5-6-94

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

MAY 6 1994

010953

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Terbuthylazine: Upgrade chronic studies and data base

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Submission #: N/A
Tox. Chem #/PC #: 125B/080814

FROM: Marion Copley, DVM, Section Head
Section 4, Tox. Br. 1
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Marion Copley 5/2/94

TO: B. Lowery/L. Schnaubelt (PM #72)
Reregistration Branch
Special Review and Reregistration Division (7508C)
and
George Ghali
Science Analysis Branch
Health Effects Division (7509C)

THRU: William Greear, MPH
Section 4, Tox. Br. 1,
Health Effects Division (7509C)
Linda J. Hansen 5/3/94 (for)

CONCLUSIONS:

The original data evaluation records for the two chronic/onco feeding rat (MRIDs 00156486 and 00157342, HED DOC.#s 002994 and 005834) and onco mouse (MRIDs 00156487, HED DOC. # 005834) studies have been reevaluated and updated (see attached DER supplements). These have been approved by the HED RfD/Peer Review Committee at a meeting held on 3/7/94. Even though the IBT 3 generation rat reproduction study was validated, the RfD Committee considered the study to be scientifically invalid. The

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RfD committee changed the NOEL and LEL for the 1983 Rabbit developmental toxicity study from less than 4.5 mg/kg/day to: NOEL = 1.5 mg/kg/day and LEL = 4.5 mg/kg/day. This study is also upgraded from supplementary to minimum. See discussion for details. The new executive summaries for the above studies are at the end of this memo.

ACTION REQUESTED:

The HED RfD committee (3/7/94) requested that TB1 downgrade the reproduction study to invalid and change the NOEL and LEL for the 1983 rabbit developmental study. In addition, DER supplements for the rat and mouse chronic/onco studies are attached.

DISCUSSION:

3-Generation Rat Reproduction Study (MRID # 00103087, HED DOC. # 002994)

The HED RfD committee concluded that although this study was validated as an IBT study, is should be downgraded to **core-invalid** for scientific reasons including a low mating index in the controls in the first generation.

Developmental Toxicity Study - rabbit (MRID # 00130744, HED DOC. # 003581)

The original DER considered the maternal and developmental NOELs to be greater than 4.5 mg/kg/day (the highest dose tested). The HED RfD Committee however, concluded that the developmental NOEL should be decreased to 1.5 mg/kg/day. It was felt that the post implantation loss (embryonic death) observed at the high dose was treatment related (11.5, 13.1, 14.9 and 22.8 % loss for controls through high dose, respectively). The 1-liners incorrectly list the core-grade for this study as supplementary while the original DER calls it core guideline. As a result of the reevaluation of the study the core classification is now considered to be core-minimum. Attached are several tables from the study report needed to upgrade the DER. The executive summary follows. No supplemental DER will be completed.

EXECUTIVE SUMMARIES:

83-5 Title of Report: GS 135299--Lifetime Carcinogenicity and Chronic Toxicity Study in Rats
Study Number: 785196

In a 2 year chronic feeding/carcinogenicity study, terbuthylazine (96.8 % ai) was administered to a total of 80/sex/dose for 24 months to Tif:RAIF(SPF) rats at dose levels of 0, 30, 150 or 750

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ppm (males - 0, 1.24, 6.97, or 41.47 mg/kg/day; females 0, 1.37, 7.81 or 52.80 mg/kg/day). Twenty/sex/dose of these were sacrificed at 24 months and 10/sex/dose at 12 months. The remaining animals that received terbuthylazine for 24 months were placed on diets lacking the test material until final sacrifice at week 112 (males) and 122 weeks (females) (MRID# 00156486)

At 30 ppm and above, percent body weight gain compared to controls was decreased in males (e.g., 10, 28 and 49 % at week 54, low to high) and females (e.g., 12, 32 and 47 % at week 54, low to high). At 30 ppm and above, food consumption was decreased in males (e.g., 9, 14 and 25 %, respectively at 54 weeks) while in females only at 150 ppm and above (10 % at 54 weeks). At 150 ppm and above in females, BUN and urinary specific gravity were increased while urinary volume and pH were decreased. These changes were noted in males at 750 ppm only. At 750 ppm (compared to controls) there were increased lesions in males (macroscopic hepatic cysts, Leydig cell nodular hyperplasia of the testis (27 vs. 9 %) and increases in benign interstitial cell tumors of the testes (13 vs. 4 %)) and females (macro and microscopic hepatic cysts, mammary carcinoma (18 vs. 5 %)). **The LEL is less than 30 ppm based on decreased percent body weight gain (males and females) and food consumption (males). The NOEL is less than or equal to 30 ppm.**

Terbuthylazine administration appeared to be associated with an increase of mammary carcinomas (but not total mammary tumors) at the high dose. This will be presented to the Cancer Peer Review Committee.

