes in mid and high dose males. Pituitary weights were decreased in mid and high dose males and in high dose females. The systemic NOEL was 50 ppm. There was an increased incidence of lung neoplasms (adenomas and adenocarcinomas) in all treated male mice which was not dose related. The incidence of these tumors was not outside the range of similar tumors observed in control CD-1 mice used in 12 studies in the investigators' laboratory. There was also an increased incidence of hyperplastic nodules in the livers of high dose male mice compared to the controls. Although the study was classified core- Minimum, and the compound was evaluated negative for oncogenicity, the current interpretation of neoplastic nodules (including hyperplastic nodules and nodular hyperplasia) is that these lesions are benign neoplasias. Therefore, Toxicology Branch can not accept the diagnosis of hyperplastic nodules, and the registrant is requested to re-examine the liver slides to determine the type of lesion, and to report them in the current conventional terminology. Pending this re-evaluation, and submission of the information relating to the concentration, homogeneity, and stability of the test diets, the study is re-classified core-Supplementary.

The two year rat study which was used to satisfy the data requirement for oncogenicity in the 1982 Registration standard has been re-classified core-Supplementary (see Chronic Studies 83-1).

A new study is required.

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83-3 Teratogenicity

Terbacil 80% a.i. was administered in the diet to 27/group of rats at levels of 0, 250, 1250, and 5000 ppm from day 6 through day 15 of gestation. The study was evaluated for the 1982 Registration Standard and a data gap was cited based on on increased post implantation loss in the treated dams and statistically significantly increased hydronephrosis in fetuses from the treated dams (MRID 000390010).

These concerns were addressed in DuPont's Response to the Terbacil Registration Standard (Acc.No. 249455). The response was accepted by the Agency in Tox. Document 003401, and the study was re-classified core-Minimum.

The NOEL for teratogenicity was > 5000 ppm. The maternal NOEL was 250 ppm based on decreased body weight at 1250 ppm and above. The requirement for a rat teratology study is satisfied. No further studies are required.

A rabbit teratology study was submitted in response to the Data Call-In Notice for terbacil. Terbacil was administered to pregnant New Zealand White rabbits at nominal doses of 0, 30, 200, and 600 mg/kg by gavage on gestation days 7 through 19. Actual mean doses were 33, 208 and 680 mg/kg. Five high dose rabbits died, and two were sacrificed in extremis. No significant differences were reported between groups with respect to corpora lutea, resorptions, or live or dead fetuses. Mean live fetal weights were significantly reduced in the high dose group. There was no significant increase in malformed fetuses in the treated animals when compared to the controls. The NOEL for teratogenicity was 600 mg/kg (HDT). The NOEL for maternal toxicity and embryotoxicity was 200 mg/kg (MRID 00150945).

This study satisfies the requirement for teratogenicity testing in the rabbit. No further studies are required.

83-4 Reproduction

Terbacil 80% was administered to 10 male and 20 female Charles River CD rats/group at dietary levels of 50 ppm and 250 ppm over three generations. The first litter of each generation was discarded, while the second litter was bred to obtain the next generation. The F_{3b} offspring were subjected to histopathological examination.

Body weight gain was significantly reduced in male but not female rats in all generations at 250 ppm, and was also reduced at 50 ppm, although this was not significant. The fertility index was reduced in the second litter of the F_3 generation in rats treated with 250 ppm. No other reproductive effects were observed in the study. No microscopic lesions of the

The study was reviewed for the 1982 Registration Standard and was evaluated to be core-Supplementary based on administration of two dose levels only, and administration of antibiotics to the test animals during the study. The review also cited study deficiencies seen in the FDA/EPA Pilot Program audit in December, 1986. These were: necropsy records not available for first litters, and incomplete breeding records.

The concerns were addressed in Acc. No. 249455, and were accepted by the Agency in Tox. Doc. 003401. The study was re-classified core-Minimum with a systemic NOEL of < 50 ppm (LDT) based on the reduction of body weight gain and a NOEL for reproductive toxicity was > 250 ppm(HDT).

The requirement for reproductive toxicity testing is satisfied. No further data are required.

84 Series Mutagenicity

84-2 Mutagenicity Tests.

No data are available on the mutagenic potential of Terbacil. Studies are required to demonstrate the potential of terbacil to produce gene mutations, chromosomal aberrations, and to interact with DNA.

85 Series Special Studies

85-1 Metabolism

No data are available on the metabolism of Terbacil. Studies are required to demonstrate the metabolism of a low dose, a high dose and multiple doses of the test compound.

C. Data Gaps

Terbacil is registered for food uses. Therefore the following Guideline toxicology studies can be required for registration.

81-1 Acute Oral
81-2 Acute Dermal
81-3 Acute Inhalation
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization

82-1 Subchronic Oral, two species rodent and nonredent
82-2 Subchronic Dermal (21-day)
83-1 Chronic Toxicity, two species rodent and nonrodent
83-2 Oncogenicity, two species
83-3 Teratogenicity, two species
83-4 Reproduction

84-2 Mutagenicity Tests.

85-1 Metabolism
85-2 Domestic Animal Safety.
85-3 Dermal Absorption

Based on this assesment of the toxicology data base the following Guideline toxicology studies have been identified as data gaps and are required.

83-1 Chronic Toxicity, two species rodent and nonrodent
83-2 Oncogenicity, two species
84-2 Mutagenicity Tests.
85-1 Metabolism

D. ADI Reassessment

The ADI was calculated from a two year feeding study in dogs(MRID 00060851) in which dogs were given 50, 250, 2500/ 10000 ppm of terbacil by dietary exposure for two years. The NOEL was 50 ppm, equivalent to 1.25 mg/kg, based on increased relative liver weights and increased serum alkaline phosphatase. The ADI was calculated to be 0.013 mg/kg using a safety factor of 100.

U.S. EPA (1986) Reference Doses(RfD) for oral exposure: Terbacil Prepared by Toxicology Branch 5/2/1986, and verified by the Agency Review Committee 6/10/1986.

E. Toxicological Issues

DuPont submitted a 2 year feeding study in CD-1 mice to the Agency in response to the Data Call-In Notice on Terbacil (MRID 00126770). The study was evaluated and classified core-Minimum, and the compound was judged not to demonstrate an oncogenic effect. However, the data showed that there was an increased incidence of hyperplastic liver nodules in the high dose males when compared to the control mice(37.1% v 12.2% in those terminally sacrificed, and 15.6% v 13.3% in mice dying during the study. The combined total was 25% high dose v 12.7% control mice).

It has been Toxicology Branch's experience that on occasion, lesions diagnosed as hyperplastic nodules have been re-classified as adenomas following re-examination of the slides. The National Toxicology Program currently classifies lesions with even partial compression as adenomas. Since the morphological description given by the study pathologist could be consistent with more differentiated adenomas, Toxicology Branch can not accept the diagnosis of "hyperplastic liver nodules". A request will be made to the registrant to conduct an independent re-analysis of the liver slides, and to report the results to the Agency using the correct current terminology.

In addition to the mouse oncogenicity study, the two year rat feeding study which had previously classified core-Minimum has been re-reviewed and has been classified core-Supplementary based on a number of inadequacies. A new study is required.

If the requested data so indicate, Terbacil will be presented for review by the Toxicology Branch Peer Review Committee with respect to its oncogenic potential.

TABLE A
GENERIC DATA REQUIREMENTS FOR TERBACIL

Data Requirement	Composition 1/	Use Patterns 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology					
ACUTE TESTING:					
81-1 - Acute Oral - Rat	TGAI	A	Yes	JES 001	No
81-2 - Acute Dermal -	TGAI	A	Yes	JES 001	No
81-3 - Acute Inhalation - Rat	TGAI	A	Yes	00125700	No
81-4 - Eye Irritation - Rabbit	TGAI	A	Yes	0157179	No
81-5 - Dermal Irritation - Rabbit	TGAI	A	No		No 4/
81-6 - Dermal Sensitization - Guinea Pig	TGAI	A	Yes	0157180	No
81-7 - Acute Delayed Neurotoxicity - Hen	TGAI	A	No		No 5/
SUBCHRONIC TESTING:					
82-1 - 90-Day Feeding -					
Rodent	TGAI	A	Yes		No
Non-rodent	TGAI	A	No		No 6/

