10-7-87

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

006352

OCT 7 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: A Review of Toxicology Data Submitted in Support of Petition 6E3409 for the use of Terbufos in/on Imported Bananas at 0.025 ppm. - EPA Accession No. 400986; Toxicology Branch Proj. No. 7-0549; Caswell No. 131A.

FROM: Alan C. Levy, Ph.D.
Toxicologist, Review Section V Alan C. Levy 10/6/87
Toxicology Branch/HED (TS-769C)

TO: William Miller - PM # 16
Registration Division (TS-767C)

THRU: Quang Q. Bui, Ph.D., D.A.B.T.
Acting Section Head, Review Section V Quang Q Bui 10/7/87

and

Theodore M. Farber, Ph.D., D.A.B.T. H for WMS 10/7/87
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: American Cyanamid Company

Action Requested: Review toxicology data submitted in support of Petition 6E3409 for the use of Terbufos in/on imported bananas at 0.025 ppm.

Background Information: A tolerance of 0.025 ppm is proposed by American Cyanamid Company for residues of the insecticide/nematicide Terbufos and its cholinesterase-inhibiting metabolites in/on the imported raw agricultural commodity bananas.

This proposed import tolerance was previously submitted to the Agency on 4/21/86 for review. The petition was not supported (memo of J. Rowe to W. Miller, 2/26/87) due to significant toxicology data gaps and the lack of acceptable studies from which an ADI could be calculated.

006352

1 of 106

In tnis action, the following studies are submitted for review:

1. Developmental toxicity study - rabbits.
2. Developmental toxicity study - rats.
3. One year oral toxicity study - dogs.
4. One year oral toxicity study - rats.
5. Eighteen month oncogenicity study - mice.
6. Dominant Lethal study - rats.
7. Acute in vivo cytogenetic assay - rats.

Studies Reviewed:

1. Developmental Toxicity Study in Rabbits - Study No. 6123-116, Dated 1/15/85, Testing Facility: Hazleton Laboratories America, Inc. (Reviewed by Dr. J. Rowe).

In the developmental toxicity study in rabbits, the following limitations preclude the proper evaluation of the maternal and/or developmental toxicity of Terbufos: inadequate number of litters in mid- and high-dose groups (FIFRA Guidelines require at least 12 per dose group), excessive maternal wastage, low insemination rate and/or implantation efficiency, high variation in the reported doses administered and overall questions regarding the conduct of the study due to apparent technical gavage errors. Doses administered were stated as 0, 0.1, 0.2 and 0.4 mg/kg. Two possible compound related abortions were noted at the low dose. Fetal data did not generally indicate a compound effect, but the limited number of litters makes this determination uncertain. Therefore, it is not considered appropriate to set maternal or developmental toxicity NOELs.

This study is classified as Core Supplementary Data due to inadequacies, and a new study is required.

2. Developmental Toxicity Study in Rats - Study No. WIL-35014, Dated 5/14/85, Testing Facility: WIL Research Laboratories, Inc. (Reviewed by Dr. J. Rowe).

In the developmental toxicity study in rats, Terbufos was administered by gavage at doses of 0, 0.05, 0.1 and 0.2 mg/kg/day during days 6-15 of gestation. No maternal toxicity was observed and the maternal toxicity NOEL is $\geq$ 0.2 mg/kg/day. There was a modest increase in the number of early resorptions (mean number/litter as well as the number of litters with 2 or more resorptions) in the mid- and high-dose groups. For the high-dose group, one rat had 8 late resorptions and the postimplantation losses/dam were slightly greater than the historical control range. Therefore, the developmental toxicity LOEL is tentatively set at 0.2 mg/kg and the NOEL at 0.1 mg/kg.

This study is classified as Core Minimum Data.

3. One Year Oral Toxicity Study in Dogs - Study No. 8414, Dated 3/12/86, Testing Facility: Tegeris Laboratories, Inc. (Reviewed by Dr. J. Rowe).

Beagle dogs were administered Terbufos by gelatin capsule at doses of 0, 15, 60, 90 and 120 ug/kg/day for one year (the 90 ug/kg dose had been 240 ug/kg until week 8 and the 120 ug/kg dose had been 480 ug/kg until week 7). The systemic toxicity NOEL was 120 ug/kg (HDT) as no consistent chronic effects (other than cholinesterase inhibition) were observed. As moderate to large depressions in plasma cholinesterase activity in both sexes were observed at all doses, a plasma cholinesterase inhibition (ChE) NOEL cannot be established (< 15 ug/kg). The plasma ChE LOEL = 15 ug/kg (LDT). The RBC ChE NOEL = 60 ug/kg. The RBC LOEL = 90 ug/kg.

This study is classified as Core Minimum Data.

As no NOEL for plasma cholinesterase inhibition was established, it is recommended that a dog study of four weeks duration be performed in order to adequately define the dose-response of Terbufos for plasma cholinesterase activity.

4. One Year Oral Toxicity Study in Rats - Study No. 85-2964, Dated 1/9/87, Testing Facility: Bio/dynamics Inc.

This study was conducted in order to establish a NOEL for chronic toxicity [The previous two-year study satisfied the Core Minimum requirements for oncogenicity, but not for systemic toxicity.]

Groups of 30 male and 30 female Charles River rats were administered Terbufos as a dietary admix at concentrations of 0, 0.125, 0.5 and 1.0 ppm. The only effects observed which appeared to be the result of compound administration were decreases in plasma and brain cholinesterase levels only at the high dose of 1.0 ppm. The systemic NOEL is 1.0 ppm (HDT). The cholinesterase inhibition NOEL is 0.5 ppm. The cholinesterase inhibition LOEL is 1.0 ppm (HDT). Both of these values are based upon plasma and brain cholinesterase levels. ChE NOEL = 0.5 ppm.

This study is Core Minimum Data.

5. An Eighteen Month Oncogenicity Study in Mice - Study No. 8422, Dated 10/14/86, Testing Facility: Tegeris Laboratories, Inc.

Groups of 65 male and 65 female Charles River CD-1 mice were administered Terbufos as a dietary admix at concentrations of 0, 3, 6 and 12 ppm. There was a possible slight increase in mortality in both sexes (especially males) at the high dose of 12 ppm. A decrease in body weight gain of 10.1% for males and 19.7% for females of the high dose was observed. Under the conditions of this study, there was no apparent indication tha

Terbufos had an oncogenic effect at any of the concentrations examined (HDT = 12 ppm) in CD-1 mice.

This study is classified Core Minimum Data.

6. Dominant Lethal Study in Rats - Study No. 6123-137, Dated 6/9/86, Testing Facility: Hazleton Laboratories America, Inc.

Groups of 10 male rats each were treated by gavage for 5 consecutive days with 0, 0.1, 0.2 and 0.4 mg/kg of Terbufos. Each male was paired with two nontreated virgin females at each mating (10 matings). Females were sacrificed and examined for numbers of implants, viable and nonviable fetuses and corpora lutea. Under the conditions of this study, the only apparent possible compound related effects on fertility were in the high-dose group (0.4 mg/kg) where the number of viable implants was slightly but significantly reduced at mating 9 and implantation efficiency was significantly lower at mating 7 as well as suggestively (not significant) lower during matings 8, 9 and 10.

This study is Acceptable.

7. Acute In Vivo Cytogenetics Assay in Rats - Study No. T4277.105002, Dated 6/19/86, Testing Facility: Microbiological Associates Inc.

There were 5 male and 5 female rats/group/time interval. The 0, 0.2, 0.6 and 1.8 mg/kg groups had animals sacrificed 12, 24 and 36 hours post dosing. Colchicine was used to arrest dividing cells at metaphase. A supplemental study was also conducted in females at 1.5 mg/kg. Bone marrow metaphase cells were examined for chromosome aberrations. Under the conditions of this assay, there were no apparent increases in chromosomal aberrations observed with any of the doses of Terbufos tested (HDT = 1.8 mg/kg for males and 1.5 mg/kg for females). TEM (positive control) caused a statistically significant increase in chromosomal aberrations.

This study is Acceptable.

006352

Toxicity Data Base Considered in Setting the Tolerance.

90 day dermal, rabbit	Systemic NOEL = 0.02 mg/kg MINIMUM
90 day feeding, rat	ChE NOEL = 0.25 ppm MINIMUM
	Systemic NOEL = 0.25 ppm
3 generation repro., rat	Repro. NOEL = 0.25 ppm MINIMUM
6 month feeding, dog	Plasma ChE NOEL = 0.0025 mg/kg (LDT)
	Systemic NOEL = not determined SUPPL.
2 year feeding/onco., rat	Brain & RBC ChE NOEL < 0.25 ppm (LDT)
	Not an oncogen - MINIMUM
1 year feeding, rat	Plasma & Brain ChE NOEL = 0.5 ppm MIN.
1 year feeding, dog	RBC ChE NOEL = 0.060 mg/kg MINIMUM
	Brain ChE NOEL = 0.060 mg/kg
	Plasma ChE LOEL = 0.015 (LDT)
	RBC & Brain ChE LOEL = 0.090 mg/kg
18 month feeding, mouse	Not an oncogen MINIMUM
developmental tox., rabbit	NOEL not determined SUPPLEMENTARY
developmental tox., rat	Dev. Tox. NOEL = 0.1 mg/kg MINIMUM

Toxicity Data Gaps.

1. 4 week feeding, dog for ChE
2. Developmental toxicity, rabbit

Referenced Petitions/Tolerances Granted.

PP#3G1340 - 0.05 ppm - corn grain, fodder & forage
PP#4F1496 - 0.05 ppm - corn grain, fodder & forage
PP#5F1640 - 0.05 ppm - in or on sugar beets, tops & roots
PP#6F1657 - 0.5 ppm - corn forage and fodder (field corn, popcorn and sweet corn), and 0.05 ppm - corn grain (popcorn) and sweet corn (kernals plus cob with husks removed)
PP#1F2433 - 0.05 ppm - cabbage, broccoli and cauliflower
PP#1F2540 - 0.05 ppm be established for sorghum grain and 0.5 ppm be established for sorghum forage and fodder for combined residues of the insecticide
PP#2F2608 - 0.05 ppm - soybean grain
PP#3F2926 - 0.05 ppm - rape and mustard seed

However, tolerances were only established for sugar beets, corn and sorghum, see CFR 40 (1983), section 180.352; and the attached computer printout.

Previous Tolerance Assessment.

Due to extensive data gaps, a provisional limiting dose (PLD) was previously established for Terbufos at 0.000025 mg/kg/day. This PLD was calculated using a ChE NOEL of 0.1 ppm (0.0025 mg/kg) from the 6 month-feeding dog study and an uncertainty factor of 100. The total contribution of published tolerances occupied 305% of the PLD.

006352

5

Tolerance Re-assessment.

With the exception of a developmental toxicity study in rabbits (classified as Supplementary Data Base), previously cited toxicology data gaps have been clarified by the registrant. Reassessment of the RfD/PADI is in order. It is proposed that using the plasma ChE LOEL from the 1-year dog study (0.015 mg/kg) and an uncertainty factor of 100 (due to the lack of a ChE NOEL) the total contribution of published tolerances would occupy 31.33% of the PADI.

Using the PADI proposed above (i.e. 0.00015 mg/kg/day), the proposed tolerance of 0.025 ppm in/on imported bananas would increase the TMRC to 34.67% of the PADI. [Refer to attached TAS sheets.] The proposed tolerance must include the parent compound (S-[[(1,1-dimethyl)thio]methyl]O,O- diethyl phosphorodithioate and its cholinesterase-inhibiting metabolites in or on the bananas.

Recommendation

A temporary tolerance of 0.025 ppm for Terbufos and its cholinesterase-inhibiting metabolites in or on bananas is toxicologically supported. However, prior to the setting of a permanent tolerance, the following data must be submitted and evaluated: 1) a WIL rabbit teratology study completed in 1984 (the Agency was recently made aware of this study: personal communication of 10/1 and 10/2/87 from J. Harris and L. Andrews of American Cyanamid to Q. Bui), 2) a four-week dog plasma cholinesterase study recently completed with an initial report drafted (personal communication from J. Harris to Q. Bui on 10/1/87), and 3) a new rabbit teratology study should the 1984 WIL study be unacceptable.

DATA EVALUATION RECORD -1

STUDY TYPE: Dose-ranging developmental toxicity study in rabbits

CHEMICAL: AC 92,100 (terbufos technical); Lot No. AC-4391-1; Purity 87.8%; clear, watery liquid; stored refrigerated (approximately 3°C) in a tightly closed container from the time of receipt throughout study period

TEST MATERIAL: AC 92,100 was blended with an appropriate amount of corn oil; desired concentrations were made up fresh every 4 to 7 days and stored at room temperature; dose levels were 0, 0.1, 0.3, 0.7, 2.0 and 4.0 mg a.i./0.5 ml/kg

STUDY I.D.:

1. Title: A range finding study with AC 92,100 in pregnant rabbits (Study No. 981-84-103)

2. Laboratory: Hazleton Laboratories America, Inc., Life Sciences Division, 3301 Kinsman Boulevard, Madison, Wisconsin 53704

3. Study #: 6123-115; American Cyanamid Protocol No. 981-84-103

4. Date of report. June 20, 1984

5. Study monitor: Dr. K. M. MacKenzie

6. Caswell # 131A; Acc No. 258787

CONCLUSIONS:

It is concluded that terbufos technical produced a dose-related increase in mortality in New Zealand White pregnant female rabbits during oral gavage of the material in corn oil at doses of 0, 0.1, 0.3, 0.7, 2.0 and 4.0 mg/0.5 ml/kg with all animals dying at the two high doses. Some of the deaths may have resulted from the method of administration, either through a regurgitation of the material into the lungs or to technical error. The data is limited but does not suggest that tebufos produced an increase in implantation losses or fetal resorptions at the two lowest doses utilized. This study was the basis for the full developmental study in rabbits based on the maternal toxicity and appears appropriate. However, the possibility of gavage error raises some concern.