The study when taken in combination with study #791229, is classified as Core-Minimum (supplementary when considered alone) and satisfies the guideline requirements for a chronic feeding and cancer study in rats (83-5).

83-5 Title of Report: Lifetime Carcinogenicity and Chronic Toxicity Study in Rats
Study Number: 791229

In a 2 year chronic feeding/carcinogenicity study, terbuthylazine (98 % ai) was administered to 80/sex/dose (98 weeks), of these 20/sex/dose (24 months) and 10/sex/dose (12 months) Tif:RAIF(SPF) rats at dose levels of 0, 6 or 30 ppm (males - 0, 0.35 or 1.6 mg/kg/day; females 0, 0.36 or 1.6 mg/kg/day). Animals fed for 98 weeks were placed on diets lacking the test material until final sacrifice at week 118 (males) and 121 weeks (females) (MRID# 00157342).

At 30 ppm there were decreases in percent body weight gain in males (7 %) and females (12 %) as well as decreases in food consumption in males (6 %) and females (11 %). **The LEL of 30 ppm**

is based on transient decreases in body weight and food consumption consistent with another study). The NOEL is 6 ppm.

Terbuthylazine administration was not associated with an increase of tumors at the doses tested.

The study when in combination with study # 785196, is classified as Core-Minimum and satisfies the guideline requirements for a chronic feeding and cancer study in rats (83-5).

83-2b Title of Report: Chronic Toxicity and Carcinogenicity Study in Mice
Study Number: 785195 (GU)

In a 2 year chronic feeding/carcinogenicity study, terbuthylazine (98 % ai) was administered to 50/sex/dose Tif:MAGF(SPF) mice at dose levels of 0, 30, 150 or 750 ppm (males - 0, 3.28, 16.99, or 86.76 mg/kg/day; females 0, 3.22, 16.66 or 88.54 mg/kg/day) (MRID# 00156487).

Percent body weight gains of males in the 750 ppm group were decreased by approximately 10 % while in females it was decreased by approximately 23 % throughout most of the study. Food consumption was decreased in males in the 750 ppm group by approximately 20 % throughout most of the study. **The LEL of 750 ppm is based on decreased body weight in females (and to a lesser extent males) and a possible decrease in food consumption in males. The NOEL is 150 ppm.**

There was no evidence that terbuthylazine administration was associated with an increase of tumors.

The study is classified as Core-Minimum and satisfies the guideline requirements for a chronic feeding and cancer study in mice.

83-3b Title of Report: Effect of TK 12 699/1 on Pregnancy of the New Zealand White Rabbit
Study number: CBG 345/341/83354

In a developmental rabbit study (MRID: 00130744), female New Zealand White rabbits were dosed from day 7 through 19 of gestation by gavage with terbuthylazine, GS 135259 (98.5% purity) in 1 % methylcellulose, 14 controls, 13 at 0.5 mg/kg/day, 15 at 1.5 mg/kg/day and 17 at 4.5 mg/kg/day. Animals were sacrificed on day 29 of gestation.

There were no signs of maternal toxicity at any dose in the main study. In a preliminary study, body weight loss was observed at 12.5 mg/kg/day but not at 5 mg/kg/day. **The maternal NOEL is**

equal to or greater that 4.5 mg/kg/day. The LEL is greater than 4.5 mg/kg/day.

Signs of developmental toxicity were limited to the 4.5 mg/kg/day group and consisted of increased post implantation loss (embryonic death) (11.5, 13.1, 14.9 and 22.8 % loss for controls through high dose, respectively). **The LEL for developmental toxicity is 4.5 mg/kg/day based on increased post implantation loss. The NOEL for developmental toxicity is 1.5 mg/kg/day.**

This study is classification core-minimum data for developmental toxicity (83-3b) and satisfies the guideline requirements for a developmental toxicity study in rabbits.