TABLE A
GENERIC DATA REQUIREMENTS FOR TERBACIL

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)?	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)? 3/
§158.135 Toxicology (Cont.)					
82-2 - 21-Day Dermal-	TGAI	A	Yes	00125785 00148066	No
82-3 - 90-Day Dermal-	TGAI	A	No		No 7/
82-4 - 90-Day Inhalation -	TGAI	A	No		No 7/
82-5 - 90-Day Neurotoxicity-	TGAI	A	No		No 7/
CHRONIC TESTING:					
83-1 - Chronic Toxicity -					
Rodent	TGAI	A	No		Yes 8/
Non-rodent	TGAI	A	Yes	00060851 00039002	No
83-2 - Oncogenicity Study -					
Rat	TGAI	A	No		Yes 8/
Mouse	TGAI	A	No		Yes
83-3 - Teratogenicity -					
Rat	TGAI	A	Yes	JES 001	No
Rabbit	TGAI	A	Yes	00150945	No
83-4 - Reproduction -	TGAI	A	Yes	JES 001	No

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TABLE A
GENERIC DATA REQUIREMENTS FOR TERBACIL

Data Requirement	Composition 1/	Use Pattern 2/	Does EPA Have Data To Satisfy This Requirement? (Yes, No or Partially)	Bibliographic Citation	Must Additional Data Be Submitted Under FIFRA Section 3(c)(2)(B)?3/
§158.135 Toxicology (continued)					
MUTAGENICITY TESTING					
84-2 - Gene Mutation	TGAI	A	No		Yes
84-2 - Chromosomal Aberration	TGAI	A	No		Yes
84-2 - Other Mechanisms of Mutagenicity	TGAI	A	No		Yes
SPECIAL TESTING					
85-1 - General Metabolism	PAI or PAIRA	A	No		Yes
85-2 - Domestic Animal Safety	Choice	A	No		No
85-3 - Dermal Absorption	PAI or PAIRA	A	No		No 7/

1/ Composition: TGAI Technical Grade Active Ingredient; PAI = Pure Active Ingredient; PAIRA = Pure Active Ingredient, Radiolabelled; Choice = Choice of several test substances determined on a case-by-case basis.
2/ The use patterns are coded as follows: A = Terrestrial, Food Crop; B = Terrestrial, Non-Food; C = Aquatic, Food Crop; D = Aquatic, Non-Food; E = Greenhouse, Food Crop; F = Greenhouse, Non-Food; G = Forestry; H = Domestic Outdoor; I = Indoor; IP = Industrial Preservative.
3/ Unless otherwise specified data must be submitted no later than six months after publication of this Standard
4/ Satisfied by 21 day dermal toxicity study
5/ Terbacil is not an organophosphate, and available data at this time does not reveal a neurotoxicological problem
6/ An adequate chronic toxicity study is available
7/ These studies are not required at this time
8/ May be satisfied by a combined chronic/oncogenicity study

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00039003 Buller R.H. and Geil, R.G. (1967) Three Generation Reproduction Study in
00068052 the Rat.
00039001 IRDC (1981) Chronic Feeding and Oncogenicity Study in Rat (125-01
00068050

00126770 Goldenthal, E.; Noman, S.; Richter, W. (1981) 2-year Feeding Study in Mice: ♦Terbacil|: 125-027. (Unpublished study received Apr 5, 1983 under 352-247; prepared by International Research and Development Corp., submitted by E.I. du Pont de Nemours & Co., Inc., Wilmington, DE; CDL:249907-A; 249908; 249906)

00150948 Solomon, H. (1984) Embryo-Fetal Toxicity and Teratogenicity Study of Terbacil by Gavage in the Rabbit: Medical Research Project No. 4512-001: Haskell Report No. 528-83. Unpublished study prepared by E.I. du Pont de Nemours & Co., Inc., Haskell Laboratory for Toxicology and Industrial Medicine. 78 p.

Tox Chem No. 821A - Terbacil

File Last Updated 2/17/87

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Acute oral LD_{50} - rat; Haskell Labs; 6/25/65	Herbicide 732 (Sinbar W.P.) 80% A.I.	114693 249455	5000 < LD_{50} < 7500 mg/kg at 2250 mg/kg - inactivity, weight loss and incoordination	IV	000705 Minimum 003401
Acute oral LD_{50}-rat Hazleton Labs; 201-173 8/14/84	Terbacil 96.1% a.i.	MRID 150946	LD_{50} = 1225(1022-1540) mg/kg M = 943(735-1187) mg/kg F = 1082(913-1282) mg/kg C Toxicity: depression, rough hair coat, ataxia.	III	Supplementary pend- clarification of description of test material
Acute dermal LD_{50} - rabbit; Haskell Labs; 6/25/65	Herbicide 732 W.P. (80% A.I.)	114693 249455	LD_{50} > 5000 mg/kg (only dose tested) No toxic signs noted	III	Minimum 003401
Acute inhalation LC_{50}- rat; Haskell Labs; #351-82; 6/2/82	Terbacil Tech 97.8% a.i.	249455	LC_{50} > 4.4 mg/L. Mass median diameter 5.5 and 3.0 u; 34% and 75% respirable. Levels tested = 3.0, 4.4 mg/L/4 hrs.	III	Minimum 003401 MRID 00125700
Dermal sensitization guinea pig; Haskell Lab; 600-85; 1/6/1986	Terbacil Tech 96.1%		Not a dermal sensitizer in male Dunkin-Hartley guinea pigs Tested as 3% and 30% solution (maximum solubility) in dimethyl phthalate		Guideline MRID 157180
Primary Eye irritation- rabbit; Haskell Labs. 201-867; 9/13/1985	Terbacil Tech 96.1%		Mild transient irritation No P.I.S.	III	Guideline MRID 150946
21 day dermal-rabbit E.I.duPont de Nemours & Co., #HL 33-36; 2/24/66	Haskell # 4215 formulation 84.8% Terbacil [redacted]	249455	LD_{50} > 5000 mg/kg(only level tested) No toxic signs. No appreciable differences in body weights, organ body weight ratios, gross and histopath - ology		Mimimum MRID 00148066 00125785

Inert ingredient information may be entitled to confidential treatment

Tox Chem No. 821A - Terbacil

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
90 day feeding-rat Haskell Labs; 6/25/65	Herbicide 732 WP 80% a.i.	114693	NOEL = 100 ppm LEL = 500 ppm(increased liver weight, vacuolization and hypertrophy of hepatocytes) Levels tested: 100, 500, 5000 ppm		Minimum 000704 00068305
2-Year feeding - dog; IRDC; #125-011; 4/6/66	Herbicide 732 W.P. (80% A.I.) (3-tert-butyl 5-chloro-6-methyl-uracil)	114693	NOEL = 50 ppm LEL = 250 ppm (Increase in thyroid/body weight ratio slight increase in liver wts. Elevated alkaline phosphatase) Levels tested = 50, 250, 2500 ppm. (2500 ppm increased gradually to 10,000 ppm)		000705 000706 000703 Minimum MRID 00060851
2-Year feeding/onco.-mice; Intl. Research and Development Corp.; MI Study 125-127; 6/81	97.8% tech. Chemical	249906 249907 249908	1. Decreased survival (significant in males at 5000/7500 ppm). 2. Increased lung ademomas in males at all levels compared with study controls,but not compared with historic controls. 3. No instances of alveolar cell hyperplasia reported. 4. For reasons 2 and 3, considered non-oncogenic. 5. Systemic NOEL = 50 ppm; systemic LEL=1250 ppm;hypertrophy of centriobular hepatocytes in males; decreased pituitary weights in males and high dose females. 6. Oncogenic NOEL > 5000/7500 ppm (HDT). Increased incidence of liver hyperplastic nodules in high dose males. Levels tested; 0, 50, 1250, 5000/7500 ppm (5000 increased to 7500 at week 54) in CD-1 strain		Minimum 003251 MRID 00126770 Downgraded to Supplementary pending re-analysis of liver slides.