This study is Core Supplementary data.

METHODS:

Since terbufos is an acutely toxic cholinesterase-inhibiting organophophate, laboratory personnel wore disposable clothing, goggles and a respirator. All wastes generated from the study were incinerated in a high-temperature incinerator. Young adult rabbits (5-6 month old virgin females) of the New Zealand White strain from Hazleton Dutchland, Inc., Denver, Pennsylvania were used. The animals were acclimated for 19 days prior to test, male and females being housed in separate rooms. All females were identified by a permanent i.d. number and all data collected was filed under that number.

There was some variation in room temperature and humidity which did not appear significant during the study period. The animals were fed pelleted forms of Purina Cerfified Rabbit Chow® 5322 and water ad libitum. Inseminated females were housed individually.

Thirty inseminated rabbits from a group of 35 animals were randomly assigned to five test groups (see test materials for dose levels). The test material was administered in corn oil by oral gavage with the dose adjusted to 100% a.i. and treatments occurring between 9:00 a.m. and 12 noon on days 7-19 of gestation. Duplicate samples of test mixtures from first and last day of dosing were sent to the sponsor for analysis of test material concentration.

Does were artificially inseminated (day 0 being day of insemination) with semen from proven breeder males with a second insemination occurring 3-4 hours later. Immediatedly prior to insemination, each doe received an injection of chorionic gonadotropin solution (250 IU in 0.25 ml 0.9% saline) via the marginal ear vein.

Animals were observed twice daily for moribundity, death and obvious toxicity. Individual body weights were recorded on days 0, 7, 10, 20, 24 and 29. All dams were examined macroscopically, regardless of their fate. On day 29, surviving dams were sacrificed by euthanasia (T-61 solution), laparotomized and the entire reproductive tract removed. Ovaries, number of corporea lutea, number and location of live and dead fetuses, early and late resorptions, empty sites and implantation scars, unusual coloration and variations in amniotic fluid or placentae and any other abnormalities were noted. Uteri that appeared nongravid were opened and placed in a 10% solution of ammonium sulfide to confirm pregnancy status.

Comments

1. Details of the method of artificial insemination were not submitted.

2. Sample data analyses were submitted but the sample concentration data sheets were inadvertently placed with the primary study and vice-versa. The sample analyses appear acceptable.

RESULTS/CONCLUSIONS:

There was a dose-related increase in mortality with 0% of the does surviving past day 15 in the 2.0 and 4.0 mg dose groups and 20, 80, 100 and 80% of the dams surviving to day 29 in the 0.7, 0.3, 0.1 and 0.0 mg dose groups, respectively. One doe in the control group which aborted on day 27 was sacrificed at that time.

Aside from death, common clinical signs in the dosed animals were salivation (seen at all dose levels except 0.1 mg) alopecia of urogenital area, and decreased food consumption. Gross necropsy examinations indicated the presence of blood in the trachea of several treated animals (1/3:0.3 mg; 2/2:2.0 mg; 1/1:4.0 mg) and one dam with oil present in the thoracic cavity (1/1:0.7mg). Evidently this is a result of the gavage technique which may have resulted in regurgitation or possibly inadvertent injection of the test material into the trachea or the thoracic cavity.

There were no animals available for mean body weight or body weight changes to be determined in the three high dose groups. Mean body weights were 3.88, 3.78 and 3.49 kg for 0, 0.1 and 0.3 mg, respectively, at day 7 on test. No appreciable change had occurred by day 20 (3.95, 3.84 and 3.49 kg, respectively), at the completion of the dosing period, nor was there any rebound phenomena by day 29 (3.92, 3.84, 3.53 kg) following withdrawal of the compound.

Implantation rates ranged from 80 to 100% for all dose groups, without regard to does surviving to day 29. Of the females surviving to day 29, there were 3/5, 4/5, 4/4 and 0/1 with implantations for 0, 0.1, 0.3 and 0.7 mg dose groups. Mean corpora lutea for all does were similar as were mean implantations. All fetuses removed from the uterus at C-section on day 29 of sacrifice were living in all dose groups. The number of litters with resorbed fetuses did not appear significantly different for these same dose groups being 1 late resorption/1 litter (0 mg), 2 early resorptions/1 litter (0.1 mg) and 1 early resorption/1 litter (0.3 mg).

It is concluded that terbufos technical produced a dose-related increase in mortality in New Zealand White pregnant female rabbits during oral gavage of the material in corn oil at doses of 0, 0.1, 0.3, 0.7, 2.0 and 4.0 mg/0.5 m/kg with all animals dying at the two high dose. Some of the deaths may have resulted from the method of administration, either through a regurgitation of the material into the lungs or to technical error. The data is limited but does not suggest that tebufos produced an increase in implantation losses or fetal resorptions at the two lowest doses utilized. This study was the basis for dose selection in the full developmental study in rabbits based on the maternal toxicity observed in the does.

DATA EVALUATION RECORD -2

STUDY TYPE: Developmental toxicity study in rabbits (New Zealand White)

CHEMICAL: AC 92,100 (terbufos technical); Lot No. AC-4391-1; Purity 87.8%; clear brown, watery liquid; stored refrigerated (approximately 4°C) in a tightly closed container from the time of receipt throughout study period

TEST MATERIAL: AC 92,100 was blended with an appropriate amount of corn oil; desired concentrations were made up fresh every 3 to 4 days and stored at room temperature; dose levels were 0, 0.1, 0.2 and 0.4 mg a.i./0.5 ml/kg

STUDY I.D.:

1. Title: Final Report, A Teratology study with AC 92,100 in Rabbits (Study No. 6123-116)

2. Laboratory: Hazleton Laboratories America, Inc., Life Sciences Division, 3301 Kinsman Boulevard, Madison, Wisconsin 53704

3. Study #: 6123-116; American Cyanamid Protocol No. 981-84-104

4. Date of report: January 15, 1985

5. Study monitor: Dr. K. M. MacKenzie

6. Caswell # 131A; Acc No. 258787; MRID No. 147532

CONCLUSIONS:

Limitations in the conduct of this study preclude the proper evaluation of the maternal and/or developmental toxicity of terbufos. These limitations include 1) inadequate number of litters available in the mid and high dose groups (FIFRA Guidelines require a minimum of 12 litters/dose group), 2) excessive maternal wastage (due to deaths, abortions/sacrifice, failure to achieve pregnancy, fully resorbed fetuses) , 3) unacceptably low insemination rate and/or implantation efficiency, 4) unacceptably high variation in the reported dosages administered, and 5) overall questions regarding the conduct of the study due to apparent technical gavage error. Further, a NOEL may not have been achieved since the observation of 2 abortions at the low dose may be a compound-related effect. The fetal data does not generally indicate a compound effect but, again the limited number of litters make this determination uncertain. Based on these limitations it is inappropriate to set maternal toxicity or developmental toxicity NOELs.

This study is Core Supplementary data due to inadequacies in the conduct of this study. A new study is required.

9A

METHODS:

A photocopy of ~~the~~ experimental methods is attached. The following comments are noted:

1. No details concerning the artificial insemination procedures were submitted, e.g., how many bucks were utilized, what was the sperm count per ml of semen administered, how was the viability of the sperm determined, etc. The validity of the insemination process is questionable in light of the extremely low successful insemination rate (56% of does) in the mid dose group.

2. As noted in the dose-ranging study the sample analyses sheets were reversed. Based on the sample analysis record (from Exhibit IA), there were some problems in administering the correct dosages, e.g., % nominal doses from the first day of dosing (samples stated as 0.1, 0.2 and 0.4 mg/0.5 ml) were 147, 145 and 125 % of estimated doses (Sample name: CL 92100). Dosing solutions from the 5th day of the teratology study still indicate an unacceptably high test concentration of 181, 138 and 118% of nominal for 0.1, 0.2 and 0.4 mg/.5 ml. In addition, it was noted that there was an apparent gradient in test material concentration with preparation sample C from the test sample being of a higher % nominal than preparations A and B. This suggests that the initial samples were sampled from bottom of test materials prepared. Test samples 6/29 and 7/3/84, at end of study, were within acceptable limits (94-103% of estimated concentration).

3. There was an apparent technical gavage error for 2 does of the high-dose group based on the observation of oil in their lungs. There may also have been a dosing error for one low dose group female since a red foci of the lungs was reported.

4. There were inadequate numbers of does (7 in mid and 10 in high dose groups) available for fetal examinations. This unduly limits the statistical power of the data to identify compound-related effects.

RESULTS

Mortality/clinical signs/gross necropsy

Four does (of total of 18 inseminated) were found dead in the high dose group, two of which died apparently from improper gavaging technique since corn oil was found in their lungs. There were 2 abortions each in the low and high dose groups (2/18 animals inseminated, respectively). Reddish material on the pan paper was reported in 1 doe of the control and two does of the mid dose groups. There were no compound-related necropsy findings reported.

Mean body weights/mean body weight changes/corrected body weights

A summary of the body weight data is presented in Table 1. There were nc statistically significant changes in treatment vs control mean body weights, body weight gains or body weight changes corrected for gravid uterine weights.

Reproductive/fetal data

Table 2 presents a summary of reproductive and fetal data (excerpted from Table 5 of the study report; this table is quite confusing in terms of presentation since N represents litter number not total of parameter presented). Of the original 18 animals inseminated/dose group, there were pregnancy rates of 94, 89, 56 and 83 percent (0, .1, .2 and .4 mg/kg, respectively). As noted under the methods section, the rate of successful insemination in the mid dose group (56%) is quite low. Additional losses in pregnant does in the high dose group occurred due to abortions and death, 2 of which were apparently due to technical error.

Maternal wastage (due to deaths, abortions/sacrifice, failure to achieve pregnancy, fully resorbed fetuses) was excessive with only 78, 39 and 56% of the inseminated does available for fetal data calculations in the low, mid and high dose groups, respectively. In the mid dose, three does had complete embryonic resorptions. The lower number of litters available in the two high dose groups, in the opinion of the reviewer, makes any conclusions concerning the compound tentative in nature.

Implantation efficiencies were also quite low for all dose groups with rates of 54.5, 63.1, 56.5 and 62.8% for control, low, mid and high dose levels. This reinforces the concern that the insemination process was inadequate in providing either viable sperm or perhaps sufficient numbers of sperm per doe.

There were no statistically significant differences between the treated and control dose groups with regard to mean corpora lutea, implantations or implantation efficiencies. In addition, there were no apparent compound-related effects with regard to mean live fetuses, sex ratios, fetal weights or fetal resorptions.

Caesarian Data

Generally, there was no clear evidence of a compound-related effect of terbufos upon fetal development, although the conclusion is tentative due to the limited number of litters at C-section. A summary table of selected C-section data is presented below (Table 3). The only statistically significant effect reported was an increase in fetal but not litter incidence of accessory left subclavian in the high dose group as compared to the controls (4 fetuses/4 litters in control vs 9 fetuses/3 litters of high dose; $p<0.05$). The authors reported a statistically significantly lower incidence of full unilateral ribs (litter incidence) or chain fusion of the sternebrae (fetal incidence) of the high dose group as compared to the controls. This is not considered biologically or necessarily statistically significant, in light of the larger number of litters available in the controls as opposed to the 0.4 mg/kg dose group.

Table 1: Mean Body Weights, Mean Weight Changes, Corrected Weights

Dose (mg/kg)	Mean b. wt.(kg) on gestation day 0	7	12	15	18	24	29	Wt. change days 0-29	Corrected wt.[b] 29-GU	29-GU-0
0.0	3.34 (.226)[a]	3.49 (.261)	3.57 (.263)	3.66 (.265)	3.67 (.258)	3.78 (.291)	3.81 (.298)	0.47 (.197)	3.39 (.301)	0.11 (.23)
0.1	3.30 (.354)	3.45 (.370)	3.54 (.385)	3.63 (.378)	3.63 (.371)	3.68 (.394)	3.71 (.380)	0.46 (.157)	3.31 (.424)	0.02 (.344)
0.2	3.26 (.384)	3.38 (.380)	3.44 (.380)	3.52 (.384)	3.49 (.380)	3.58 (.410)	3.65 (.408)	0.39 (.181)	3.08 (.276)	-0.07 (.205)
0.4	3.38 (.326)	3.49 (.358)	3.53 (.340)	3.64 (.339)	3.60 (.302)	3.70 (.414)	3.81 (.372)	0.49 (.168)	3.37 (.315)	0.04 (.218)

[a] Mean b.wt.(SD); [b] weight at day 29 minus gravid uterine wt. (GU) or weight at day 29 minus GU -weight at day 0, respectively

DISCUSSION

Limitations in the conduct of this study preclude the proper evaluation of the maternal and/or developmental toxicity of terbufos. These limitations include 1) inadequate number of litters available in the mid and high dose groups (FIFRA Guidelines require a minimum of 12 litters/dose group), 2) excessive maternal wastage (due to deaths, abortions/sacrifice, failure to achieve pregnancy, fully resorbed fetuses) , 3) unacceptably low insemination rate and/or implantation efficiency, 4) unacceptably high variation in the reported dosages administered, and 5) overall questions regarding the conduct of the study due to apparent technical gavage error. Further, a NOEL may not have been achieved since the observation of 2 abortions at the low dose may be a compound-related effect. The fetal data does not generally indicate a compound effect but, again the limited number of litters make this determination uncertain. Based on these limitations it is inappropriate to set maternal toxicity or developmental toxicity NOELs.