NOTE: Although the current registration is for non food use with limited nondietary exposure (water cooling towers) the following data gaps have been identified for the technical if a food use registration should be requested in the future:

83-1b chronic oral dog study
83-4 2 generation reproduction study
85-1 general metabolism study

The following study requirements (technical) have been satisfied:

81-1 - 81-6 acute toxicity studies
82-1 will be or is satisfied by 83-1
82-2 subchronic (28 day) dermal rat
83-1a chronic feeding rat
83-2a cancer rat
83-2b cancer mouse
83-3a,b rat and rabbit developmental
84-2 mutagenicity series

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Reviewed by: William B. Greear, MPH 5/3/94
Section 4, TB1 (7509C)
Secondary Reviewer: Marion P. Copley, DVM 5/2/94
Section 4, TB1 (7509C)

SUPPLEMENTAL DATA EVALUATION REPORT
(ORIGINAL DER-DOC # 002994, 005834)

Study Type: 2-year Chronic Feeding/Cancer - rat (83-5)

Tox. Chem. No.: 125B P.C.Code: 080814

MRID: 00157342

Test Material: Terbuthylazine

Synonyms: GS 13529 Technical, Belclene™ 329

Study Number: 791229

Sponsor: Ciba-Geigy, LTD., Basle, Switzerland

Testing Facility: Ciba-Geigy, LTD., 4332 Stein, Switzerland

Title of Report: Lifetime Carcinogenicity and Chronic Toxicity Study in Rats

Author: W. Gfeller, W Basler, F. Zak, R. Hess

Report Issued: June 17, 1983

Executive Summary:

In a 2 year chronic feeding/carcinogenicity study, terbuthylazine (98 % ai) was administered to 80/sex/dose (98 weeks), 20/sex/dose (24 months) and 10/sex/dose (12 months) Tif:RAIF(SPF) rats at dose levels of 0, 6 or 30 ppm (males - 0, 0.35 or 1.6 mg/kg/day; females 0, 0.36 or 1.6 mg/kg/day). Animals fed for 98 weeks were placed on diets lacking the test material until final sacrifice at week 118 (males) and 121 weeks (females) (MRID# 00157342).

At 30 ppm there were decreases in percent body weight gain in males (7 %) and females (12 %) as well as decreases in food consumption in males (6 %) and females (11 %). **The LEL of 30 ppm is based on transient decreases in body weight and food consumption consistent with another study). The NOEL is 6 ppm.**

Terbuthylazine administration was not associated with an increase of tumors at the doses tested.

The study when in combination with study # 785196, is classified as Core-Minimum and satisfies the guideline requirements for a chronic feeding and cancer study in rats (83-5).

Special Review Criteria (40 CFR 154.7) None

Discussion:

Note: This reevaluation of the original review differs with respect to the following:

1) There are no discrepancies with the initial review. However the conclusions have been put into executive summary format.

Few animals (8-22/sex/dose)were alive at the terminal sacrifice. Percent body weight gain of male rats in the 30 ppm group was slightly decreased during the first 26 weeks (e.g. 7 % at 13 weeks). Percent body weight gain of female rats in the 30 ppm group was decreased by up to approximately 13 % during the second year of the study. Food consumption was decreased in males during the first 13 weeks (e.g. 6 %, week 13) and in females (e.g., 12 %, week 13). No significant differences were noted thereafter. there were no adverse effects on survival, hematology, clinical chemistry, urinalysis, organ weights macroscopic and microscopic lesions.

TERB83-5.RA2

Reviewed by: William B. Greear, MPH 5/3/94
Section 4, TB1 (7509C)
Secondary Reviewer: Marion P. Copley, DVM 5/2/94
Section 4, TB1 (7509C)

SUPPLEMENTAL DATA EVALUATION REPORT
(ORIGINAL DER Doc # 002994, 005834)

Study Type: 2-year Chronic Feeding/Cancer - rat (83-5)

Tox. Chem. No.: 125B P.C.Code: 080814

MRID: 00156486

Test Material: Terbuthylazine

Synonyms: GS 13529 Technical, Belclene™ 329

Study Number: 785196

Sponsor: Ciba-Geigy, LTD., Basle, Switzerland

Testing Facility: Ciba-Geigy, LTD., 4332 Stein, Switzerland

Title of Report: GS 135299--Lifetime Carcinogenicity and Chronic Toxicity Study in Rats

Author: W. Gfeller, W Basler, F. Zak, R. Hess

Report Issued: June 16, 1983

Executive Summary:

In a 2 year chronic feeding/carcinogenicity study, terbuthylazine (96.8 % ai) was administered to a total of 80/sex/dose for 24 months to Tif:RAIF(SPF) rats at dose levels of 0, 30, 150 or 750 ppm (males - 0, 1.24, 6.97, or 41.47 mg/kg/day; females 0, 1.37, 7.81 or 52.80 mg/kg/day). Twenty/sex/dose of these were sacrificed at 24 months and 10/sex/dose at 12 months. The remaining animals that received terbuthylazine for 24 months were placed on diets lacking the test material until final sacrifice at week 112 (males) and 122 weeks (females) (MRID# 00156486)

At 30 ppm and above, percent body weight gain compared to controls was decreased in males (e.g., 10, 28 and 49 % at week 54, low to high) and females (e.g., 12, 32 and 47 % at week 54, low to high). At 30 ppm and above, food consumption was decreased in males (e.g., 9, 14 and 25 %, respectively at 54 weeks) while in females only at 150 ppm and above (10 % at 54 weeks). At 150 ppm and above in females, BUN and urinary specific gravity were increased while urinary volume and pH were decreased. These changes were noted in males at 750 ppm only. At 750 ppm (compared to controls) there were increased lesions in

males (macroscopic hepatic cysts, Leydig cell nodular hyperplasia of the testis (27 vs. 9 %) and increases in benign interstitial cell tumors of the testes (13 vs. 4 %)) and females (macro and microscopic hepatic cysts, mammary carcinoma (18 vs. 5 %)). **The LEL is less than 30 ppm based on decreased percent body weight gain (males and females) and food consumption (males). The NOEL is less than or equal to 30 ppm.**

Terbuthylazine administration appeared to be associated with an increase of mammary carcinomas (but not total mammary tumors) at the high dose. This will be presented to the Cancer Peer Review Committee.

The study when taken in combination with study #791229, is classified as Core-Minimum (supplementary when considered alone) and satisfies the guideline requirements for a chronic feeding and cancer study in rats (83-5).

Special Review Criteria (40 CFR 154.7) None

Discussion:

Note: This reevaluation of the original review differs with respect to the following:

1) Hematological effects in females in the 150 ppm group are considered to be marginal and of little biological significance.

2) Organ weight changes noted in the initial review are considered to be variable. They probably only reflect changes in body weight and are of little biological relevance.

3) Inflammatory cell infiltration of the lung and nodular hyperplasia of the thyroid are not considered to be compound related and probably reflect normal biological variation.

Percent body weight gain of males in the 30, 150 and 750 ppm groups was decreased (e.g., 10, 28 and 49 % at week 54, respectively). Percent body weight gain of females in the 30, 150 and 750 ppm groups was also decreased (e.g., 12, 32 and 47 % at week 54, respectively). The decreases were maintained throughout the study and were slightly greater in females at week 105 (16 %, 35 % and 61 %). Food consumption was decreased in males in the 30, 150 and 750 ppm groups (e.g., 9, 14 and 25 %, respectively) at 54 weeks. In females food consumption was also slightly decreased at 54 weeks (5, 10 and 10 %). Females in the 750 ppm group had consistent but small decreases in RBC, HGB and HCT (e.g., 4, 3.5 and 5 %, respectively at week 52). Males in

the 750 ppm groups had increases in BUN (e.g., 43 %) at 52 weeks. Males in this group also had decreases in urinary pH (14 %) and volume (47 %) and increases in specific gravity (1 %) at week 52. Females in the 150 and 750 ppm groups had increases in BUN (e.g., 40, and 56 % for mid and high doses) at 52 weeks. Females at the 750 ppm group similarly had decreases in urinary pH (14 %) and volume (47 %) and increases in specific gravity (1 %) at week 52. Males in the 150 ppm group also had decreases in urinary pH (14 %) and volume (38 %) and increases in specific gravity (1 %). Organ weight data were generally uninterpretable. Animals in the 750 ppm group had decreases in the absolute weight of several organs, however, the relative weights (to body weight) were increased. This can probably be attributed to the large decreases in body weight as the dose increased.