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Tox Chem No. 821A - Terbacil

Study/Lab/Study #/Date		EPA Accession No	Results: L_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
2-Year feeding/oncogenic -rat; IRDC; #125-010; 4/7/66	Herbicide 732 W.P. (80% A.I.) (3-tert-butyl 5-chloro-6-methyl uracil)	114693	Systemic NOEL = 250 ppm Systemic LEL = 2500/10,000 ppm (HDT) (Impaired weight gain, slight increase in liver weight) Levels tested- 0,50,250,2500ppm (2500 ppm was increased to 10000ppm) Oncogenic NOEL>2500/10,000 ppm(HDT)		000701 000703 000705 000706
Teratology - rat; Haskell Lab; #481-79 (Project#3143); 2/20/80	Sinbar (Tech) 96.6%	099540 249455	Teratogenic NOEL > 5,000 ppm (HDT) Embryotoxic NOEL = 250 ppm Embryotoxic LEL = 1250 ppm (decrease of number of implantations and live fetuses) Maternal NOEL = 250 ppm Maternal LEL = 1250 ppm (reduction in body weight) Levels tested = 250, 1250, 5000 ppm		Minimum 003401
Teratology- rabbit; Haskell Lab.; # 528-83; 2/21/84	Terbacil Tech. 96.1% pure	255763	Teratogenic NOEL >600 mg/kg/day(HDT) Maternal NOEL = 200 mg/kg/day Embryotoxic NOEL = 200 mg/kg/day Levels tested in New Zealand White strain by gavage- 0, 30, 200 and 600 mg/kg/day		MINIMUM 004443
3-Generation reproduction - rat; IRDC;#125-012; 3/23/67	Herbicide 732 W.P. (80% AI) (3-tert-butyl (5-chloro-6-1	114693 249455	Reproductive NOEL > 250 ppm (HDT) Sys NOEL < 50 ppm(LDT)(Slight decrease in body weight gain) Levels tested = 50, 250 ppm		000701 000703 000706 Minimum

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DER'S

Reviewed by: Joycelyn Stewart, Ph.D. 2/1/89
Section II, Tox. Branch I(IRS) (TS-769C)
Secondary reviewer: Marion Copley, DVM. 2/1/89
Section II, Tox. Branch I(IRS) (TS-769C)

81-1

007177

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral- Rat

TOX. CHEM. NO.: 821A

ACCESSION NUMBER:

MRID NO.: 150946

TEST MATERIAL: Terbacil 96.1%

SYNONYMS: H # 14,673

STUDY NUMBER(S): 201-713

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

TESTING FACILITY: Hazleton Laboratories America, Inc.
Vienna, Virginia,

TITLE OF REPORT: Acute Oral Toxicity in Rats

AUTHOR(S): Farrow, M.G., Butts, D.L., and Cortina, T.

REPORT ISSUED: 8/14/1984.

CONCLUSION: The data presented demonstrate an acute oral LD_{50} of 1255(1022-1540) mg/kg for male mice, 934(735-1187) mg/kg for female rats, and 1082(913-1283) mg/kg combined. However, Toxicology Branch notes a discrepancy in the description of the test compound. The performing laboratory describes the test compound as a white powder, while the registrant describes it as tan crystals. The Agency needs to be assured that the compound that was reported is the one actually tested. The study is classified core-Supplementary until the discrepancy is addressed.

Toxicity Category: III

Classification: core-Supplementary

MATERIALS: Terbacil 96.1%, described as a white powder, was the test chemical. The test compound was suspended in corn oil. Male and female Sprague-Dawley rats were the test animals. Males were 49 days old and weighed 225 to 286 grams, and females were 75 days old and weighed 200 to 240 grams at study start.

METHODS: Animals were randomly assigned to dosage groups. They were identified with unique ear tags, and were housed individually. Food and water were available ad libitum. Groups of five male and five female rats were administered terbacil

at doses of 333, 500, 750, 1125, and 1600 mg/kg by gavage in a single oral dose after an overnight fast. They were observed for toxic and pharmacological signs at 1, 2, 4 hours post dosing, and daily thereafter for 14 days. Individual body weights were recorded prior to treatment, on day 7, and at study termination. Necropsies were performed on all animals sacrificed at study termination, and on those found dead during the study.

STATISTICAL ANALYSIS: Mortality data were analysed separately and combined for male and female rats by probit analysis.

QUALITY ASSURANCE: A signed and dated quality assurance statement is included in the submission.

RESULTS: Four/five of the high dose male and female rats were found dead on Day 1 of the study. At the next highest dose, all females and two males died on Day 1 or Day 2. One mid-dose female was found dead. Animals in the other dosage groups survived. Clinical signs reported frequently in animals treated with Terbacil were: depression, rough hair coat, and ataxia. Less frequently reported were urine staining and prostration,the incidences of which increased with the doses. All survivors were reported to be normal by Day 10 of the study. All survivors gained weight except for one female administered 500 mg/kg of terbacil. No gross pathological lesions were reported when the survivors were necropsied. In animals found dead, gross lesions were reported in lungs, stomach, intestine, and urinary bladder. The LD_{50} was calculated to be 1255(1022-1540) mg/kg for male rats; 934(735-1187) mg/kg for female rats, and 1082(913-1283) mg/kg combined.

DISCUSSION: The data presented is consistent with the registrant's calculation of the LD_{50}. Toxicology Branch notes that the performing laboratory describes terbacil as a white powder, while the registrant describes the chemical as light tan crystals. In order to adequately evaluate the study, Toxicology Branch needs an accurate description of the test chemical. Toxicology Branch also notes that although a range finding study was used to determine the doses for the acute oral study in rats, neither the study nor the results were presented to the Agency. The study is classified core-Supplementary pending clarification of the description of the test material. The data presented place terbacil in Toxicity Category III for oral toxicity.

Reviewed by: Joycelyn Stewart, Ph.D. 8/1/89
Section II, Tox. Branch I(IRS) (TS-769C)
Secondary reviewer: Marion Copley, DVM 8/3/89
Section II, Tox. Branch I(IRS) (TS-769C)

81-4
007177

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation TOX. CHEM. NO.: 82[illegible]A

ACCESSION NUMBER: MRID NO.: 157-179

TEST MATERIAL: 2,4(1H,3H)-Pyrimidinedione,5-chloro-3-(1,1-dimethylethyl)-6-methyl-

SYNONYMS: Terbacil; 3-tert Butyl-5-chloro-6-methyluracil; Haskell No 14673.

STUDY NUMBER(S): 201-867

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

TESTING FACILITY: Hazleton Laboratories America Inc. Vienna, Virginia.

TITLE OF REPORT: Primary Eye Irritation in Rabbits

AUTHOR(S): Gargus, J.L.; Burlew, P.L.; Pinamont, A.M.; Henry, J.E. and Chromey, N.C.

REPORT ISSUED: 9/13/1985

CONCLUSION: The data presented demonstrates that terbacil produced mild and transient eye irritation when applied to the eyes of male and female New Zealand White rabbits.

Toxicity Category: III

Classification: Guideline

MATERIALS: New Zealand White rabbits (4 male, 5 female) were the test animals. Males weighed 2362 -2703 grams and females weighed 2205-2698 grams at study start. The test chemical was Terbacil 96.1% pure. It was described as a tan powder.

METHODS: Animals were acclimated to the laboratory for at least one week prior to start of the study. They were uniquely identified with ear tags, and were housed individually. Food and water were available ad libitum. Prior to instillation of the test compound the eyes of each animal were examined for corneal defects using 2% fluorescein sodium. A 19 mg aliquot of Terbacil was placed into the conjunctival sac of the left eye of each rabbit, and held in place for one second. The treated eyes of one male and two females were rinsed for one minute with warm water. Eyes of the other animals were left unwashed. The untreated right

eye of all animals were used as controls. Eye irritation was scored at 24, 48, and 72 hours and on days 4 and 7 using the Draize system. After the 24 hour examination, fluorescein sodium staining was used for the ocular examinations. Body weight was recorded for all animals at initiation and termination of the study. At study termination, all surviving animals were sacrificed and discarded.

RESULTS: No corneal or iris damage was reported in any animals. Conjunctival redness (Grades 1 and 2) was reported in all animals with unwashed eyes. At 48 hours 3 of 6 unwashed eyes had mild conjunctival redness which was reversed within 72 hours.

Grade 1 conjunctival redness was reported in the eye of one animal with washed eyes. This was reversed within 24 hours. No conjunctival chemosis or discharge was reported in any of the animals.

Five rabbits from the unwashed eye group and one from the washed eye group demonstrated blinking and rubbing after the compound was instilled. All animals gained weight during the study.

DISCUSSION: The data presented demonstrate slight conjunctival irritation which was reversed in all animals within 72 hours. Washing decreased the duration of the irritation. The data presented place terbacil in Toxicity Category III for eye irritation.

Reviewed by: Joycelyn Stewart, Ph.D.
Section II, Tox. Branch I (IRS)(TS-769C)
Secondary reviewer: Marion Copley, ~~D.V.M.~~ DVM 3/14/88
Section II, Tox. Branch I (IRS) (TS-769C)

81-6

007177

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization-Guinea Pig TOX. CHEM. NO.: 821A

ACCESSION NUMBER: MRID NO.: 157-180

TEST MATERIAL: 2,4,(1H,3H)-Pyrimidinedione, 5-chloro-3 (1,1 dimethylethyl) 6-methyl-

SYNONYMS: o Terbacil; o 3-tert Butyl-5-chloro-6-methyluracil

STUDY NUMBER(S): 600-85

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

TESTING FACILITY: Haskell Laboratory for Toxicology and Industrial Medicine
Newark, Delaware.