Table 2: Caesarean Data

		0 mg/kg	0.1 mg/kg	0.2 mg/kg	0.4 mg/kg
No. animals on test		18	18	18	18
No. (%) pregnant		17(94)	16(89)	10(56)	15(83)
Aborted/sacrificed		0	2	0	2
Died		0	0	0	3
Examined at C-section		17	14	10	10
Corporea lutea	N*	17	16	9[b]	15
	Mean(SD)	13(4.4)	12(4.9)	12(4.0)	12(3.1)
Implantations	N*	17	16	10	15
	Mean(SD)	7(2.8)	7(2.8)	6(3.0)	7(2.4)
Implantation efficiency(%)	N*	17	16	9[b]	15
	Mean(SD)	54.5(20.88)	63.1(28.84)	56.5(32.11)	62.8(17.57)
Live fetuses	N*	17	14	10	10
	Mean(SD)	6(3.0)	6(2.8)	5(3.7)	7(2.9)
Sex ratio (M/M+F)x100	N*	16	14	7[a]	10
	Mean(SD)	59.9(17.44)	46.3(12.54)	53.4(12.52)	55.1(19.21)
Fetal b.wts.(g)					
Males	N*	16	13[c]	7[a]	10
	Mean(SD)	44.9(6.33)	44.2(7.70)	43.4(5.06)	45.1(4.55)
Females	N*	15	14	7[a]	10
	Mean(SD)	43.7(5.78)	45.7(7.08)	39.5(3.80)	43.4(4.76)
Total resorptions	N*	17	14	10	10
	Mean(SD)	1(.7)	1(1.2)	1(1.5)	0(0.5)
Early	N*	17	14	10	10
	Mean(SD)	1(.7)†	0(0.9)	1(1.6)	0(0.5)
Late	N*	17	14	10	10
	Mean(SD)	0(.0)†	1(1.2)	0(0.0)¶	0(0.0)¶

† stated in Table 5 as: SD= .6/early and 0.2/late, ¶ stated as SD= .4 and .3, resp.; [a] 3 does had fully resorbed embryos, not included in calculation of group mean; * Note: N = # does--not parameter presented ; [b] corpora lutea stated as regressing in one doe; [c] only one fetus (female) reported for doe number F03733

006352

Table 3: Selected Fetal Alterticns[a]

	0 mg/kg	0.1 mg/kg	0.2 mg/kg	0.4 mg/kg
No. ltrs. examined	16	14	7	10
No. fetuses examined	105	83	50	73
VISCERAL FINDINGS.....				
Major vessels:				
accessory left subclavian	4/4[(a)]	1/2	0/0	3/9*
left carotid arising from inominate	2/2	2/2	0/0	3/3
common truncus	0/0	1/1	0/0	0/0
ductus absent	0/0	1/1	0/0	0/0
descending aorta circumvents outer renal cortex	0/0	1/1	0/0	0/0
Gall bladder:				
absent	0/0	0/0	2/2	0/0
SKELETAL FINDINGS.....				
Vertebrae:				
presacral (27)	1/1	2/2	0/0	3/3
presacral (25)	0/0	0/0	0/0	1/1
Ribs:				
full unilateral	15/12	9/7	5/2	6/3
Sternebrae:				
Chain fusion	7/5	1/1	2/1	0/0

[a] litter no./fetal no.; * statistically significantly different from control fetal incidence ($p<0.041$)

Terbufos toxicology review dated 10/7/87

Page _____ is not included in this copy.

Pages 15 through 19 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

DATA EVALUATION RECORD -1

STUDY TYPE: Dose-ranging developmental toxicity study in rats

CHEMICAL: AC 92,100 (terbufos technical); Lot No. AC-4391-1; Purity 87.8%; clear, watery liquid; stored at room temperature, avoiding heat, strong oxidizers and alkalis, and is stable under these conditions.

TEST MATERIAL: AC 92,100 was blended with an appropriate amount of corn oil; desired concentrations were made up fresh daily and stored at room temperature; dose levels were 0, 0.40, 0.80, 1.40, 3.00 and 6.00 mg/kg/day (Group = WIL-35013) and 0.05 and 0.20 mg/kg/day (Group WIL-35013A: ancillary group)

STUDY I.D.:

1. Title: A range-finding teratology study with AC 92,100 in rats, Final Report

2. Laboratory: WIL Research Laboratories, Inc., 1407 Montgomery Township Road 805, Ashland, Ohio 44805-9281

3. Study #: WIL-35013; American Cyanamid Sponsor No. 981-84-156

4. Date of report: August 24, 1984

5. Study monitor: D. E. Rodwell, M.S.

6. Caswell # 131A; Acc No. 258787

CONCLUSIONS:

The oral administration of terbufos at dosages of 0. 0.4, 0.8, 1.4, 3.0 and 6.0 mg/kg/d produced a dose-and time-related mortality with all compound-treated dams dying by day 16 of gestation. Gross examination of the treated dams indicated that at lower dosages (0.4 and 0.8 mg/kg/d) there was a dose/time related increase in early resorptions. Auxiliary dose levels (.05 and 0.2 mg/kg/d) did not produce any evidence of maternal or developmental toxicity. Based on these findings, dose levels of 0.05, 0.1, and 0.2 mg/kg/day were established for the primary developmental toxicity study.

This study was designed as a dose-ranging study for a full study and appears generally acceptable for that purpose. It is designated as Core Supplementary data.

006352

METHODS:

Two shipments of virgin female Sprague-Dawley COBS®CD® rats were received from Charles River Breeding Laboratories, Inc., Portage, MI. Forty females were assigned to six group of five each (WIL-35013) and an auxillary group of ten females (WIL-35013A). The animals were 71 days of age upon receipt and were quarantined for 14 days, acceptable animals being identified by a metal ear-tag. All animals were housed individually in wire-mesh cages. Animals were given feed and water ad libitum and were housed in a controlled environment with temperature at 72°±3 F, relative humidity at 40% and 12 hour light/12 hour dark cycle.

At the conclusion of quarantine, animals judged to be in good health and with a body weight >220 grams were mated with resident males. The selected females were approximately 12 weeks old when mated with body weights ranging from 238-318 g (WIL-35013) and from 250-290 g (WIL-35013A) on day 0 of gestation. Evidence of mating was confirmed by the presence of a copulatory plug and this day was defined as day 0 of gestation and the animals separated.

The bred females were consecutively assigned in a block design to groups containing five rats each. Two additional dose groups were initiated at a later date.

Samples of the vehicle (Mazola® corn oil) and prepared test article were collected prior, at initiation and conclusion of dosing in both studies and forwarded to American Cyanamid Company for analyses. The test mixtures were administered orally by gastric intubation from day 6-15 of gestation. A dosage of 10 ml/kg instead of 5 ml/kg specified by the protocol was used, resulting in severe body weight losses and excessive mortality which required the initiation of two additional breeding groups at lower dosage levels (see Test Material for doses).

Detailed clinical observations were recorded individually from days 0-20 of gestation. A gross necropsy was performed on all dams which died or were sacrificed during the course of the study. Maternal body weights were recorded on gestation days 0, 6, 9, 12, 16 and 20 and mean body weight changes were calculated for each corresponding interval of gestation and for days 6-16, 16-20 and 0-20.

All surviving maternal animals were sacrificed with CO_2 on gestation day 20 and the abdominal and thoracic cavities opened and examined. The uterus and ovaries were exposed and the number of corpora lutea recorded. The number and location of viable and nonviable fetuses, early and late resorptions and the total number of implantation sites were recorded in utero. The individual uterine distribution was documented. Uteri with no evidence of macroscopic implantation were excised, opened and placed in 10% ammonium sulfide solution for detection of early implantation losses.

RESULTS/DISCUSSION:

006352

Due to the deviation in the protocol (dosages were 2x the amount specified in the protocol), there was a dose-related mortality with all treated animals dying during the treatment period. Examination on the day of death indicated that in the 1.4, 3 and 6 mg/kg/d dose groups, animals were dead on day 7 of

Mean body weights(gm)

	Control	0.4 mg/kg/d	0.05 mg/kg/d	0.2 mg/kg/d
Day 0	265	267	273	280
" 6	287	291	299	310
" 9	299	283	307	320
" 12	317	293	327	338
" 16	354	A	358	369
" 20	426	A	419	430

A = all animals died or sacrificed moribund

Mean body weight changes(gm)

	Control	0.4 mg/kg/d	0.05mg/kg/d	0.2 mg/kg/d
Day 0-6	23	24	26	30
" 6-9	12	-8(5)*	8	10
" 9-12	18	-3(3)	20	18
" 12-16	36	---	31	31
" 16-20	73	---	61	61
" 6-16	66	---	59	59
" 0-20	162	---	147	150

* number of living dams

gestation. During days 8 or 9, dams of the 0.8 mg/kg/d group died and all animals in the 0.4 mg/kg/d dose group died during days 10-16 of gestation. Necropsy findings attributed this compound toxicity to cardiovascular arrest or cerebral hemorrhage. No deaths occurred in the two auxiliary groups of 0.05 and 0.2 mg/kg/d during the test period. No unusual gross pathology was reported for the control group or the two auxiliary dose groups at sacrifice.

Due to the complete mortality in the first study no mean body weights or body weight changes were available beyond the first few days of compound treatment. Mean body weight and body weight gain data for the control group and dose groups 0.4, 0.05 and 0.2 mg/kg/d are presented above. There is a depression in mean body weight and body weight gain in the 0.4 mg/kg/d dose group as compared to the control values. The two auxiliary dose levels did not appear to produce any depression in absolute body weights or mean body weight gains.

Pregancy rates among the first test group were 100, 100, 80, 100 and 80% (0, .4, .8, 1.4, 3.0 and 6.0 mg/kg/d, respectively). For the auxiliary dose groups pregnancy rates were 60 and 100% (.05 and .2 mg/kg/d, respectively). Examination of the necrospy data reveals that terbufos, in addition to the acute toxicity, produced a dose/time-related increase in early resorptions (see necropsy table below). Dosages of 1.4 mg/kg/d and greater resulted in early maternal mortality (gestation day 7) with normally appearing uterine implants. The next lower dose produced a combination of early resorptions (2 dams) and normally developing implants (2 dams) with a slight delay in time of maternal

Necropsy Findings (dead/sacrificed prior to laparotomy; taken from Appendix A)

006352

Group 2(.4 mg): -4 dams died of cardiovascular arrest; 1 died of cerebral hemorrhage (during days 10-16 of gestation)
-complete or significant early resorptions in all animals

Group 3(.8 mg): - 1 dam sacrificed moribund; 2 died of cardiovascular arrest; 2 died from cerebral hemorrhage (during days 8 or 9 of gestation)
- 1 nongravid; 2 complete early resorptions; 2 normally developing implantations

Group 4(1.4 mg): - 1 sacrificed moribund; 4 died of cardiovascular arrest (during gestation day 7)
- 1 non-gravid; 4 with normally developing implantations

Group 5(3.0 mg): - 5 died of cardiovascular arrest (during gestation day 7)
- 5 with normally developing implantations

Group 6(6.0 mg): - 4 died of cardiovascular arrest (during gestation day 7)
- 1 non-gravid; 4 with normally developing implantations

Fetal Data

Group: (mg/kg)		Viable fetuses	Dead fetuses	Early resorp.	Late resorp.	Implant. sites	Corp. Lutea
0	total	79	0	5	0	84	87
	$\bar{x}$(SD)	15.8(1.9)	0.0	1.0(1.2)	0.0	16.8(0.8)	17.4(0.9)
.05	total	45	0	5	0	50	56
	$\bar{x}$(SD)	15.0(1.0)	0.0	1.7(1.2)	0.0	16.7(2.1)	18.7(4.0)
.20	total	75	0	3	0	78	85
	$\bar{x}$(SD)	15.0(1.9)	0.0	0.6(0.9)	0.0	15.6(1.1)	17.0(0.7)

death (gestation days 8 or 9). At the lowest dose tested in this study(.4 mg/kg/d), there was complete or almost complete early resorptions in all animals on day 7 of gestation.

Fetal data available for the control and auxiliary dose groups is presented in the table directly above. There does not appear to be any significant fetal effect at the two dose levels administered based on the mean live fetal count or mean early resorption as compared to the control group. There is a suggestion of a lower mean implantation rate in the 0.05 mg/kg/d dose group, however this is questionable, since only 3 gravid dams were available in this group.

006352

In conclusion, the oral administration of terbufos at dosages of 0. 0.4, 0.8, 1.4, 3.0 and 6.0 mg/kg/d produced a dose-and time-related mortality with all compound-treated dams dying by day 16 of gestation. Gross examination of the treated dams indicated that at lower dosages (0.4 and 0.8 mg/kg/d) there is a dose/time related increase in early resorptions. Auxiliary dose levels (.05 and 0.2 mg/kg/d) did not produce any evidence of maternal or developmental toxicity. Based on these findings, dose levels of 0.05, 0.1, and 0.2 mg/kg/day, were established for the primary developmental toxicity study.

DATA EVALUATION RECORD -2

STUDY TYPE: Developmental toxicity study in rats

CHEMICAL: AC 92,100 (terbufos technical); Lot No. AC-4391-1; Purity 87.8%; clear, watery liquid; stored at room temperature, avoiding heat, strong oxidizers and alkalis, and is stable under these conditions.

TEST MATERIAL: AC 92,100 was blended with an appropriate amount of corn oil; desired concentrations were made up fresh daily and stored at room temperature; dose levels were 0, 0.05, 0.10, and 0.20 mg/kg/day.