Males and females in the 750 ppm group had increases in **macroscopic** lesions (cysts) in the liver (i.e., none in the controls, as compared to 4 in males and 10 in females). Only females in the 750 ppm group exhibited an increase in **microscopic** lesions (e.g., 4 in controls as compared to 14 in the high dose). Males in the 750 ppm group had increases in Leydig Cell nodular hyperplasia (e.g., 9, 4, 7 and 27 %, controls to high dose). Males in the 750 ppm group also had increases in benign interstitial cell tumors of the testes (e.g., 4, 5, 3 and 13 %, control to high dose). These were outside the historical control[1] mean and range (2.7%; 0 - 7.5 %). Females in the 750 ppm group had increases in mammary gland carcinomas (e.g. 5, 11, 4 and 18 %, controls to high dose). This is double the historical control[1] mean and just outside the range (9.6 %; 2.6 - 16.5 %). In addition, at the 1-year interim sacrifice, 1 female in the 750 ppm group had already developed a carcinoma. If all mammary gland tumors (adenoma, fibroadenoma and carcinoma) were combined however, there is no apparent increase in tumor rate.

TERB83-5.RAT

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[1]Historical control data attached to this DER. Received by FAX on 4/27/94 from C. Breckenridge to M Copley.

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Reviewed by: William B. Greear, MPH Section 4, TB1 (7509C) Linda P. Hansen for 5/2/94
Secondary Reviewer: Marion P. Copley, DVM Section 4, TB1 (7509C) Marion Copley 5/2/94

SUPPLEMENTAL DATA EVALUATION REPORT
(ORIGINAL DER Doc # 005834)

Study Type: 2-year Chronic Feeding/Cancer - mouse (83-5)

Tox. Chem. No.: 125B P.C.Code: 080814

MRID: 00156487

Test Material: Terbuthylazine

Synonyms: GS 13529 Technical, Belclene™ 329

Study Number: 785195 (GU)

Sponsor: Ciba-Geigy, LTD.

Testing Facility: Ciba-Geigy, LTD.

Title of Report: Chronic Toxicity and Carcinogenicity Study in Mice

Author: W. Gfeller

Report Issued: August 1982

Executive Summary:

In a 2 year chronic feeding/carcinogenicity study, terbuthylazine (98 % ai) was administered to 50/sex/dose Tif:MAGF(SPF) mice at dose levels of 0, 30, 150 or 750 ppm (males - 0, 3.28, 16.99, or 86.76 mg/kg/day; females 0, 3.22, 16.66 or 88.54 mg/kg/day).

Percent body weight gains of males in the 750 ppm group were decreased by approximately 10 % while in females it was decreased by approximately 23 % throughout most of the study. Food consumption was decreased in males in the 750 ppm group by approximately 20 % throughout most of the study. **The LEL of 750 ppm is based on decreased body weight in females (and to a lesser extent males) and a possible decrease in food consumption in males. The NOEL is 150 ppm.**

There was no evidence that terbuthylazine administration was associated with an increase of tumors.

The study is classified as Core-Minimum and satisfies the guideline requirements for a chronic feeding and cancer study in mice.

Terbuthylazine 83-5 mouse

Special Review Criteria (40 CFR 154.7) None

Discussion:

Note: This reevaluation of the original review differs with respect to the following:

1) Hematological changes (RBC, HCT, HGB) in females at 750 ppm are of no biological significance.

2) Clinical chemistry changes (decreases in urea, sodium and cholesterol) are of no biological significance.

3) Urinalyses changes are not of serious toxicological significance then considered in the absence of other signs.

4) The NOEL is 150 ppm and the LEL is 750 ppm.

Survival was unaffected by treatment. Survival in the males at 750 ppm was about 50 % compared to controls of about 20 %. Female survival rate at termination was approximately 40 %. Percent body weight gains in males at 750 ppm were decreased about 10 % at 105 weeks. In females in the 750 ppm group it was decreased by 23 % at 105 weeks. Statistically significant decreases in mean body weight gain were up to 34 % less than controls throughout most of the study. Food consumption was decreased about 20 % in males at 750 ppm, throughout most of the study. There were spurious changes in hematology and clinical chemistries. There were several differences in organ weights and organ to body weight ratios, however, they were not considered to be treatment related. Urine volume was decreased in all male mice at the low, mid and high dose groups (37 %, 74 % and 60 %, respectively). This is consistent with an increase in specific gravity of 0.01 %, 2 % and 1% for low, mid and high doses. Other urinalysis parameters were not affected. These changes in the males do not appear to be biologically significant since there were no other signs of toxicity associated with them, other than decreased food consumption in males.