TITLE OF REPORT: Skin Sensitization Test of Terbacil(IND-732-53). in Guinea Pigs for EPA Pesticide Registration.

AUTHOR(S): Henry, J.E.; Redgate, D.; and Chromey, N.C.

REPORT ISSUED: 1/6/1986

CONCLUSION: Topical concentrations of 30% and 3% of terbacil followed by intradermal injections of 1% did not produce dermal sensitization in male Duncan Hartley guinea pigs when the animals were subjected to challenge doses of the test compound. The compound is not a dermal sensitizer.

Classification: Guideline

MATERIALS: Male Duncan Hartley guinea pigs were the test animals. Terbacil 96.1% pure, described as light tan crystals, was the test chemical.

METHODS: Guinea pigs were assigned unique identification numbers and were housed individually in stainless steel cages in environmentally controlled animal rooms with temperatures of 23 ± 2°C, relative humidity of 50 ± 10%, and a 12 hour light and dark cycle. Food and water were available ad libitum.

A preliminary range finding study was conducted in three animals using 0.05 mL of 30% (the maximum solubility), 15%, and 1.5% of terbacil in dimethyl phthalate. The solutions were applied to. 27

shaved intact skin, and the irritation responses were scored at approximately 24 and 48 hours post administration using the Draize scale.

The main study was conducted in three phases. In the primary irritation phase, 0.5 mL of the test compound was applied to the shaved intact skin of ten unexposed guinea pigs at concentrations of 30% and 3% in dimethyl phthalate. Responses were scored 24 and 48 hours after treatment. The concentrations used in the main study were based on the observation of no erythema or edema in the preliminary study.

Two days post dermal application of the test compound, the animals were treated weekly with intradermal injections of 0.1 mL of a 1% suspension of terbacil in dimethyl phthalate for four weeks. Skin responses were evaluated 24 hours after each treatment. After a two week rest period, the treated guinea pigs were challenged with one drop of 30% terbacil on the left front shoulder, and one drop of 3% terbacil on the right front shoulder. Ten control guinea pigs of the same age were treated with similar concentrations of terbacil. Responses were scored 24 and 48 hours after application of the test compound. The Draize scale was used to score the dermal reactions.

RESULTS: No erythema or edema was observed during the range-finding study. Based on this, concentrations of 30% and 3% were chosen for the main study.

In the main study, no erythema or edema was reported during the primary irritation phase. During the induction phase, all guinea pigs demonstrated moderate to strong erythema after each injection. Erythema and edema were reported in one guinea pig after the first injection, in four guinea pigs after the second injection, and in one guinea pig after the third injection.

During the challenge phase, mild erythema was reported in one control guinea pig at the 30% concentration site and in one test group guinea pig at the 30% and the 3% concentration site 24 hours post treatment. No irritation was reported 48 hours post treatment.

DISCUSSION: The data presented confirms the registrant's conclusion that terbacil did not produce dermal sensitization in guinea pigs under the test conditions.

Reviewed by: Joycelyn Stewart, Ph.D. 11/17/88 83-1
Section II, Tox. Branch I(IRS) (TS-769C)
Secondary reviewer: Marion Copley DVM 12/15/88
Section VII, Tox. Branch (TS-769C)

007177

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

DATA EVALUATION REPORT COVER

STUDY TYPE: Chronic Feeding Dog TOX. CHEM. NO.: 821A

ACCESSION NUMBER: N/A MRID NO.: 00060851

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

SYNONYMS: Sinbar Weed Killer, Herbicide 732, IND 732-15

STUDY NUMBER(S): 125-011

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

TESTING FACILITY: IRDC
Mattawan, Michigan

TITLE OF REPORT: Two Year Feeding Study in the Dog.

AUTHOR(S): Wazeler, F.X.

REPORT ISSUED: 3/17/1967

Classification: Minimum

CONCLUSION: The previous reviews (copies attached) accurately represent the results of the study. This reviewer concurs with the evaluation of increased thyroid weight in the mid and high dose dogs in the review by D. Ritter, 12/20/1973, Toxicology Document 000706. The NOEL is 50 ppm (LDT). The study is deficient by current standards. However, considering the study duration, and the lack of overt toxicity shown in the study it has been decided to accept the study in place of the one year dog study which is required under Subdivision F Guidelines.

The study showed the following deficiences:

1. Only three animals/sex/dose were carried for the duration of the study. However, the study was two years in length.

2. Serum chemistry was not complete. However, the major biochemical, hematology, and urinalysis parameters were examined.

3. Histopathology was limited, but the critical organ systems were covered.

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L. Berry
4/4/1967

007177

Summary

Two Year Feeding Study in the Dog

16♂ and 16♀ Beagles
80% wettable powder used

1 Control		4♂ 4♀
1st Test	50 ppm	4♂ 4♀
2nd Test	250 ppm	4♂ 4♀
3rd Test	2500 ppm (+ 10,000)	4♂ 4♀

Results

No changes in appearance or behavior

No changes in food consumption, etc.

No laboratory changes

No compound related gross or microscopic pathologic

Slight increase in relative liver weight in 2500-10,000 ppm group at one and two years.

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Two Year Feeding Study in the Dog

In the two year feeding study young purebred male and female Beagle dogs four to six months old were fed diets containing Herbicide 732 (80% wettable powder) at levels of 50, 250, or 2500 ppm of the active ingredient. The upper dietary level was periodically increased from the 26th to the 46th week of the study to a final concentration of 10,000 ppm. All the animals had periodic physical examinations, individual food consumption and individual body weight measurements weekly. After 12 months of compound administration one male and one female dog and the control in each of the test groups were sacrificed and necropsied. The rest of the dogs were continued on studies for the entire period. Periodic hematological and 24 hour urine studies were obtained. Periodic blood glucose, total protein, total albumin BUN, alkaline phosphatase, prothrombin time, SGOT and SGPT, plus cholesterol determinations were done. Complete urinalysis were done on the 24 hour samples periodically.

Results

Behavior, Appearance, and Mortality

No adverse compound-related alterations in behavior or appearance occurred among any of the control or treated dogs used for this study. No mortalities occurred during the two year course of treatment.

Physical Examination

Essentially WNL throughout the study.

Body Weight

The usual fluctuations were noted. There was no evidence obtained in this study of an adverse influence of the test compound on body weight, even at the 2500 - 10,000 ppm dietary level.

Food Consumption

Food consumption was stable. Average daily water intake and urine output was stable.

Laboratory Tests

Hematology

No unusual alterations in hematology were seen in any of the test dogs at any period of examination during this feeding study which could be attributed to the compound effect.

Incidental changes involved a neutropenia and lymphocytosis in one dog at the 250 ppm level, and elevation in bands in seven of eight dogs at 2500 -10,000 ppm dietary level after one month. This elevation was transient.

Biochemical Studies

The only impressive liver function tests were elevations of alkaline phosphatase activity at 18 months or 24 months in four of the eight dogs at the 2500-10,000 ppm level. One control dog also exhibited elevated alkaline phosphatase activity. Other liver functions tests including enzyme studies exhibited WNL throughout the study in particularly these were WNL during the periods of elevated alkaline phosphatase.

Urinalysis

Qualitative and quantitative analysis of the urine specimens obtained from the control and test dogs at specific intervals during this feeding study did not reveal changes suggestive of a compound effect.

The usual bilirubin, or albumin, was noted.
UNA UNA

Pathological Studies

The usual gross examination and microscopic examination was done including specimens of liver and kidneys from the 250 ppm dietary level was sacrificed after one year.

Results

Gross Pathology and Organ Weights

No compound related gross pathologic lesions were seen at necropsy examination in any of the treated dogs which were sacrificed after one or two years of compound administration.

Compound related variations in organ weights were limited to a slight increase in relative liver weight observed in dogs from the 2500-10,000 ppm group. This increase was seen at both the one and two year sacrifices.

UNITED ST ES ENVIRONMENTAL PROTECTIO GENCY

007177

SUBJECT: Terbacil and its hydroxylated metabolites calculated as terbacil in or on alfalfa (hay and forage), and birdsfoot trefoil (hay and forage) at 5 ppm and in or on milk, meat and meat by-products of cattle, goats, hogs, horses and sheep at 0.1 ppm.

DATE: December 20, 1973

FROM:

TO: Mr. Lee TerBush
Acting Chief
Coordination Branch

Pesticide Petition No.: 4F1428 - duPont
Wilmington, Delaware

Related Petitions: 6F0510, 7F0549

Tolerances have been established at 0.1 ppm on citrus fruits and pineapple CFR 180.209 for terbacil per se.