STUDY I.D.:

1. Title: A teratology study with AC 92,100 in rats, Final Report

2. Laboratory: WIL Research Laboratories, Inc., 1407 Montgomery Township Road 805, Asnland, Ohio 44805-9281

3. Study #: WIL-35014; American Cyanamid Sponsor No. 901-84-157

4. Date of report: May 14, 1985

5. Study monitor: D. E. Rodwell, M.S.

6. Caswell # 131A; Acc. No. 258787; MRID 147533

CONCLUSIONS:

Pregnant COBS®CD female rats were orally administered technical terbufos in corn oil (gavage) during days 6-15 of gestation at dose levels of 0, 0.05, 0.10 and 0.20 mg/kg/day. No frank maternal toxicity, at any dose level, was evidenced based on clinical signs, mortality, gross necropsy findings or mean body weight depression (absolute or relative). Based on the lack of frank maternal toxicity, the maternal toxicity NOEL is set at $\geq$ 0.2 mg/kg/day.

The developmental toxicity LEL is tentatively set at 0.20 mg/kg/day and the NOEL at 0.10 mg/kg/day based upon the observation of a modest increase in the number of early resorptions (mean number/litter as well as the number of litters with 2 or more fetal resorptions) seen in the high dose groups as compared to the control. Further support for this observation being compound-related is the observation of 100% early resorption rates obtained in the dose-ranging study in dams administered 0.4 mg/kg/day and the fact that the mean implantation loss in the high dose group is outside the historical control range.

This study is designated as Core Minimum data. The developmental toxicity NOEL is tentatively set at 0.1 mg/kg/day. The test facility is requested to submit any additional, more recent historical data concerning the incidence of fetal resorptions reported for control dams.

006352

METHODS:

A photocopy of the methods from the study is attached. The following comments are noted:

1. A statement regarding Quality Assurance is included.

2. The homogeneity and concentration analysis of the test substance appears acceptable.

3. The age of the females is around 13 weeks at the initiation of the study. This is 5 weeks over the recommended maximum age of 8 weeks in the EPA test Guidelines, but the reviewer does not consider this as limiting the sensitivity of the test to establish potential developmental effects.

RESULTS:

Clinical signs/mortality data/gross necropsy

No compound-related deaths were observed. There is a higher incidence of hair loss among the treated groups than the controls, although it is not dose-related, e.g.:

	0 mg/kg	.05 mg/kg	.1 mg/kg	.2 mg/kg
hair loss left inguinal area	0/0*	20/2	12/1	0/0
hair loss right forepaw	10/1	53/7	23/2	32/3
hair loss left forepaw	10/1	58/8	23/2	33/3

*total incidence/nos. of animals

The biological significance of the hair loss in the treated groups is uncertain. No compound-related gross necropsy changes were noted.

Mean body weights/body weight gains

Summary tables for mean body weights and body weight gains are presented on the next page. There is no statistically significant depression in maternal mean body weights during or following compound administration. While there is a small difference in weight gains between the mid and high dose groups and the controls for periods 9-12 (statistically significantly lower for the mid dose group), 12-16 and 16-20, these differences are minor and not dose-related. There is no rebound phenomenon observed in these dose groups following compound withdrawal, a phenomenon which may be observed for many compounds upon cessation of their administration.

Reproductive/fetal data

A summary of reproductive/fetal data is presented on page 4. Pregnancy rates were 96-100%. Terbufos produced no abortions and no dams delivered early. Mean corpora lutea were similar among all dose groups. Mean implantations were somewhat lower in the treated dose groups, although not statistically different from controls. There was modest increase in the litter incidence for resorptions (primarily early) in the mid and high dose groups as compared to controls (control=12, low= 7, mid= 16 and high= 16). The number of litters with two or more resorptions (early or late) was higher in the high dose group than the controls (4/16.7% in control vs 7/28% in high dose). The postimplantation losses/dam in the high dose group were slightly outside the historical control range presented in the report (1.3/dam in high vs 0.1-1.2/histor. con.).

006352

MEAN BODY WEIGHTS(g): (from Table 3 of report)

Day	0 mg/kg/day	.05 mg/kg/day	.10 mg/kg/day	.2 mg/kg/day
0	253	250	245	250
6	283	276	272	280
9	290	285	282	288
12	309	301	297	306
16	340	333	326	333
20	403	396	385	392

(none sigificantly different from control using Dunnett's test)

MEAN BODY WEIGHT GAINS(g): (from Table 4 of report)

Day	0 mg/kg/day	.05 mg/kg/day	.10 mg/kg/day	.2 mg/kg/day
0-6	30	26	27	30
6-9	8	9	10	8
9-12	19	16	15*	18
12-16	30	31	28	27
16-20	63	64	60	60
6-16	57	57	53	53
6-20	120	120	113	112
0-20	150	146	140	142

* significantly different from control ($p<0.05$) using Dunnett's test

The increased resorptions in the two dose groups is reflected by the lower mean live fetuses per dam (15.0/control vs 13.7/mid and 13.6/high). In the high dose group one dam had 8 late resorptions. There was no significant effect upon mean fetal weights or sex ratios. Although the authors reported a statistically significant decrease in the mean number of female fetuses in all treated dose groups as compared to the control, this was related to a higher mean number of female fetuses in the control group. This is not considered a compound-related effect.

Fetal alterations: malformations/variations

There were no apparent compound-induced changes noted. Selected fetal alterations are presented on page 5. Historical data from the laboratory are also presented for comparative purposes. One fetus had multiple anomalies (head smaller than normal, anophtnalmia, facial papillae and pinnae misplaced, upper jaw elongated, lower jaw malformed and small in size) in the high dose group but this was within the range of historical control values. In addition, there were two fetuses of one litter with severe malaligned sternebra but this was also within the range for the litter incidence of this finding in the historical controls. Gastroschisis was observed in one control fetus.

A common observation among all treatment groups was 14th rudimentary rib (10 ltrs/control, 11 ltrs/low, 10 ltrs/mid and 12 ltrs/high). There was a small but consistent increase in the number of fetuses and litters with the finding of renal papillae not developed and/or distended ureters as compared to the control group but this was not reported as a statistically significant difference. The fetal alterations in the treatment groups receiving terbufos were outside the fetal incidence or litter incidence ranges for the historical control data. However, since the findings were not dose-related this variation is not considered to be a true, biologically significant effect of the compound.

006352

Reproductive/fetal data[a]

	Control	.05 mg/kg	.10 mg/kg	.20 mg/kg
# dams assigned	25	25	25	25
# dams pregnant	24	24	24	25
Pregnancy index(%)	96	96	96	100
# dams aborted/delivered	0	0	0	0
# dams pregnant and dead	0	0	0	0
# litters examined	24	24	24	25
$\bar{x}$ corpora lutea (S.D.)	16.5(2.0)	16.3(1.5)	16.3(2.4)	16.7(2.1)
$\bar{x}$ Implantations (S.D.)	15.9(2.0)	15.3(1.6)	14.9(1.4)	15.0(1.6)
$\bar{x}$ Pre-implant. loss(%)[b]/ mean # lost per dam	4.0/.58	6.0/1.04	8.0/1.4	10.0/1.7
$\bar{x}$ Total resorp./dam[ltrs]	0.83[12]	0.5[7]	1.2[16]	1.3[16]
$\bar{x}$ early resorp./dam(S.D.)[ltrs]	0.8(1.2)[12]	0.5(0.9)[7]	1.2(1.2)[16]	1.0(1.1)[15]
$\bar{x}$ late resorp./dam(S.D.)[ltrs]	0.0(0.0)[0]	0.0(0.0)[0]	0.0(0.0)[0]	0.3(1.6)[1]
# litters >2 resorptions(%)	4(16.7)	4(16.7)	6(25.0)	7(28.0)
$\bar{x}$ Dead fetuses per dam	0.0	0.0	0.0	0.04
$\bar{x}$ Post-implant. loss(S.D.)	0.8(1.2)	0.5(0.9)	1.2(1.2)	1.3(2.1)*
$\bar{x}$ Live fetuses per dam(S.D.)	15.0(1.9)	14.8(1.9)	13.7(1.9)	13.6(3.0)
$\bar{x}$ Fetal weights (g)[S.D.][c]	3.6[0.3]	3.6[0.4]	3.8[0.5]	3.6[0.4]
Sex ratio (% males)	42.0	51.0	52.0	53.0
Sex(males): $\bar{x}$(S.D.)	6.2(2.0)	7.5(1.9)	7.1(2.1)	7.2(2.5)
Sex(females): $\bar{x}$(S.D.)	8.8(2.3)	7.2(2.1)†	6.6(2.1)†	6.4(2.5)†

[a] taken from summary data in report; [b] % of corp. lutea; [c] mean weights per dam; † statistically significantly different from control ($p<0.05$; Chi Square test); * historical control range for post-implantation losses/dam = 0.6 (0.1-1.2)

DISCUSSION:

Pregnant COBS®CD female rats were orally administered technical terbufos in corn oil (gavage) during days 6-15 of gestation at dose levels of 0, 0.05, 0.10 and 0.20 mg/kg/day. No frank maternal toxicity, at any dose level, was evidenced based on clinical signs, mortality, gross necropsy findings or mean body weight depression (absolute or relative). Maternal toxicity was demonstrated in the dose-ranging study at dose levels of 0.4 mg/kg/day or greater (100% mortality) but not at 0.2 mg/kg/day. While the high dose group could have been higher in the full study (perhaps at 0.3 mg/kg/day), the steepness of the dose-response curve for mortality suggests that the doses chosen are reasonably justified.

Terbufos did not produce any increase in abortions or premature deliveries. There was a slight increase in the litter incidence of resorptions (primarily early in nature) which was reflected in the lower numbers of live fetuses obtained upon C-section in the mid and high dose groups. In addition one high dose dam had 8 late resorptions. The number of litters with two or more resorptions (early or late) was higher in the high dose group than the controls (4/16.7% in control vs 7/28% in high dose). The postimplantation losses/dam in the high dose group were slightly outside the historical control range presented in the report (1.3/dam in high vs 0.1-1.2/histor. con.). There were no compound-induced fetal alterations (frank malformations or variations) of an external, visceral or skeletal nature.

Fetal Alterations(%)(taken from tables 6-9 of report)†

	0 mg/kg	.05 mg/kg	.10 mg/kg	.20 mg/kg	Historical range¶
No. fetuses examd.	361	354	329	341	*
No. litters	24	24	24	25	619
MALFORMATIONS					
External: multiple anomalies	0/0[a]	0/0	0/0	0.3/4.0	0-0.3/ 0-4.3
Skeletal: malaligned sternebrae (severe)	0/0	0/0	0/0	0.6/4.2[b]	0-0.4/ 0-5.0
VARIATIONS					
Visceral: renal papillae not developed a/o distended ureters (litters affected)	6.6/33.3 (8)	10.6/54.2 (13)	11.6/45.8 (11)	11.8/48.0 (12)	0-7.5/ 0-31.8
Skeletal: 14th rudimentary rib (litters affected)	13.9/41.7 (10)	13.1/45.8 (11)	9.1/41.7 (10)	11.0/50.0 (12)	0-20.4/ 0-63.0

[a] fetal incidence/litter incidence; * 8587 fetuses examined externally; 5249 fetuses examined viscerally and 5744 fetuses examined skeletally; ¶ % fetuses/ % litters (range); no statistically significant alterations reported; [b] only 24 of dams examined for skeletal changes- one dam had only one fetus which was examined viscerally (dam no. 13648, fetus no. 11)

Based on the lack of frank maternal toxicity, the maternal toxicity NOEL is set at $\geq$ 0.2 mg/kg/day. The developmental toxicity LEL is tentatively set at 0.20 mg/kg/day and the NOEL at 0.10 mg/kg/day based upon the observation of a modest increase in the number of early resorptions (increased litters as well as the number of litters with 2 or more fetal resorptions) seen in the high dose groups as compared to the control. Further support for this observation being compound-related is the observation of 100% early resorption rates obtained in the dose-ranging study in dams administered 0.4 mg/kg/day and the fact that the mean implantation loss in the high dose group is outside the historical control range.

Terbufos toxicology review dated 10/7/87

Page _____ is not included in this copy.

Pages 30 through 36 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy
Review Section V/HED (TS-769C) 9/25/87

Secondary Reviewer: for Irving Mauer, Ph.D. I. Mauer 9/29/87
Geneticist
Toxicology Branch/HED (TS-769C)

I. Study Type: Dominant Lethal
(Guideline § 84-1)

Study Title: Dominant Lethal Study with AC 92,100 in Rats

EPA Identification Numbers:

EPA Identification: 6E 3409
EPA Accession: 400986
EPA Record: 192160
Caswell: 131A
Tox. Branch Project: 7-0549
Document:
MRID: 161571

Sponsor: American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08540

Testing Laboratory: Hazleton Laboratories America, Inc.
3301 Kinsman Blvd.
P.O. Box 7545
Madison, WI 53707

Study Number: Hazleton - 6123-137
American Cyanamid Company - 980-85-193

Study Date: June 9, 1986

Study Author: Karen M. MacKenzie, Ph.D.

Test Material: Name: AC 92,100 (Terbufos)
Lot No.: HM3-81
Description: liquid
Purity: 89.6%

Vehicle: corn oil (USP equivalent, Lot 13F-0705, Sigma Chemical Co.)

Positive Control: triethylenemelamine (TEM) - Lot No. 23048, Polysciences, Inc. (vehicle: 0.85% saline).

006352

Test Animal: Charles River Crl:CD® (SD)BR rats (6-week old males and virgin females) obtained from the Portage, MI facility of Charles River Breeding Laboratories.

II. Materials and Methods: Five groups of 10 male rats each of the CRL:CD® (SD) BR strain were treated by oral gavage for 5 consecutive days with the following: 0 (control), 0.1, 0.2 or 0.4 mg/kg body weight of AC 92,100; and a positive control group which received triethylenemelamine (TEM) intraperitoneally in a daily dose of 0.05 mg/5 ml of saline/kg body weight. After treatment, each male was paired with two nontreated virgin females 5 days/week for a total of 10 weeks (matings 1 through 10 - a total of 20 females/male) to evaluate dominant lethality. Approximately 15 days after the midpoint of the mating period, the females were sacrificed and the number of implants, viable and nonviable fetuses and number of corpora lutea were recorded. [The above summary of Materials and Methods was extracted from the Hazleton report.] A copy of "materials and methods" from the Hazleton report is appended (Test Material, Test System, Procedures, and Data Analyses and Maintenance).

Sample Identification and Purity: Technical AC 92,100 (Lot No. HM3-81) used in this study was analyzed by high pressure liquid chromatography. The content of phosphorodithioic acid, S-(tert-butylthio) methyl O,O-diethyl ester was determined to be 89.6%.

Analysis of Dosing Solutions:

Nominal Concentration (mg/ml)	Assay Results (mg/ml)	% Nominal
0 (Corn Oil Blank)	0.0000	-
0.100	0.0814	81
0.200	0.179	90
0.400	0.381	95

Mean = 89% Standard Deviation = 7% Range = 81-95%

The above data are extracted from the appendix to the final report (American Cyanamid Company).

The assay for the low dose (0.1 mg/ml) was only 81% of the desired concentration. This is considered to be low. The mid- and high-dose assays were 90 and 95%, respectively, and are considered to be within acceptable limits. Because there were no apparent compound related effects at the mid dose (0.2 mg/kg), the low assay at 0.1 mg/ml is not considered to have an influence on the integrity of the study.

Statistical methodology was described in detail.

A Quality Assurance statement was included.

006352

III. Results

A. Clinical Observations (males): During the Dosing Phase, the following observations were made - small movable tissue mass (hind mid-ventral region of control animal No. C40793), salivation, chromadacryorrhea and alopecia (sores). No more than one animal in any group had a positive observation.

During the Mating Phase, the following observations were made - small movable tissue mass (see above paragraph), bloody crust, malocclusion and sores (paw). No more than one animal in any group had a positive observation.

None of the above observations were considered to be related to compound administration.

B. Body Weights (males):

Summary of Body Weight Data

Week on Study	AC 92,100 (mg/kg body weight) 0	0.1	0.2	0.4	TEM[a]
Start	284.1[b]	286.1	298.6	271.6	282.6
	22.40[c]	20.96	13.30	15.32	23.10
1	320.3	325.7	346.9	314.0	325.9
	29.99	25.21	15.28	22.56	29.10
4	418.2	427.7	458.8	414.4	424.7
	44.54	36.27	23.89	34.09	43.88
7	485.8	494.9	524.2	485.7	500.0
	53.75	47.67	26.68	41.83	56.58
10	534.8	539.6	569.6	523.4	541.6
	65.77	53.04	29.23	49.12	67.27

NOTE: 10 male rats/group
a = TEM (triethylenemelamine) given at a dose of 0.05 mg/kg body weight.
b = group mean c = ± Standard Deviation
Data extracted from Hazleton report, Table 2, pages 11 & 12.

Body Weight Gain

Body Weight (gm)	AC 92,100 (mg/kg body weight) 0	0.1	0.2	0.4	TEM[a]
Initial	284.1[b] 22.40[c]	286.1 20.96	298.6 13.30	271.6 15.32	282.6 23.10
Final	534.8 65.77	539.6 53.04	569.6 29.23	523.4 49.12	541.6 67.27
Gain	250.7	253.4	270.9	251.7	259.0

NOTE: 10 male rats/group
a = TEM (triethylenemelamine) given at a dose of 0.05 gm/kg body weight.
b = group mean c = ± Standard Deviation
Data extracted from Hazleton report, Tables 2 and 4, pages 11 & 12 and 14.

It did not appear that the administration of AC 92,100 (up to a dosage level of 0.4 mg/kg) or TEM had any effect on body weight gain.

C. Fertility Indices and Implantation Data: The following two pages have been photocopied from the Hazleton report (Table 5, pages 15 and 16). The table presents the following parameters: Fertility Indices (%), Viable Implants (number and %), Nonviable Implants (number and %), Corpora Lutea and Implantation Efficiency (%). Values are group means (0, 0.1, 0.2 and 0.4 mg/kg of AC 92,100 as well as TEM at 0.5 mg/kg) for each of the 10 matings.

Also included in this review is a photocopy, from the Hazleton report, of Figure 1 (page 17), depicting the "Profile of Nonviable Fetuses for 10 Weeks after Treatment". This indicates the percent of nonviable implants for time periods following treatment.

With the following two exceptions, AC 92,100 did not appear to have an effect on fertility indices or the number and percent of viable or nonviable implants: mating 9 for the 0.4 mg/kg group, the number of viable implants was slightly but significantly reduced; mating 7 for the 0.4 mg/kg group, implantation efficiency was significantly lower and, although not statistically significant, was also lower during the last three matings (8, 9 and 10).

Administration of TEM (0.05 mg/kg) appeared to cause an increase in the number and percent of nonviable implants during matings 1 through 4. There was a concomitant decrease in the percent of viable implants during the same mating intervals.

Terbufos toxicology review dated 10/7/87

Page _____ is not included in this copy.

Pages 41 through 46 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

006352

Primary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy 9/25/87
Review Section V/HED (TS-769C)

Secondary Reviewer: for Irving Mauer, Ph.D J. W. Hausewirth 9/29/87
Geneticist
Toxicology Branch/HED (TS-769C)

I. Study Type: Acute in vivo cytogenetics assay (Guideline § 84-2)

Study Title: The Acute In Vivo Cytogenetics Assay in Rats with AC 92,100

EPA Identification Numbers:
EPA Identification: 6E 3409
EPA Accession: 400986
EPA Record: 192160
Caswell: 131A
Tox. Branch Project: 7-0549
Document:
MRID NO. 161570

Sponsor: American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08540

Testing Laboratory: Microbiological Associates, Inc
5221 River Road
Bethesda, MD 20816

Study Number: Microbiological Associates - T4277.105002
American Cyanamid Company - 980-85-178

Study Date: June 19, 1986

Study Author: Donald L. Putman, Ph.D.

Test Material: Name: AC 92,100 (Terbufos)
Lot No.: HM3-81
Description: clear, lightly brown, water-like liquid (American Cyanamid)
light yellow liquid (Microbiol. Assoc.)
Purity: 89.6%

Vehicle: corn oil (lot A14A from Eastman Chemical Company and lot MAY156J from Giant Food)

Positive Control: triethylenemelamine (TEM) - lot 34898, Polysciences, Inc. (vehicle: sterile distilled water at a concentration of 0.1 gm/ml at a dose of 0.5 mg/kg).

006352

Test Animal: Male and female Sprague-Dawley rats, 6-8 weeks of age, from Charles River Breeding Laboratories, Inc. Kingston, NY.

II. Materials and Methods: Sprague-Dawley rats, 6-8 weeks of age, were obtained from Charles River Breeding Laboratories, Inc., Kingston, NY.

A preliminary range-finding study was conducted using 2 males and 2 females per group. AC 92,100 was administered by intraperitoneal (IP) injection (5 ml/kg) at dose levels of 0.01, 0.1, 1, 10 or 100 mg/kg. Animals were observed for signs of toxicity or death and were sacrificed on the third day.

In the dose-finding study, there were 5 treated groups plus a vehicle control (0, 0.1, 0.3, 1, 3 and 10 mg/kg). The control and two highest dose levels contained 10 males and 10 females and the other 3 groups contained 5/sex. Approximately 22 hours after IP administration, 5 males and 5 females from each group were given an IP injection of 1 mg of colchicine per kg body weight and were sacrificed 24 hours after AC 92,100 administration. At 34 hours after compound administration, the remaining 5 rats/sex (vehicle and two highest dose groups) were given colchicine and sacrificed 36 hours after AC 92,100 administration. Bone marrow cells were collected, fixed and stained for evaluation of the mitotic index as an indicator of bone marrow toxicity.

In the cytogenetics study, there were 5 males and 5 females/group/time interval. The control, 0.2, 0.6 and 1.8 mg/kg groups had animals sacrificed 12, 24 and 36 hours post dosing (5 ml/kg IP). The positive control group (TEM - 0.5 mg/kg) had rats sacrificed only after 24 hours. Also, up to 5 additional animals of each sex were designated as replacements in the event of death in the high-dose group only. Colchicine, used to arrest dividing cells at metaphase, was given IP (1 mg/kg) to all rats two to four hours prior to sacrifice. A supplemental study was conducted, in females only, at 1.5 mg/kg (negative and positive controls) at 12, 24 and 36 hours (TEM positive control only at 24 hours). In the supplemental study, due to a miscalculation of volume, colchicine was administered at 0.4 mg/kg to the 12 and 24 hour groups.

Two to four hours after colchicine administration, the animals were sacrificed and femur bone marrow was aspirated. At least 3 slides of cell suspensions were prepared from each animal. Where possible, a minimum of 50 metaphase cells from each rat were examined and scored for chromatid and chromosome gaps and breaks, fragments, and structural rearrangements. A valid test was indicated by the vehicle (negative) control group having $< 4\%$ aberrations (other than gaps) and the positive control having a statistically significant ($p < 0.05$) increase in aberrations/cell/animal over the negative control value.

A copy of the Microbiological Associates report Materials and Methods section is appended to this review.

III. Results

In the preliminary range-finding study (0.01 - 100 mg/kg), 10 mg/kg was the lowest dose which caused one or more deaths.

In the dose-finding study, 10/10 of both sexes died at 10 mg/kg and, at 3 mg/kg, 6/10 males and 10/10 females died. There were no deaths at lower doses. Clinical signs at 3 mg/kg (survivors) were crusty nose, lacrimation, diarrhea, piloerection and tremors. Slight tremors were noted at 1 mg/kg, with lower doses and control showing no clinical signs. Body weight loss was observed in surviving males at 3 mg/kg and in females (but not males) at 1 mg/kg. Therefore, a high dose of 1.8 mg/kg was chosen for the cytogenetic study (See Table 1).

In the cytogenetics study, one male in the high-dose group died and was replaced. At the high dose (1.8 mg/kg) 13/20 females died (the 2 available replacement rats were sacrificed at 16 hours due to technician error and were not used in the study). the high-dose animals had slight body weight loss (See Table 2). Because of excessive mortality in high-dose females, a supplemental study using negative control, 1.5 mg/kg AC 92,100, and TEM was carried out. Eight of 15 rats died at 1.5 mg/kg (of 5 dosed replacements, 3 survived) with treated animals exhibiting crusty eyes and nose, lacrimation, excessive salivation, diarrhea and tremors.

The number and types of chromosomal aberrations are presented in Table 3. There were no apparent effects caused by the administration of AC 92,100. TEM caused a statistically significant increase in chromosomal aberrations.

Doses of AC 92,100 were examined which caused: mortality at 3 and 10 mg/kg in males and 1.5-10 mg/kg in females; clinical signs at doses as low as 1.5 mg/kg in females; and body weight loss as low as 1.8 mg/kg in males and 1.5 mg/kg in females. There was no apparent cytogenetic effect of doses tested (up to 1.8 mg/kg). The TEM positive control had a statistically significant increase in aberrations over the negative controls indicating the acceptability of the test. It is apparent that females are more sensitive, in terms of mortality, than are males.

NOTE: On page six of the report, the mid-test dose and low-test dose are indicated to be in gm/kg rather than the correct unit of "mg".

006352

Table 1

Body Weights in Dose-Finding Study with AC 92, 100 in Rats

Treatment	Sex	Group Mean Body Wts.(gm)[a] Pretreat.	24 Hr.	36 Hr.	% Change[b] 24 Hr.	36 Hr.	Mortality[c]
Corn Oil	M	279±16	287±16	277±12	2.9	-0.7	0/10
	F	206±16	213±21	205±13	3.4	-0.5	0/10
10 mg/kg[d]	M	283±13	-	-	-	-	10/10
	F	208±11	-	-	-	-	10/10
3 mg/kg	M	278±11	243±8	226±1	-12.6	-18.7	6/10
	F	205±13	-	-	-	-	10/10
1 mg/kg	M	272±17	279±18	NA[e]	2.6	NA	0/5
	F	204±9	194±12	NA	-4.9	NA	0/5
0.3 mg/kg	M	279±8	285±11	NA	2.2	NA	0/5
	F	205±10	210±14	NA	2.4	NA	0/5
0.1 mg/kg	M	267±15	278±15	NA	4.1	NA	0/5
	F	205±22	213±20	NA	3.9	NA	0/5

Table 2

Effect Of AC 92,100 on Body Weights after Single Treatment

Treatment	Sex	Group Mean Body Wts.(gm) Pretreat.	12 Hr.	24 Hr.	36 Hr.	% Change 12 Hr.	24 Hr.	36 Hr.
Corn Oil	M	277±13	286±17	284±12	300±13	3.2	2.5	8.3
	F	207±14	216±17	206±13	222±18	4.3	-0.5	7.2
1.8 mg/kg	M	277±16	276±26	268±20	269±19	-0.4	-3.2	-2.9
	F	205±16	192±16	184±NA	NA	-6.3	-10.2	NA
0.6 mg/kg	M	280±15	294±15	281±18	297±17	5.0	0.4	6.1
	F	205±10	214±9	203±9	213±10	4.4	-1.0	3.9
0.2 mg/kg	M	282±11	293±14	285±17	306±8	3.9	1.1	8.5
	F	204±8	212±8	207±8	213±13	3.9	1.5	4.4
TEM - 0.5 mg/kg	M	267±14	NA	265±18	NA	NA	-0.7	NA
	F	205±6	NA	201±6	NA	NA	-0.2	NA
Corn Oil	F	191±9	195±12	193±10	200±6	2.1	1.0	4.7
1.5 mg/kg	F	188±9	186±12	169±11	151±NA	-1.1	-10.1	-19.7
TEM - 0.5 mg/kg	F	192±10	NA	190±9	NA	NA	-1.0	NA

a = Mean ± Standard Deviation

b = % Change = $\frac{\text{(Post-treatment Weight - Pretreatment Weight) x 100}}{\text{Pretreatment Weight}}$

c = Reported at number of rats dead/number of rats tested

d = mg/kg of AC 92,100

e = Not Applicable

006352

Data extracted from Microbiological Associates report, Tables 1, 2 and 3 (pages 10-12).