TOXICOLOGICAL REVIEW

The toxicity of terbacil (3-tert-butyl-5-chloro-6-methyl uracil) has been defined for the purpose of establishing tolerances in RAC's in connection with PP Nos. 6F0510 and 7F0549 (reviews of 10/5/66 and 1/16/67, O.G. Fitzhugh). Final reports of long term rat and dog feeding studies had been submitted but not evaluated before the tolerances were set. Therefore, since finite residues in milk are proposed, we herewith submit our evaluation of those data and our recommendations will be based in part on them.

Two Year Dog Feeding Study (#125-011)

007177

Methods:

16 male and 16 female purebred young adult beagles were randomized into four groups, each containing four males and four females. Each group received terbacil at 0, 50, 250 or 2500 - 10,000 ppm in the diet for two years*, following a three week control period.

Food consumption and body weights were measured weekly and periodic detailed physical examinations were done; in addition, daily observations for signs of toxicity or pharmacologic action were made.

12 months into the study, one male and one female from each group were killed and necropsied.

Laboratory tests during the control period and at 1, 2, 3, 6, 12, 18 and 24 months included:

Hematology: total and differential WBC's, Hct., Hb., sed rates and RBC's.

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* As the Formulation, Herbicide 732, 80% WP in terms of AI.

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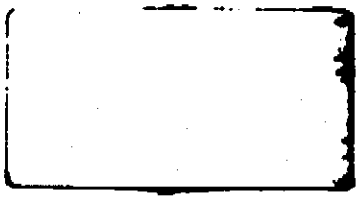

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Plasma Biochemistry: Glucose, total protein, total albumin, BUN, Alk. P., prothrombin time, SGOT, SGPT and Serum Cholesterol, as well as BSP retention times.

Urinalyses: pH, Sp. Gr., bilirubin total N, sediments, formed elements and albumin.

Pathological Examination:

Gross Examination:

At the completion of one year of compound feeding, one male and one female dog from the control and each dietary level were sacrificed by exsanguination while anesthetized with sodium pentobarbital and subjected to necropsy examination. Major organs were weighed and representative tissues were collected into 10 per cent neutral formalin for subsequent histologic processing and microscopic examination. Specimens of brain, liver, kidney, spleen, fat, muscle, testes, blood, urine and feces were collected at necropsy from each dog, frozen and forwarded to the sponsor.

After two years, all remaining dogs were sacrificed and necropsied as described above.

Microscopic Examination:

The following tissues from each control and 2500-10,000 ppm dietary level dog sacrificed after one or two years of compound feeding were paraffin embedded, sectioned, stained with hematoxylin and eosin and examined microscopically:

brain	spleen	liver
spinal cord	lymph node	gall bladder
peripheral nerve	thymus	kidney
pituitary	bone marrow	urinary bladder
thyroid	salivary gland	testis or ovary
parathyroid	stomach	prostate or uterus
adrenal	small intestine	skeletal muscle
lung	large intestine	bone
heart	pancreas	

Specimens of liver and kidneys from the 250 ppm dietary level dogs sacrificed after one year were also prepared and examined.

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4

Results:

No adverse effects on any parameter were noted except that a dose-related increase on thyroid gland/body weight ratios were noted at termination; a marginal increase was seen at 250 ppm and a definite increase in this parameter was seen at the high dose level.

Conclusions:

Terbacil did not induce any overt signs of toxicity in dogs apart from a mild increase in thyroid weights at the 250 ppm levels and above. Accordingly, we conclude that the NEL for this study is 50 ppm terbacil in the diet of dogs for two years.

— Rat

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Reviewed by: Joycelyn Stewart, Ph.D. 9/14/84
Section II, Tox. Branch I(TS-769C)
Secondary reviewer: Marion Copley DVM, 9/24/84
Section II, Tox. Branch I(TS-769C)

83-2

007177

Reviewed 9/23/1983: Gessert

DATA EVALUATION REPORT COVER

STUDY TYPE: Chronic Feeding/Oncogenicity- Mouse TOX. CHEM. NO.: 821A

ACCESSION NUMBER: 249906-249908 MRID NO.: 00126770

TEST MATERIAL: 3-tert-butyl-5-chloro-methyluracil

SYNONYMS: Terbacil 97.8% , H-11,056

STUDY NUMBER(S): 125-0

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

TESTING FACILITY: IRDC
Mattawan, Michigan,

TITLE OF REPORT: Two Year Feeding Study of Terbacil in male and female Charles River CD-1 mice.

AUTHOR(S): Richter, W.R.; Geil, R.C.; Homan, S.P.; Jefferson, B.A. and Blair, M.

REPORT ISSUED: 6/19/1981

Classification: Although the study was previously classified core-Minimum, it is now reclassified core-Supplementary, based on the lack of analysis of the test and control diets and the reported increased incidence of "hyperplastic liver nodules" in high dose male mice. The sponsor is requested to forward the analyses of the test diets to the Agency and to re-evaluate the liver slides using current conventional terminology for the lesions observed. The information requested is important in the evaluation of the oncogenic potential of terbacil The study may be upgraded when the requested information has been submitted and reviewed.

CONCLUSION: The previous review (attached) accurately represents the results of the study. However, on re-review of the study, the following comments are made.

1. The MTD was reached in at least one sex as reflected in the significant decrease in body weight gain in high dose male mice. There was also a significant decrease in survival in that group.

2. The report states that a number of samples were collected during the study and shipped to the sponsor for analysis. The results of the analyses were not included in the submission. The samples were: a) pooled

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urine and fecal samples collected from 10 mice/sex/group at 24 months, b) pooled brain, liver, kidney, spleen, muscle, testes, fat, cardiac blood, urine and feces from the control and each test group at sacrifice, and c) samples of the control and treated diets collected at weeks 3, 22, 36, 37, 52, 63, 70, 80, 89, and 100. The registrant is requested to submit these data.

3. Although the study was reviewed and found to be non-oncogenic under the study conditions, an increased incidence of liver hyperplastic nodules was reported in high dose males as compared to the controls (37.1 v 12.2 percent of those terminally sacrificed, and 15.6 v 13.3 percent of animals which died on study; total incidence 25 percent high dose v 12.7 percent control). It has been Toxicology Branch's experience that, on occasion, lesions diagnosed as "hyperplastic nodules" have been re-classified as adenomas following re-evaluation of the slides. The National Toxicology Program currently classifies lesions with even partial compression as adenomas. Since the morphological description given by the study pathologist could be consistent with more differentiated adenomas, Toxicology Branch cannot accept the diagnosis of liver hyperplastic nodules for the lesions observed in high dose male mice. The registrant is requested to conduct an independent review of the liver slides and report the results using the current conventional terminology. Until this has been done, the study is classified core-Supplementary.

007177

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

SEP 23 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor/V. Walters (25)
Registration Division (TS-767)

THRU: William L. Burnam, Chief
Toxicology Branch/HED (TS-769)

SUBJECT: Two-Year Feeding Study in Mice. Terbacil Registration Standard

Registrant: E.I. duPont de Nemours and Co.
Wilmington, Delaware 19898

To satisfy the requirement for an oncogenic study in a second species, the registrant submitted data from a 2-year feeding study conducted by International Research and Development Corporation in Charles River CD-1 Mice. Our review of their report is attached.

Conclusions:

1. There was an increased incidence of lung adenomas in males at all dosage levels over the controls. However, there was no relationship between dose and the incidence of lung adenomas.

2. There is no significant difference in the incidence of malignant tumors between the controls and the treated groups.

3. Historical control data indicate an incidence of lung tumors in most studies which are equal to or exceed the incidence in the treated male mice in this study.

4. Weighing the above-cited evidence, we consider terbacil to be not oncogenic in the Charles River CD-1 mice.

Roland A. Gessert

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

DLG has RDI 9-20-83

TS-769:th:TOX/HED:RAGessert:5-27-83:card #4
DCR-17477:AUTHOR'S Disket:9/9/83:efs

Thru WBS 9/22/83

Two-Year Feeding Study of Terbacil in Male and Female Charles River CD-1 Mice. Conducted by International Research & Development Corporation, Mattawan, Michigan for E.I. DuPont De Nemours & Co. Haskell Laboratory. June 19, 1981. Study No. 125-027. Accession Nos.: 249906, 249907, 249908.

Material Tested: Terbacil, H-11,086, 97.8% pure technical chemical.