Table 3

Chromosomal Damage in Bone Marrow of Rats

Treatment	Sex	Time (Hr)	Cells with Aberrations	Aberrations			Aberrations from Severely Damaged Cells
				Gaps	Breaks	Rearrangements	
Corn Oil 5 ml/kg	M	12	0	0	0	0	0.0
		24	0	1	0	0	0.0
		36	0	0	0	0	0.0
AC 92,100 1.8 mg/kg	M	12	0	0	0	0	0.0
		24	0	0	0	0	0.0
		36	1	1	1	0	0.004
0.6 mg/kg	M	12	1	2	1	0	0.004
		24	0	0	0	0	0.0
		36	0	1	0	0	0.0
0.2 mg/kg	M	12	1	1	1	0	0.004
		24	1	0	1	0	0.004
		36	0	1	0	0	0.0
TEM 0.5 mg/kg	M	24	54	0	56	42	1.27*
Corn Oil 5 ml/kg	F	12	1	1	1	0	0.004
		24	1	1	1	0	0.004
		36[a]	0	0	0	0	0.0
AC 92,100 1.8 mg/kg	F	12[b]	1	1	1	0	0.005
		24	All Found Dead				
		36	All Found Dead				
0.6 mg/kg	F	12	2	1	2	0	0.008
		24	0	0	0	0	0.0
		36	1	0	1	0	0.004
0.2 mg/kg	F	12	1	4	1	0	0.004
		24	0	0	0	0	0.0
		36	2	1	3	0	0.008
TEM 0.5 mg/kg	F	24	68	0	95	27	1.645*
Corn Oil 5 ml/kg	F	12	2	2	2	0	0.008
		24	1	1	1	0	0.004
		36	1	0	1	0	0.004
AC 92,100 1.5 mg/kg	F	12	2	1	1	1	0.008
		24[c]	0	0	0	0	0.0
		36[d]	0	0	0	0	0.0
TEM 0.5 mg/kg	F	24	104	0	146	57	3.25*

* = Statistical Significance $p < 0.01$

NOTES: 5 rats/group; 50 cells evaluated/rat (250/group)

a = Collection tube broke, no bone marrow cells analyzed for 1 rat

b = 4 surviving rats at this interval

c = 1 rat found dead

d = 1 surviving rat at this interval

006352

Data extracted from Hazleton report, Tables 4, 5 & 6 (pages 13-15).

IV. CONCLUSIONS

Under the conditions of this assay, there were no apparent increases in chromosomal aberrations observed with any of the doses of AC 92,100 tested (HDT = 1.8 mg/kg for males and 1.5 mg/kg for females). TEM (positive control) caused a statistically significant increase in chromosomal aberrations.

V. CORE CLASSIFICATION: Acceptable

Terbufos toxicology review dated 10/7/87

Page _____ is not included in this copy.

Pages 53 through 56 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy 006352
Review Section V/HED (TS-769C) 9/25/87

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T. Quang Q. Bui 4/25/87
Acting Section Head
Review Section V/HED (TS-769C)

I. Study Type: Chronic Toxicity (One year)
(Guideline § 83-1)

Study Title: A One-Year Dietary Toxicity Study with AC 92,100 in Rats (TERBUFOS)

EPA Identification Numbers:

EPA Identification: 6E 3409
EPA Accession: 400986
EPA Record: 192160
Caswell: 131A
Tox. Branch Project: 7-0549
Document:

Sponsor: American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08540

Testing Laboratory: Bio/dynamics Inc.
P.O. Box 43
East Millstone, NJ 08873

Study Number: Bio/dynamics Inc. - Project No. 85-2964

Study Date: January 9, 1987

Study Author: Ira W. Daly, Ph.D., D.A.B.T.

Recommendation:

The systemic No Observed Effect Level (NOEL) is 1.0 ppm (highest dose tested - HDT). The cholinesterase inhibition NOEL is 0.5 ppm. The cholinesterase inhibition Lowest Observed Effect Level (LOEL) is 1.0 ppm (HDT). These are based upon plasma and brain cholinesterase levels.

Core Classification: Core Minimum Data

006352

Test Material:

006352

Name: AC 92,100
Lot Nos.: AC 5087 13 (containers A and B), 1C, 1L, 1M, 1H, 2C, 2L, 2M, 2H, 3C, 3L, 3M, 3H, 4C, 4L, 4M, 4H, AC 5293-32C, AC 5293-32L, AC 5293-32M and AC 5293-32H.
Description: yellow liquid
Purity: 89.6% Active Ingredient (100% as received)

Vehicle: corn oil and methylene chloride (1:1)

Test Animal: CD® (COBS)® rats were obtained from Charles River Breeding Laboratories, Inc., Kingston, NY 12484. At initiation, the animals were 42 days of age. Males weighed an average of 201 gm (range of 177-221) and the females, 148 gm (range of 130-173).

II. Materials and Methods: Four groups of 30 male and 30 female Charles River CD® (COBS)® rats each were administered AC 92,100 as a dietary admix (with corn oil and methylene chloride in a 1:1 ratio) at concentrations of 0 (control), 0.125, 0.5 and 1.0 ppm. A copy of the Materials and Methods section from the Bio/dynamics report is appended.

The report indicated that the following analyses were documented by the sponsor: identity, strength, purity and composition; synthesis, fabrication and/or derivation of the test substance; and stability. Aliquots of test substance solutions were sent to the sponsor periodically. The determination of stability, homogeneity and concentration of the test substance with carriers under the conditions of the study were the responsibility of the sponsor.

Statistical methodology was described in detail.

A Quality Assurance statement was included.

The reviewer has no comment regarding the Materials and Methods section.

III. Results

A. Mortality: Table 1 presents the mortality observed during this one-year study.

There were no indications that the mortality was related to compound administration.

006352

Table 1

006352

Mortality of Rats Receiving AC 92,100 (Terbufos) for One Year

Males

Group	Dose (ppm)	Rat No.	Date of Death	Days on Test	Type of Death
1	0	1005	4/28/86	306	Moribund Sacrifice
2	0.125	-	-	-	-
3	0.5	3027	6/12/86	351	Moribund Sacrifice
		3029	5/2/86	310	Spontaneous Death
4	1.0	-	-	-	-

Females

1	0	1501	3/24/86	271	Moribund Sacrifice
2	0.125	-	-	-	-
3	0.5	3524	3/15/86	262	Moribund Sacrifice
4	1.0	4521	10/1/85	97	Accidental Death *

Study Start Date: June 27, 1985

* = Killed accidently during bleeding.

Data extracted from Bio/Dynamics report, Appendix B (report pages 45 - 49).

006352

B. Physical Observations: The observations noted were of the type commonly seen in rats during this type of study. Findings included chromodacryorrhea, excess lacrimation, alopecia, scabbing of the ears due to ear tags and nasal discharge. During approximately the last six months of this study, chromodacryorrhea, excess lacrimation and alopecia were noted in a slightly greater number of high-dose females than in the control, low- or mid-dose females. This difference was not observed in males. Table 2 indicates the number of females in each group which were noted to have these observations at each time period.

Table 2

Physical Observations Possibly Related to The Administration of AC 92,100 (Terbufos) for One Year: Females - Number of Animals with Observations

	Week:	0	1	2	3	4	8	12	16	20	24	28	32	36	40	44	48	52
	Dose (ppm)																	
No. of Animals: Examined	0	30	30	30	30	30	30	30	30	30	30	30	30	30	30	29	29	29
	0.125	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
	0.5	30	30	30	30	30	30	30	30	30	30	30	30	30	30	29	29	29
	1.0	30	30	30	30	30	30	30	30	29	29	29	29	29	29	29	29	29
Chromodacryorrhea	0	0	0	0	0	0	0	0	0	1	2	2	2	2	1	2	2	2
	0.125	0	0	0	0	0	0	1	1	1	1	1	1	1	0	1	1	3
	0.5	0	0	0	0	0	0	1	1	1	2	3	3	3	2	2	1	2
	1.0	0	0	0	0	0	0	2	2	3	4	5	6	6	4	5	6	7
Excess Lacrimation	0	0	0	0	0	0	1	0	0	0	2	2	2	2	0	2	2	2
	0.125	0	0	0	0	0	0	1	1	1	1	1	2	1	1	2	1	2
	0.5	0	0	0	0	0	0	0	1	1	2	3	1	2	0	1	1	2
	1.0	0	0	0	0	0	0	1	2	4	3	4	6	5	6	4	5	6
Alopecia	0	0	1	2	2	1	4	3	4	3	3	3	3	2	2	2	3	2
	0.125	2	0	4	7	8	8	7	9	4	5	4	6	4	4	3	4	6
	0.5	0	1	1	2	2	3	3	2	2	4	5	4	3	0	2	2	3
	1.0	1	1	6	8	8	12	9	8	6	11	10	6	6	6	9	10	10

Data extracted from Bio/dynamics report Appendix C (report pages 57 - 61).

C. Ophthalmoscopic Examination: Ophthalmic findings are presented in Table 3.

None of the findings observed after six and twelve months were considered by the Veterinary Ophthalmologist (Lionel F. Rubin, V.M.D.) to be related to compound administration.

In a previous 2 year feeding study (MRID 00049236, dated 7/31/74) in rats at doses of 0, 0.25, 1.0 and 8.0 (dose of 8.0 was initially 2.0, then 4.0 and finally 8.0) ppm for males and 0, 0.25, 1.0 and 4.0 (dose of 4.0 was initially 2.0, then 4.0, then 8.0 and finally 4.0) ppm for females, ocular lesions were reported as follows: exophthalmia, film on eye, eye rupture and loss of lacrimation in high-dose females during the first year of the study (exophthalmia also in low- and mid-dose females and at a lower incidence in control females); corneal scarring and cataracts in males and females of the high-dose group but also seen at a lower incidence in mid-, low-dose and control groups.

The only ophthalmic finding in the one-year rat study that appeared as though it might be related to compound administration was conjunctivitis, associated with dental abnormalities, infectious in origin or xerosis. Gross clinical observations (Table 2) indicated a possible increase in the number of female rats with chromodacryorrhea and excess lacrimation. These observations were not considered by the Veterinary Ophthalmologist to be a result of compound administration. The extent of ophthalmic "lesions" in the present one-year study does not appear to be as great as the findings reported in the prior rat study. The high dose (2.0-8.0 ppm) in the first study was higher than the maximum dose (1.0 ppm) examined in the current study.

D. Body Weights: Mean body weights of treated males and females at all dose levels were slightly below control values during the study. The most severe difference in body weight of treated rats was a value of 7.3% less than control for males (week 43, 0.5 ppm) and 5.8% less than control for females (week 27, 0.5 ppm). Statistically significant decreases were noted in males at the 0.125 ppm dose at weeks 33, 35 and 37; at the 0.5 ppm dose at weeks 33, 35, 37, 39 and 43; and at the 1.0 ppm dose at week 39 (no dose group mean was as much as one Standard Deviation from the control mean). There were no statistically significant differences in females. Mean body weight gains for males were 547.2, 505.4, 505.4 and 522.9 gm (control to high dose, respectively) and for females, 272.0, 259.1, 257.6 and 262.1 gm (control to high dose, respectively).

Table 4 shows group mean body weights at various intervals.

Table 3

Ophthalmoscopic Findings†

Dose (ppm)	Male C	Male L	Male M	Male H	Female C	Female L	Female M	Female H
MONTH 6 EVALUATION								
Conjunctivitis, infectious in origin or associated with dental abnormalities or xerosis	0	4*	6	3	2	1	2	6*
Phthisis	1	0	0	0	1	0	0	0
Focal retinopathy	0	1	0	0	1	0	2	0
Retinal degeneration	0	0	0	0	0	1	0	0
Cataract and iritis	0	0	0	1	0	0	0	0
TERMINAL EVALUATION								
Conjunctivitis (chromodacryorrhea), secondary to dental abnormality, infectious disease, or xerosis	2	5	5	1	2	2	2	8
Corneal scar, infectious in origin or secondary to corneal xerosis	0	1	1	1	3	1	0	0
Focal retinopathy, infectious in origin	0	2	0	1	1	0	2	0
Retinal degeneration	0	0	0	0	0	2	0	0
Phthisis bulbi, secondary to trauma or endophthalmitis	1	0	0	1	2	0	0	1
Focal posterior polar cataract	0	0	0	1	0	0	0	1
Posterior subcapsular cataract	0	1	0	0	0	0	0	0
Cataract	0	0	0	1	0	0	0	0
Lens luxation	0	1	0	0	0	0	0	0
Optic nerve atrophy	0	0	0	0	1	0	0	0

* = one rat with corneal scar

† = C: Control L: 0.125 ppm M: 0.5 ppm H: 1.0 ppm

006352

This table is based on evaluations determined by Lionel F. Rubin, V.M.D., and are presented in the report as Appendix D (report pages 63-66).

Table 4

Mean Body Weights of Rats Receiving AC 92,100 (Terbufos) for One Year

006352

Dose (ppm)		Males 0	Males 0.125	Males 0.5	Males 1.0	Females 0	Females 0.125	Females 0.5	Females 1.0
Week									
-1	Mean	143.6	143.0	143.4	144.3	117.1	116.8	116.9	116.9
	S.D.	7.3	7.7	7.3	7.5	6.8	7.3	6.5	6.5
	%a	-	-0.4	0.0	0.0	-	-0.3	-0.2	-0.2
0		203.2	199.6	200.2	199.9	150.4	146.9	148.1	147.9
		9.6	9.7	12.3	10.3	12.1	10.2	6.6	7.2
		-	-1.8	-1.5	-1.6	-	-2.3	-1.5	-1.7
1		261.1	255.0	257.6	256.3	176.7	170.0	172.4	170.2
		13.0	16.4	18.0	13.8	15.3	11.2	8.8	9.8
		-	-2.3	-1.3	-1.8	-	-3.8	-2.4	-3.7
4		367.6	365.6	363.6	364.9	220.2	214.7	218.3	216.4
		21.2	25.4	27.4	20.6	18.2	15.2	13.4	14.0
		-	-0.5	-1.1	-0.7	-	-2.5	-0.9	-1.7
8		475.7	466.4	466.2	474.7	264.6	262.2	260.9	261.6
		27.2	36.4	42.2	32.7	24.9	18.8	18.5	22.6
		-	-2.0	-2.0	-0.2	-	-0.9	-1.4	-1.1
12		540.1	524.8	530.8	539.1	292.7	286.2	285.3	285.5
		32.1	46.8	52.1	41.7	29.1	19.9	20.3	25.1
		-	-2.8	-1.7	-0.2	-	- 2.2	-2.5	-2.5
19		605.9	582.2	581.8	593.5	314.6	312.8	312.2	314.6
		42.4	57.1	59.7	61.5	38.6	25.2	30.0	28.4
		-	-3.9	-4.0	-2.0	-	-0.6	-0.8	0.0
27		647.1	614.3	614.3	629.2	335.0	323.1	315.7	323.2
		49.6	63.4	66.1	65.2	45.5	29.8	36.1	34.0
		-	-5.1	-5.1	-2.8	-	-3.6	-5.8	-3.5
35		692.2	648.7*	645.8*	659.2	359.1	349.8	340.0	353.2
		53.5	67.2	71.6	68.8	51.6	36.5	44.7	40.6
		-	-6.3	-6.7	-4.8	-	-2.6	-5.3	-1.6
43		705.4	665.9	654.1*	664.8	381.1	368.7	364.9	376.3
		58.0	67.0	72.1	69.3	57.2	40.4	48.9	47.3
		-	-5.6	-7.3	-5.8	-	-3.3	-4.3	-1.3
51		750.4	705.0	705.6	722.8	422.4	406.0	405.7	410.0
		67.8	78.4	84.7	82.9	69.3	49.0	65.7	69.8
		-	-6.1	-6.0	-3.7	-	-3.9	-4.0	-2.9

006352

a = % difference from control value * = Statistical Significance: $p < 0.05$

Data extracted from Bio/dynamics report Appendix E (report pages 69 - 72 and 79 - 82).

As the differences from control values were relatively slight for both males and females, and there was not an apparent dose response, it is questionable as to whether there is a compound related decrease in body weight gain.

E. Food Consumption: Mean food consumption values (gm/kg B.W.) were essentially the same in all dose groups for both sexes. The variability observed is considered to be within expected limits.

F. Test Substance Intake and Dietary Analyses: Mean test substance intake values were calculated based on individual body weight, food consumption data and nominal dose levels. Mean test substance intake over the one-year duration of the study calculated from mean weekly substance intake values was as follows:

Group	Dose Level (ppm)	AC 92,100 (mg/kg/day) Male	Female
II	0.125	0.007	0.009
III	0.5	0.028	0.036
IV	1.0	0.055	0.071

[The above data were directly from the Bio/dynamics' report (page 21).]

Using a conversion factor of .10 for young rats and 20 for older rats, the calculated mg/kg/day approximates the ppm concentrations.

G. Cholinesterase Levels: Mean plasma cholinesterase levels were significantly depressed in high-dose males at 6 and 12 months and in high-dose females at all intervals (1.5, 3, 6 and 12 months). The depression appeared to be more pronounced in females than in males. Low- and mid-dose values were similar to controls.

There was no apparent depression of mean erythrocyte cholinesterase levels in any treated groups, of either sex, at any interval.

Brain cholinesterase levels (determined after 12 months) were significantly depressed ($p < 0.01$) in both sexes at the high level. In addition, the mean value for low-dose males, though significant to $p < 0.05$, was 96% of control (control mean $\pm$ S.D. is 9.5 ± 0.5; low dose, 9.1 ± 0.3 micro M/gm/min.).

Mean percent and absolute cholinesterase data are presented in Table 5.

006352

Table 5

Cholinesterase Inhibition in Rats Receiving AC 92,100 (Terbufos) for One Year

Dose Level (ppm)	Months: Plasma 1.5	3	6	12	Erythrocyte 1.5	3	6	12	Brain 12
Males									
0	100[a]	100	100	100	100	100	100	100	100
	0.330[b]	0.373	0.423	0.574	5.2	6.1	7.1	8.7	9.5[c]
	0.054	0.087	0.076	0.115	1.3	0.9	0.3	0.6	0.5
0.125	97	87	89	94	106	102	100	102	96*
	0.321	0.324	0.376	0.542	5.5	6.2	7.1	8.9	9.1*
	0.054	0.051	0.051	0.100	1.1	0.7	0.3	0.6	0.3
0.5	91	85	87	84	100	102	97	107	97
	0.300	0.318	0.370	0.480	5.2	6.2	6.9	9.3	9.2
	0.042	0.050	0.075	0.105	0.9	0.4	0.3	1.2	0.3
1.0	93	82	75*	71†	94	93	96	98	92†
	0.308	0.307	0.317*	0.410†	4.9	5.7	6.8	8.5	8.7†
	0.074	0.060	0.066	0.077	0.9	0.7	0.3	0.6	0.3
Females									
0	100	100	100	100	100	100	100	100	100
	1.512	2.098	2.581	2.234	5.6	4.5	6.9	7.6	9.2
	0.349	0.633	0.588	0.414	0.2	1.7	0.7	0.6	0.4
0.125	99	94	107	113	105	109	104	104	101
	1.498	1.973	2.757	2.523	5.9	4.9	7.2	7.9	9.3
	0.371	0.389	0.359	0.510	0.6	2.2	0.5	0.7	0.5
0.5	91	99	96	103	100	107	101	100	100
	1.381	2.074	2.475	2.302	5.6	4.8	7.0	7.6	9.2
	0.329	0.714	0.712	0.604	0.4	1.8	0.4	0.8	0.6
1.0	58†	56†	49†	67*	102	96	99	99	90†
	0.880†	1.179†	1.272†	1.500*	5.7	4.3	6.8	7.5	8.3†
	0.235	0.202	0.446	0.634	0.6	1.4	0.5	0.7	0.9

a = Whole number = % of control; second line = mean; third line = Standard Deviation

b = micro M/ml/min. c = micro M/gm/min.

Statistical Significance: * = $p < 0.05$; † = $p < 0.01$

Data extracted from Bio/dynamics report Appendix H (report pages 138 - 267). 006352

H. Clinical Chemistry: The following parameters were examined at months 3, 6 and termination: Serum Glutamic Oxaloacetic Transaminase, Serum Glutamic Pyruvic Transaminase, Alkaline Phosphatase, Lactic Dehydrogenase, Blood Urea Nitrogen, Glucose, Cholesterol, Total Protein, Albumin, Globulin, A/G Ratio, Total Bilirubin, Direct Bilirubin, Sodium, Potassium, Chloride, Calcium and Gamma Glutamyl Transpeptidase.

There were no findings in any of the parameters examined that indicated a compound related effect.

I. Hematology: The following parameters were examined at months 3, 6 and termination: Hemoglobin Concentration, Hematocrit, Erythrocyte Count, Platelet Count, Total Leukocyte Count and Leukocyte Differential.

There were no findings in any of the parameters examined that indicated a compound related effect.

J. Urinalysis: The following parameters were examined at months 3, 6 and termination: Appearance, Specific Gravity, pH, Protein, Glucose, Ketones, Bilirubin, Occult Blood and Microscopic.

There were no findings in any of the parameters examined that indicated a compound related effect.

K. Terminal Organ and Body Weights; Organ/Body Weight Ratios; and Organ/Brain Weight Ratios: At terminal necropsy (after 12 months) there was a significant reduction in mean testes weights ($p < 0.05$) and testes-to-brain weight ratios ($p < 0.01$) in high-dose males. There was a significant reduction in kidney weights ($p < 0.05$) and kidney-to-brain weight ratios in the mid- ($p < 0.05$) and high-dose ($p < 0.01$) females. There were no other findings regarding absolute or relative weights which were statistically different from control values.

Mean absolute organ weights and organ-to-body weight ratios are presented in Table 6.

006352

006352

Table 6

Organ Weights: Absolute and Organ-to-Body Weight Ratio of Rats Receiving AC 92,100 (Terbufos) for One Year †

Dose (ppm)	Male				Female			
	0	0.125	0.5	1.0	0	0.125	0.5	1.0
Terminal B.W.[a]	729.3	684.2	685.3	700.4	402.2	383.7	383.1	389.3
± S.D.	66.7	79.8	84.9	85.2	69.5	50.8	63.1	68.8
Brain: Weight gm	2.210	2.240	2.209	2.229	2.016	2.028	2.014	2.048
S.D.	0.101	0.098	0.077	0.115	0.101	0.113	0.103	0.122
Org. to B.W.	3.05	3.32	3.27	3.22	5.15	5.37	5.38	5.41
S.D.	0.31	0.44	0.41	0.39	0.86	0.74	0.81	0.93
Heart: Weight gm	1.869	1.832	1.790	1.824	1.305	1.323	1.248	1.307
S.D.	0.217	0.195	0.209	0.240	0.169	0.144	0.124	0.179
Org. to B.W.	2.57	2.70	2.62	2.62	3.29	3.48	3.31	3.41
S.D.	0.25	0.31	0.22	0.31	0.44	0.41	0.40	0.51
Kidneys: Weight gm	4.243	4.106	4.065	3.994	2.748	2.587	2.481*	2.517*
S.D.	0.650	0.526	0.760	0.442	0.415	0.270	0.397	0.317
Org. to B.W.	5.83	6.04	5.97	5.75	7.01	6.81	6.55	6.59
S.D.	0.78	0.72	1.06	0.68	1.59	0.84	0.90	0.99
Liver: Weight gm	18.988	17.909	17.740	17.800	10.272	9.778	9.792	9.815
S.D.	3.270	3.112	3.039	3.294	1.786	1.388	2.017	1.765
Org. to B.W.	2.59	2.63	2.59	2.54	2.57	2.55	2.55	2.54
S.D.	0.30	0.33	0.34	0.32	0.32	0.20	0.22	0.31
Lungs: Weight gm	1.951	1.937	1.912	1.868	1.451	1.473	1.437	1.447
S.D.	0.188	0.216	0.169	0.176	0.134	0.164	0.129	0.137
Org. to B.W.	2.68	2.85	2.81	2.69	3.68	3.89	3.82	3.81
S.D.	0.23	0.33	0.27	0.29	0.56	0.62	0.52	0.49
Spleen: Weight gm	0.943	0.938	0.946	0.918	0.548	0.547	0.505	0.694[c]
S.D.	0.159	0.145	0.157	0.191	0.154	0.128	0.089	0.611
Org. to B.W.	1.29	1.38	1.39	1.32	1.40	1.43	1.33	1.83
S.D.	0.17	0.22	0.21	0.26	0.43	0.34	0.20	1.74
Thymus: Weight gm	0.199	0.158	0.168	0.171	0.151	0.157	0.210	0.162
S.D.	0.071	0.037	0.049	0.044	0.047	0.055	0.162	0.066
Org. to B.W.	2.71	2.32	2.45	2.43	3.72	4.03	5.35	4.02
S.D.	0.89	0.54	0.60	0.52	0.96	1.17	3.66	1.10
Thyroid: Weight gm	0.0347	0.0385	0.0358	0.0381	0.0271	0.0249	0.0262	0.0266
[b] S.D.	0.0095	0.0108	0.0075	0.0083	0.0087	0.0074	0.0070	0.0064
Org. to B.W.	4.81	5.68	5.32	5.48	6.69	6.52	6.99	6.96
S.D.	1.41	1.60	1.37	1.16	1.59	1.90	2.01	1.86
Testes/: Weight gm	3.657	3.530	3.561	3.344*	0.0545	0.0500	0.0558	0.0546
Ovaries S.D.	0.427	0.285	0.300	0.454	0.0194	0.0121	0.0229	0.0218
Org. to B.W.	5.05	5.23	5.27	4.83	13.87	13.31	14.78	14.18
S.D.	0.69	0.77	0.75	0.82	5.25	4.27	6.10	5.80

a = Body Weight b = With parathyroids * = Statistical Significance: $p < .05$

c = Of 29 spleen weights: 27-0.699 or less; 1-1.637; 1-3.657

† = Organ to Body Weight - organ weight (gm) ÷ B.W. times: 100 for liver; 1,000 for brain, heart, kidneys, lungs, spleen and testes; 10,000 for thymus, thyroid and ovaries.