Charles River CD-1 mice were obtained at 4 weeks of age from the Charles River Breeding Laboratories at nearby Portage, Michigan. They were randomly assigned to 4 male and 4 female groups of 80 mice each as follows:

Dosage	Dosage Level ppm	Number of Mice Male	Female
I	0 (control)	80	80
II	50	80	80
III	1250	80	80
IV	5000/7500*	80	80

*Dose level increased to 7500 ppm at week 54.

The mice were housed individually in suspended wire-mesh cages in controlled temperature, humidity, and light (12 hrs light/12 hrs dark). Ad libitum well water and Purina Rodent/Laboratory Chow were provided.

Individual ear punches identified mice for treatments, laboratory data, and necropsy.

The treatment levels of 50, 1250, and 5000/7500 ppm in the diet are based on an 8 week range-finding study. Diets were prepared weekly and refrigerated until use.

The mice were observed 3 times daily during the week and twice daily on weekends and holidays for signs of toxicity and mortality. Detailed examinations, including size and location of palpable masses, were conducted weekly. Individual body weights were recorded weekly at weeks 0-26, week-28, and monthly thereafter. Individual food and chemical consumption was measured and recorded weekly. If an accurate measurement of food consumption could not be obtained due to spillage, etc., that week's measurement was not included in the mean calculation.

"Clinical laboratory tests were conducted on 10 mice/sex/group at 1, 3, 6, 12, 18, and 24 months of the study. Blood was obtained by puncture of the orbital sinus plexus. Hematology determinations included hemoglobin, hematocrit, erythrocyte count, total leucocyte count, and differential leucocyte count. Urine and fecal samples,

pooled by sex and group, were collected from 10 mice/sex/group at 24-months, frozen, and shipped to the sponsor." (page 8 of study)

All surviving mice were killed and necropsied at the end of the study. In the necropsy the external body surface and orifices were examined. Then the mouse was opened and the organs examined in place and after removal from the body. The eyes, testes, and sternum bone marrow were collected in Bouin's fixative. All other tissues and the carcass were fixed in phosphatase buffered neutral 10% formalin. Mice which died or were sacrificed during the study were necropsied in the same manner.

"The following organs were trimmed free of fat and extraneous connective tissue and weighed fresh: spleen, liver/gallbladder, (2), testis (2), heart, lung, thymus, and brain. The pituitary and adrenal (2) were weighed after fixation.

At the time of terminal sacrifice, samples of brain, liver, kidney, spleen, muscle, testis, fat, cardiac blood, urine and feces were pooled by sex and group from the control and each test group, frozen and sent to the Sponsor for residue analysis." (page 8)

H&E stained sections were examined microscopically from the following tissues: adrenals; fore, mid, and hind brain; eyes and Harderian glands; ovaries or testes with epididymides; heart and coronary vessels; esophagus; stomach; jejunum; colon; kidneys; urinary bladder; prostate, or uterine body and cervix; gall bladder; 2 lobes of liver; lung and mainstem bronchi; mediastinal, mesenteric, and regional lymph nodes; mammary gland; mandibular salivary gland; sciatic nerve; pancreas; pituitary; skin; cervical and thoracic spinal cord; spleen; thymus (where present); trachea; thyroid with parathyroid; sternum bone marrow; and any tissue with gross lesions.

"Also 3 coronal sections through the head (including the nasal cavity, paranasal sinuses, tongue, oral cavity, nasopharynx, and middle ear) were examined from 10 mice/sex/dose." (page 9)

In classifying liver lesions, hyperplastic nodules were not considered the same as hepatocellular adenomas, but were described by the IRDC pathologist as "circumscribed, expansive lesion of parenchymal cells whose architecture is very similar to that of normal liver parenchyma...Portal triads and central veins are present within the lesion. The nodule is not encapsulated but compression of the surrounding parenchyma is evident". (page 9-10)

In hepatocellular adenomas, ... "The usual liver architecture of central veins and portal triads is not present within the tumor. The neoplasm is expansive (also) and compresses adjacent parenchyma but does not infiltrate." (page 10)

Statistics: Statistical comparisons were by analysis of variance (one-way classification), Bartlett's test for homogeneity of variances, and the appropriate t-test (for equal or unequal variances), "as described by Steel and Torrie using Dunnett's multiple comparison tables to judge significance of differences".

Diets were sampled frequently during the study and furnished to DuPont for assay.

Results:

Survival at End of Two-Years (Table I)

	0 ppm		50 ppm		1250 ppm		5000/7500 ppm	
Male	49/80	61%	39/80	49%	41/80	51%	35/80	44%*
Female	42/80	52.5%	40/80	50%	33/80	41%	36/80	45%

*Significantly different from controls. $p < 0.05$

Survival compared to controls at the end of the study was less in all the treatment groups. Statistical significance was seen only in the males on the high treatment level.

Body Weights:

No biologically significant differences could be seen in mean body weights and mean food consumption values in the treatment versus the control groups.

No significant differences were seen in efficiency of feed utilization.

Hematology:

Red blood cell counts in males were significantly lower than in controls ($p < 0.05$) at the high dose at 6 months and ($p<0.01$) at 18 months; and significantly lower than controls ($p < 0.01$) at the low dose at 18 months.

Hemoglobin values were slightly but significantly reduced ($p <0.05$) in males on the high dose at 3 and at 18 months, and in low dose females at 6 months.

Hematocrit was increased ($p < 0.01$) in the mid dose males at 1 month and decreased in the low and high dose males at the 6th month and in the high dose males at the 18th month.

Total leucocyte counts were significantly higher in low dose females ($p < 0.01$) and high dose males and females ($p < 0.05$) at one-month.

Neutrophils were significantly higher ($p < 0.05$) in high dose males at 3 months.

Lymphocytes were significantly higher ($p < 0.05$) in low dose males at one month, high dose males at 3 months, and low dose females at 18 months.

None of the changes appear to carry any toxicological significance especially in relation to administration of the chemical.

Gross Necropsy - There were no macroscopic changes between controls and treated mice.

Organ Weights:

The liver (with gall bladder) weighed significantly greater ($p < 0.01$) in the high dose males and females.

The mean liver weights of the low dose females were significantly less ($p < 0.01$) than controls.

The kidney weights in the low dose females ($p < 0.01$) and in the high dose males and females ($p < 0.05$) were significantly less than controls.

Relative testes weights were less in the low dose males ($p < 0.05$).

Adrenal weights were increased in the low dose males ($p < 0.05$) and decreased in the mid dose males.

Mean relative brain weights were decreased ($p < 0.05$) in the high dose males.

Pituitary weights were significantly decreased ($p < 0.01$) in the mid and high dose males and in the high dose females.

FINDINGS IN THE LIVER:
Hyperplastic Nodules, Males

0 ppm		50 ppm		1250 ppm		7500 ppm		
6/49	12.2%	5/39	12.8%	7/41	17.1%	13/35	37.1%	Terminal Sacrifice
4/30	13.3%	4/41	9.8%	5/39	12.8%	7/45	15.6%	Deaths
10/79	12.7%	9/80	11.3%	12/80	15.0%	20/80	25.0%	

Hypertrophy of Centrilobular Hepatocytes, Males

50 ppm		1250 ppm		7500 ppm		
0/49	0/39	6/41	14.6%	33/35	94.3%	Terminal Sacrifice
0/30	0/41	0/39		14/45	31.1%	Deaths
0	0	6/80	7.5%	47/80	58.8%	

Histopathology - Non-Neoplastic Lesions

Hyperplastic nodules were found in livers of males at all levels including controls, with an increased incidence seen at the high dose level, and possibly at the mid-dose level.

Also, in the males hypertrophy of centrilobular hepatocytes were seen in livers of high dose mice and in some of the mid-dose mice. The NOEL for these effects appear to be somewhere between 50 ppm and 1250 ppm.

The hypertrophy of centrilobular hepatocytes may be said to reflect (or be reflected in) the increased liver weights in the high dose males.

There was no increase in incidence of neoplastic lesions in the livers of treated mice.

No other non-neoplastic lesions can be related to administration of the test chemical.

Neoplastic Lesions

The following incidence of neoplasms was seen in lungs:

	Control		50 ppm		1250 ppm		7500 ppm	
	M	F	M	F	M	F	M	F
No. examined	80	80	80	79	80	79	80	80
Adenocarcinoma (%)	2.5	6.25	5.0	0	1.25	2.5	3.75	3.75
Numbers	2	5	4	0	1	2	3	3
Adenoma (%)	13.75	17.5	25.0	26.6	30.0	16.5	23.75	12.5
Numbers	11	14	20	21	24	13	19	10
Total lung tumors (%)	16.25	23.75	30.0	26.6	31.25	19.0	27.5	16.25
Numbers	13	19	24	21	25	15	22	13

The above data appear to indicate an increased incidence of lung tumors in males at all dosage levels over controls, even though the incidence at the high dose is lower than in the low and intermediate dose levels.

The "normal" incidence of lung tumors is known to be high in mice. We do not have specific values for the incidence of lung tumors in the CD-1 Charles River mouse so we requested this information from the International Research and Development Laboratories for control mice from other studies conducted in their laboratory at approximately the same time under the same conditions and receiving the same diet as the controls in this study.

IRDC submitted control data from 12 studies conducted between 1978-1981 in their laboratory, using Charles River CD-1 mice. The incidence of lung tumors were as indicated on the attached chart. In 5 of the 12 studies the incidence of lung tumors in controls exceeded 30%; in 3 others the incidence exceeded 25%. In only one study was there a "low" incidence of lung tumors (6.8%).

1. There was an increased incidence of lung adenomas in males at all dosage levels over the controls. However, there was no relationship between dose and the incidence of lung adenomas.

2. There is no significant difference in the incidence of malignant tumors between the controls and the treated groups.

3. Historical control data indicate an incidence of lung tumors in most studies which are equal to or exceed the incidence in the treated male mice in this study.

4. Weighing the above-cited evidence, we consider terbacil to be not oncogenic in the Charles River CD-1 mouse.

Data meet Core-Minimum requirements.

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IDRC HISTORICAL CONTROL Data - Lung Tumors - Mouse

	A	B	C	D	E	F	G	H	I	J	K	L
Adenoma - incidence (M)	27/80	3/59	31/135	31/101	13/49	16/100	26/120	18/60	1/118	11/75	20/120	18/60
% incidence (M)	33.8	5.1	22.9	30.7	26.5	16	21.6	30	0.8	14.7	16.7	30
incidence (F)	18/80	12/60	21/132	36/100	9/50	21/101	25/120	7/59	4/120	9/75	24/120	13/60
% incidence (F)	22.5	20	15.9	36	18	20.7	20.8	11.9	3.3	12	20	21.7
Carcinoma - incidence (M)	5/80	1/59	4/135	6/101	5/49	9/100	5/120	1/60	21/118	2/75	1/120	5/60
% incidence (M)	6.2	1.7	2.9	5.9	10.2	9	4.2	1.7	17.8	2.7	0.8	8.3
incidence (F)	6/80	0/60	2/132	7/100	1/50	8/101	2/120	3/59	18/120	1/75	4/120	7/60
% incidence (F)	7.5	0	1.5	7	2	7.9	1.7	5.1	15	1.3	3.3	11.7
Total lung tumors % (M)	40	6.8	25.8	36.6	36.7	25	25.8	31.7	18.6	17.4	17.5	38.3
Total lung tumors % (F)	30	20	17.4	43	20	28.6	22.5	17	18.3	13.3	23.3	33.4

	Male	Female
Adenoma - total incidence	215/1077	199/1077
total % incidence	20	18.5
Range of % incidence	0.8 - 30.7	3.3 - 36
Carcinoma - total incidence	65/1077	59/1077
total % incidence	6	5.5
Range of % incidence	0.8 - 17.8	0 - 15

NOTE: Letters correspond to specific studies.

Reviewed by: Joycelyn Stewart, Ph.D.
Section II, Tox. Branch I(TS-769C)
Secondary reviewer: Marion Copley DVM,
Section II, Tox. Branch I(TS-769C)

8207177

Reviewed 9/7/1967: C. Berry, DHEW and 12/20/1973: D. Ritter, Tox. Branch

DATA EVALUATION REPORT COVER

STUDY TYPE: Chronic Feeding - Rat TOX. CHEM. NO.: 821A

ACCESSION NUMBER: N/A MRID NO.: 00060850

TEST MATERIAL: 3-tert-butyl-5-chloro-methyluracil

SYNONYMS: Herbicide 752, Sinbar Weed Killer.

STUDY NUMBER(S): 125-010

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

TESTING FACILITY: IRDC
Mattawan, Michigan,

TITLE OF REPORT: Two Year Feeding Study in the Albino Rat

AUTHOR(S): Wazeter, F.X.

REPORT ISSUED: 3/17/1967

Classification: Supplementary

CONCLUSION: The previous reviews (attached) accurately represents the results of the study. However, the study is deficient by current standards and cannot satisfy the requirement for a chronic and/or oncogenicity study based on the following reasons.

1. An insufficient number of animals was used at start of the study(36/sex/dose).

2. An intercurrent infection was present in the animal colony.

3. An insufficient number of animals survived until termination of the study. The highest survival rate was in the high dose females with 16 survivors.

4. A large number of animals which died during the study were not necropsied due to tissue autolysis, and no histological examinations were done.

5. An insufficient number of sacrificed animals had complete microscopic examinations (only control and high dose animals were examined).

6. An insufficient number of tissues was examined. In the low dose group liver only was examined and in the mid dose group liver and kidney were examined at the one year sacrifice. In the mid dose group liver only was examined at the terminal sacrifice.

7. Biochemical examinations consisted of liver function tests only, and only 6 animals/sex/group were examined.

8. The investigators reported the presence of hyperplastic nodules in some of the test animals. In view of the current interpretation of these lesions, Toxicology Branch is concerned that the test compound might have induced neoplastic lesions.

Summary

Two Year Feeding Study in Albino Rats

1st Control	36	36
2nd Control	36	36
# 1 Test	36	36
# 2 Test	36	36
# 3 Test	36	36
	180	180

Three Test Groups

#1 50 ppm

#2 250 ppm

#3 2500 ppm - after 28 weeks ↑ every 2 weeks by 500 ppm to 5000 ppm by 36 weeks - then ↑ every 2 weeks by 1000 ppm to 10,000 ppm by 46 weeks - then 10,000 ppm maintained.

Results

No adverse compound related behavior or appearance changes

and [redacted] at 2500-10,000 ppm level exhibited significantly lower rate of body weight gain (maximum 24-2%; (♂) 14-1%)

No changes in food consumption

No changes in LFT, U/A or CBC

No compound related gross pathological lesions at necropsy

Only compound related variation in organ weight was a slight ↑ in liver weight in rats at the 2500-10,000 ppm level after two years.

Compound related histologic changes at one year were limited to the livers of rats at 250 ppm and 2500-10,000 ppm i. e. hepatocyte vacuolation and/or hypertrophy.

And at 2 years the only liver changes (as above) were seen in the rats from the 2500-10,000 ppm group and not the 250 ppm group.

There was no indication of any compound related carcinogenic effect at any dietary level.

Two Year Feeding Study in the Albino Rat .

Methods

180 male and 180 female albino rats were used for this study. The animals were divided into two control groups and three test groups of 36 male and 36 female rats each. Herbicide 732 was incorporated into the standard powdered laboratory diet. Compound in the diet was prepared in such a manner that the rats received Herbicide 732 (80% wettable powder) at dietary levels equivalent 50, 250 or 2500 ppm of the active ingredient. Begining in the 28th week of the study the dietary levels of the compound of the group receiving the highest concentration (2500 ppm) was increased every two weeks by 500 ppm increments until a dietary level of 5,000 ppm was reached in the 36th week study. Thereafter the dietary levels were increased by 1,000 ppm increments every two weeks until 10,000 ppm was attained in the 46th week of study. The latter concentration was maintained for the duration of the study.

Control and test animals were observed daily for mortality, alteration in general appearance and behavior, and gross signs of pharmacodynamic and/or toxic effects.

Body weights, food consumption, and compound consumption values were measured weekly for the first 27 weeks and at biweekly intervals thereafter.

The usual hematologic studies were performed at regular intervals throughout the 24 months of feeding. SGOT, SGPT and plasma alkaline phosphatase studies were performed at the same intervals.

Urinalysis were performed at the same intervals.

Results

General Behavior and Appearance--No adverse compound induced alterations in behavior and appearance were observed at any of the dietary levels during the study. Incidental findings, however, involved the incidence of occasional pneumonia in the test animals, eventually necessitating therapy with penicillin and Streptomycin. Therapy was successful. Post treatment incidence and severity of the disease was much less. Nodules and masses appeared on the body beginning in the fifth month of the study and gradually increasing in incidence in all groups thereafter, particularly in the second year of the study.

Body Weights

Male rats in the 50 and 250 ppm dietary levels compared favorably with respect to body weight to the two control groups throughout the period of the study.

Male rats at the 2500-10,000 ppm dietary level exhibited gains in mean body weight comparable to both control groups during the first year of the study. A slight decrease in body weight was exhibited from the 67th week to the termination of the study. This group exhibited a 10% or greater decrease in mean body weight in control groups from the 65th to the 101st week of the study. A maximum decrease of 17% occurred

during the 89th week of feeding.

Female Rats

The test groups of female rats at the 50 and 250 ppm dietary levels exhibited essentially similar gains in mean body weights as the two control groups throughout the two years of feeding the test compound.

Female rats at the 2500-10,000 ppm dietary levels exhibited mean body weights which were much less than those of the control groups. This difference appeared early in the study and gradually increased through the 81st week. On decreases of 23 and 27% respectively were observed at the termination of the study the females rats at the 2500-10,000 ppm dietary levels weighed approximately 20-24% less than the control groups of female rats.

Food Consumption etc.

No meaningful differences in food consumption were found between the control groups and the test groups of rats used for this study.

Survival

No significant differences were found between the control and test groups of rats of either sex with respect to mortality in this study.

Laboratory Tests

Hematology--No compound related abnormalities were revealed.

Biochemistry--No compound related alterations were noted.

Urinalysis—No unusual alterations in urinalysis were seen.

Incidental findings not considered to be related to the feeding of the test compound included an occasional positive reaction for occult blood and albumin. These occurred with similar frequency in the control and test groups of rats. Albuminuria is a common finding in the urine of the laboratory rat, the significance of which remains obscure.

Pathological Studies

Methods

Gross Observations

After one year of feeding, sufficient rats from each dietary level were sacrificed by decapitation to reduce group numbers in each group to 30 of each sex. All surviving rats were sacrificed after two years of feeding the compound. All rats that were sacrificed or died on study were subjected to necropsy examination, unless precluded by autolysis. Major organs were weighed and representative tissues were collected. The usual microscopic observations were made including brains, spinal cord and peripheral nerve sections.

Masses and grossly undiagnosed lesions from lower dietary levels sacrificed at two years or from rats from any group which died during the study were also processed and and examined microscopically.

Results

No compound-related gross pathologic lesions were observed in rats which died during the study or were sacrificed after one or two years.

Of note in the necropsy observations in the two year sacrificed animals is the high incidence of enlarged or hemorrhagic pituitary glands, most marked in the females but having the approximate same incidence between control and test group animals. Also noted was an approximate 25% incidence of subcutaneous abdominal masses in both control and test group animals. A higher number of deaths due to pneumonia was noted in both test and control animals. Nephritis was noted. The only compound related variation in organ weights was a slight increase in liver weight among rats in the 2500 to 10,000 ppm level sacrificed after two years of study.

Histopathology

Compound related microscopic changes were found only in the livers of rats from 2500 to 10,000 ppm and 250 ppm dietary groups sacrificed after one year of feeding and only in livers of rats on the 2500 to 10,000 ppm levels sacrificed after two years of feeding. These changes consisted of enlargement of centrolobular hepatocytes with the usual coarse granularity of the cytoplasm replaced by cytoplasm which was more homogeneous but still contained some coarse granules. Nuclei of these cells often appeared larger than normal hepatocyte nuclei. In many rats, primarily females the enlarged hepatocytes contained one to several spherical vacuoles within the cytoplasm.

Although compound related liver changes were seen in one of four rats from the 250 ppm dietary level after one year of compound feeding, no compound related liver changes were found in any of the 22 rats from this level which were sacrificed after two years.

Although liver masses were described at the two year sacrifice in some control and treated rats, these lesions in all cases were hyperplastic nodules and there was no indication of compound related carcinogenesis of liver or other tissues associated with the feeding of this material to rats. There was not an increase incidence of portal lympocytic infiltrate, focal necrosis, bile duct proliferation, bile duct cyst, nodular hyperplasia, telangiectasia, reticulum cell sarcoma in the liver. Extreme arteritis was noted in the pancreas of one of the 2500 to 10,000 ppm test group animals. This finding was probably not of significant interest. In the incidence of neoplasms by site (Table 62) is the relatively high incidence of mammary fibroid abnormal or with the incidence of the control group was the same or less as the incidence in the test animals.

UNITED ST ES ENVIRONMENTAL PROTECTIO GENCY

SUBJECT: Terbacil and its hydroxylated metabolites calculated as terbacil in or on alfalfa (hay and forage), and birdsfoot trefoil (hay and forage) at 5 ppm and in or on milk, meat and meat by-products of cattle, goats, hogs, horses and sheep at 0.1 ppm.

DATE: December 20, 1973

FROM:

TO: Mr. Lee TerBush
Acting Chief
Coordination Branch

Pesticide Petition No.: 4F1428 - duPont
Wilmington, Delaware

Related Petitions: 6F0510, 7F0549

Tolerances have been established at 0.1 ppm on citrus fruits and pineapple CFR 180.209 for terbacil per se.

TOXICOLOGICAL REVIEW

The toxicity of terbacil (3-tert-butyl-5-chloro-6-methyl uracil) has been defined for the purpose of establishing tolerances in RAC's in connection with PP Nos. 6F0510 and 7F0549 (reviews of 10/5/66 and 1/16/67, O.G. Fitzhugh). Final reports of long term rat and dog feeding studies had been submitted but not evaluated before the tolerances were set. Therefore, since finite residues in milk are proposed, we herewith submit our evaluation of those data and our recommendations will be based in part on them.

Two Year Rat Feeding Study (#125-010)

Methods:

Charles-River CD rats were randomized into two control and three test groups of 36 males and 36 females each and were given 0, 50, 250 or 2500 ppm AI* in the diet for two years. The 2500 ppm group received increments of 500 ppm or 1000 ppm every two weeks until a level of 10,000 ppm was attained in the 46th week.

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* As Herbicide 732; 80% WP.

1 19

Daily observations were made for mortality, appearance, behavior and/or gross signs of toxicity.

Body weight and feed consumption were measured at appropriate intervals, and food efficiency values were calculated.

Clinical observations:

Hematology consisted of total and differential leucocytes, RBC, Hct., Hb., performed on six male and six females per group at 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 months.

Biochemistry examinations consisted of SGOT, SGPT and Alk. P. at similar intervals but on different rats in each group.

Urinalyses were performed at similar intervals and consisted of detection of glucose, albumin, bilirubin, occult blood, Sp. Gr., pH and formed elements.

Pathological examination was done at one year and at termination. The following tissues were prepared and examined histologically (*) organ weights obtained:

Brain*	Peripheral N.	Pituitary*
Adrenal*	Heart*	Spleen*
Thymus*	Salivary gland	Sm. Intestine
Pancreas	Kidney*	Gonads*
Spinal Cord	Eye	Thyroid*
Lung*	Aorta	Lymph Node
Bone Marrow	Stomach	Lge. Intestine
Liver*	Bladder	Prostate or Uterus
	Skel. M.	

Results:

No effects on appearance or behavior were noted at any time during the study.

Body weights of the low and middle dose rats increased normally but those of the high dose group leveled off at about 1 year into the study. Feed consumption and utilization were not affected by terbacil intake.

A respiratory epizootic occurred in all groups during the study which required tetracycline, penicillin and streptomycin therapy. The problem subsequently abated but did not disappear entirely.

Hematological, urological and biochemical parameters were not appreciably altered during the study.

Mortality from incidental causes, principally pneumonia, was high in all groups, with 100% dying in the 250 ppm female group.

Histopathological examination of representative tissues failed to demonstrate any clear-cut dose-related adverse effects at any level of terbacil administration.

Conclusions:

Few toxic effects, if any, can be attributed to terbacil in the diet of rats for two years. Therefore, we conclude that the NEL is 250 ppm based on retarded weight gain in the high dose group (2500 to 10,000 ppm).

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

007177

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 adverse reproductive effects were seen (MRID 00126770).

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_{2b} 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.

0071777

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

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Sinbar

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 Herbicide 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 F_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 F_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 lesions 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 lesions 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.

Reviewed by: Joycelyn Stewart, Ph.D. 2/27/89
Section II, Tox. Branch I IRS(H7509C)
Secondary reviewer: Marion Copley D.V.M. MPC 3/23/89
Section II, Tox. Branch I IRS (H-7509C)

007177

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

DATA EVALUATION REPORT COVER

STUDY TYPE: Teratology

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 Crescent to Taylor 10/1/93. Tox. Document 003401

007177

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 13, 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 19 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

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

007177

MEMORANDUM

DATE: SEP 14 1981

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Terbacil Teratology Study
CASWELL NO. 821A

FROM: 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 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.

007177

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:s11:CM#2:RM.816:X73710:9/10/81 card 1

Reviewed by: Joycelyn Stewart, Ph.D. 3/7/89
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.

007177 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

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

	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		4/2		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 dogs 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.

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END