Data extracted from Bio/dynamics report, Appendix J (report pages 284 - 293).

006352

006352

Although there was a statistically significant reduction in absolute and organ-to-brain weight ratios for testes in high-dose males and for kidneys in high- and mid-dose females, there was no decrease in organ-to-body weight ratio and no associated histopathological findings. Thus, there was only a remote possibility of a compound related effect.

L. Gross Pathology: Gross findings were either essentially the same for treated and control groups or were observed to occur sporadically.

It is not considered that compound administration had an effect on gross pathological observations.

M. Microscopic Pathology: There did not appear to be any microscopic pathological observations which were considered to be compound related. Table 7 shows the number of rats in each group which were diagnosed as having benign and/or malignant neoplasms.

From a review of the above table as well as the microscopic findings noted in the report, it does not appear that compound administration had an effect on the incidence of either benign or malignant neoplasms or on the finding from any examined tissue after one year of exposure.

IV. CONCLUSIONS/DISCUSSION

The systemic No Observed Effect Level (NOEL) is 1.0 ppm (highest dose tested - HDT). The cholinesterase inhibition NOEL is 0.5 ppm. The cholinesterase inhibition Lowest Observed Effect Level (LOEL) is 1.0 ppm (HDT). These are based upon plasma and brain cholinesterase levels.

The only definitive compound related effect appeared to be on cholinesterase inhibition at the high dose (1.0 ppm) only. Statistically significant decreases in plasma levels were observed at 6 and 12 months in males and at all four intervals (1.5, 3, 6 and 12 months) in females. Brain cholinesterase inhibition was reported in high-dose males and females at terminal sacrifice (12 months). The low-dose (0.125 ppm) decrease in male brain level to 96% of control was reported as statistically significant. However, because of the relatively slight difference from the control level plus the mid-dose value of 97% (not statistically significant), it is felt that the low dose is within biological limits and not of toxicological significance. It is therefore concluded that the high dose (1.0 ppm) caused a decrease in cholinesterase levels in plasma at 6 and 12 months in males as well as at all four intervals in females, and in brain of both sexes at terminal sacrifice (only interval measured).

006352

Table 7

Reported Neoplasms in Rats Administered AC 92,100 (Terbufos) for One Year

	Number of Animals Affected							
	Males				Females			
Dose (ppm)	0	0.125	0.5	1.0	0	0.125	0.5	1.0
BENIGN								
Thyroid	30*	30	30	30	30	30	30	30
Medullary cell adenoma	2	1	1	0	2	0	2	0
Follicular cell adenoma	0	0	1	0	0	0	0	0
Pituitary	30	30	29	29	30	30	30	30
Pars distalis: adenoma	2	6	2	3	7	5	6	7
Adrenal Cortex	30	30	29	30	30	30	30	30
Adenoma	0	1	0	0	0	0	0	0
Thymus	16	30	29	30	25	30	29	30
Thymoma	0	1	0	0	0	0	0	0
Liver	30	30	30	30	30	30	30	30
Hepatocellular adenoma	0	0	0	0	0	0	1	0
Mammary Gland	27	25	25	27	30	30	28	30
Fibroadenoma	0	0	0	0	0	0	1	0
MALIGNANT								
Brain	30	30	30	30	30	30	30	30
Malignant glioma	1	0	1	0	0	0	0	0
Lung	30	30	30	30	30	30	30	30
Metastatic neoplasm	0	0	0	0	1	0	0	0
Mammary Gland	27	25	25	27	30	30	28	30
Carcinoma (3 neoplasms)	0	0	0	0	1	0	0	0
Carcinoma	0	0	0	0	0	1	0	2
Zymbal's Gland	0	0	1	0	0	1	0	0
Squamosebaceous cell carcinoma	0	0	1	0	0	1	0	0
Adrenal Cortex	30	30	29	30	30	30	30	30
Carcinoma	0	0	0	0	0	0	0	1
Thyroid	30	30	30	30	30	30	30	30
Medullary cell carcinoma	0	0	0	0	0	0	0	1

006352

* = Number of animals examined.

Data extracted from Bio/dynamics report (Table IV, report pages 1283 - 1295 and Table V, report pages 1297 -1567).

The only statistically significant differences in organ weights were decreases in high-dose testes and mid- and high-dose kidneys in females regarding absolute (gm) weight and organ-to-brain weight ratios, but not in organ-to-body weight ratios. As there were no apparent associated compound related histopathological findings concerning either of these organs, the toxicological significance of these findings is not known with certainty.

V. CORE CLASSIFICATION: Core-Minimum Data

Systemic NOEL = 1.0 ppm (HDT)
Cholinesterase Inhibition NOEL = 0.5 ppm
Cholinesterase Inhibition LOEL = 1.0 ppm (HDT)
(Cholineserase NOEL and LOEL based upon plasma and brain cholinesterase values.)

006352

Terbufos toxicology review dated 10/7/87

Page _____ is not included in this copy.

Pages 71 through 80 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Primary Reviewer: Alan C. Levy, Ph.D. Alan C. Levy 006352
Review Section V/HED (TS-769C) 9/25/87

Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T. Quang Q. Bui 9/25/87
Acting Section Head
Review Section V/HED (TS-769C)

I. Study Type: Chronic Toxicity and Oncogenicity
(Guideline § 83 - 1, 2)

Study Title: Chronic Dietary Toxicity and Oncogenicity Study with AC 92,100 (TERBUFOS) in Mice

EPA Identification Numbers: EPA Identification: 6E 3409
EPA Accession: 400986
EPA Record: 192160
Caswell: 131A
Tox. Branch Project: 7-0549
Document:

Sponsor: American Cyanamid Company
Agricultural Research Division
P.O. Box 400
Princeton, NJ 08540

Testing Laboratory: Tegeris Laboratories, Inc.
9705 N. Washington Boulevard
Laurel, MD 20707

Study Number: Tegeris Laboratories, Inc. - Project 8422

Study Date: October 14, 1986

Study Author: Thomas E. Shellenberger, Ph.D.

Recommendation: Under the conditions of this study, there was no apparent indication that AC 92,100 had an oncogenic effect at any of the concentrations examined (HDT = 12 ppm) in CD-1 mice. The suggestion of a possible slight increase in mortality was observed in both sexes (especially males) at the high dose of 12 ppm. There was a slight, but statistically significant, decrease in body weight gain throughout the 18 months in both sexes at the high dose. Body weight gains were 10.1% below controls for males and 19.7% below controls for females. There was little or no effect on food consumption in males and a slight decrease in females of the high-dose group. This study is Core Minimum.

Test Material: Name: AC 92,100
Lot No.: HM3-81
Description: clear, light brown liquid
Purity: 89.6%

006352

Vehicle: corn oil and methylene chloride (1:1)

Test Animal: CD-1 mice from Charles River Breeding Laboratories, Inc., Wilmington, MA. At initian, the animals were 5-6 weeks of age. Males weighed an average of 24.03 gm (range of 18.3-28.9) and the females, 20.24 gm (range of 13.8-24.1).

006352

II. Materials and Methods: Four groups of 65 male and 65 female Charles River CD-1 mice each were administered AC 92,100 as a dietary admix (with corn oil and methylene chloride in a 1:1 ratio) at concentrations of 0 (control), 3, 6 and 12 ppm. A copy of the Materials and Methods section from the Tegeris Laboratories report is appended.

Statistical methodology was described in detail.

A Quality Assurance statement was included.

The reviewer has no comments regarding the Materials and Methods section.

III. Results

A. Mortality: Table 1 indicates the mortality observed during this 18-month study.

In males, the number of animals which did not reach terminal sacrifice (and the % mortality) were 7 (12.7%), 5 (9.1%), 3 (5.5%) and 15 (27.3%) in the 0, 3, 6 and 12 ppm groups, respectively. There is a suggestion that during the course of the study, the possible increase in high-dose mortality may have been due to compound administration. In addition, although the first two males to be dead were controls, by week 32, the number of dead high-dose males had surpassed the controls. At 12 months (interim sacrifice), mortality was 2 in controls and 7 in high dose. At week 65, 3 controls and 12 high dose were dead. The author of the report concluded that, "Even though the apparent doubling of the mortality rate in high-dose animals suggests a possible effect of the test material, the 27.3% mortality of these animals equating to 72.7% survival represent excellent survival to 80 weeks, especially in an open colony system. The survival rate is equal to or better than has been obtained in control males in similar studies conducted in this laboratory. [Reviewer's Comment: no historical mortality data accompanied the report.] Therefore, the apparent higher mortalities obtained in high-dose males and females are considered to be random occurrances unrelated to the test material."

In females, although mortality was slightly greater in the high-dose mice compared to controls at 80 weeks (19 versus 15), from weeks 54-75, approximately twice as many high-dose females as controls succumbed. Mortality was as follows: 15 (27.3%), 8 (14.5%), 12 (21.8%) and 19 (34.5%) in the 0, 3, 6 and 12 ppm groups, respectively.

In conclusion, it is the reviewer's opinion that there is the possible suggestion of increased mortality in groups receiving 12 ppm of AC 92,100, especially in male mice. The observed mortality rate does not have an impact on the acceptability of the study according to FIFRA guidelines § 83-2.

006352

Table 1

Mortality of Mice Receiving AC 92,100 (Terbufos) for 18 Months

Dose	Males				Females			
ppm	0	3	6	12	0	3	6	12
Week								
1	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0
12	1	0	0	0	0	0	0	0
13	1	0	0	0	0	0	0	0
14	1	0	0	0	0	0	0	0
15	1	0	0	0	0	0	0	0
16	1	0	0	0	0	0	1	0
17	1	0	0	0	0	0	1	0
18	1	0	0	0	0	0	1	0
19	2	0	0	0	0	0	1	0
20	2	0	0	1	0	0	1	0
21	2	0	0	1	0	0	1	0
22	2	0	0	1	0	0	1	0
23	2	0	0	1	0	0	1	0
24	2	0	0	2	0	1	2	0
25	2	0	0	2	0	1	2	0
26	2	0	0	2	1	1	2	0
27	2	0	0	2	2	1	2	0
28	2	0	0	2	2	1	2	0
29	2	0	0	2	2	1	2	0
30	2	0	0	2	2	1	2	1
31	2	0	0	2	2	1	2	1
32	2	0	0	4	2	1	2	1
33	2	0	0	4	2	1	2	2
34	2	0	0	5	2	1	2	2
35	2	0	0	5	2	1	2	2
36	2	0	0	5	2	1	2	2
37	2	0	0	5	3	1	2	2
38	2	0	0	5	3	1	2	2
39	2	0	0	5	3	1	2	2
40	2	0	0	5	3	1	2	2

Dose	Males				Females			
ppm	0	3	6	12	0	3	6	12
Week								
41	2	0	0	5	3	1	3	3
42	2	0	0	5	3	1	3	3
43	2	0	0	5	3	1	3	4
44	2	0	0	5	3	1	3	4
45	2	0	0	6	3	1	3	4
46	2	0	0	6	3	1	3	4
47	2	0	0	6	3	1	3	4
48	2	0	0	6	4	1	3	4
49	2	0	0	7	4	1	3	4
50	2	0	0	7	4	1	3	4
51	2	0	0	7	4	1	3	5
52	2	0	0	7	4	1	3	6
53*	2	0	1	7	4	1	4	7
54	2	0	1	8	4	1	4	8
55	2	0	1	8	4	1	4	8
56	2	1	1	9	4	1	5	8
57	2	1	1	9	4	1	5	8
58	2	1	1	9	4	1	5	9
59	2	1	1	9	4	1	5	10
60	2	1	1	10	5	1	5	10
61	3	1	2	10	5	1	5	10
62	3	1	2	10	6	1	5	12
63	3	1	2	11	7	1	5	12
64	3	1	2	11	7	1	5	12
65	3	2	2	12	7	2	5	14
66	3	2	2	12	7	2	8	14
67	3	2	2	12	8	2	8	14
68	3	3	2	12	8	3	8	14
69	3	3	2	12	8	3	8	14
70	4	3	2	13	8	4	8	15
71	4	3	2	13	9	4	9	17
72	4	4	3	13	9	5	9	17
73	5	5	3	13	9	6	9	17
74	5	5	3	13	9	6	9	17
75	6	5	3	13	9	6	9	17
76	7	5	3	13	11	7	9	17
77	7	5	3	13	15	7	11	18
78	7	5	3	14	15	7	12	18
79	7	5	3	14	15	8	12	19
80	7	5	3	15	15	8	12	19

* = 10 animals/sex/group sacrificed during week 53 (12 month interim sacrifice).
NOTE: 65 mice/sex/group at the start of the study

Data extracted from Tegeris Laboratories report, Table T-4.2.3 (report pages 90 - 95) and Table T-4.3.1 (report pages 96 - 105).

B. Clinical Observations: A variety of clinical signs were noted during the course of the study. Those reported to have occurred with some frequency or to have been described as a "mass" are presented in Table 2.

Table 2

Clinical Observations for Mice Receiving AC 92,100 for up to 18 Months*

Dose (ppm)	Male				Female			
	0	3	6	12	0	3	6	12
OBSERVATION								
Ocular Discharge	0/2*	0/1	0/1	0/0	0/0	0/1	0/1	0/0
Ocular Opacity	1/3	1/2	0/4	0/6	1/3	0/3	0/6	0/5
Alopecia	0/7	0/5	1/3	2/1	1/1	0/0	1/2	1/1
Distended Abdomen	0/1	0/1	0/0	1/0	0/4	0/3	0/1	0/0
Prolapsed Penis	0/1	0/1	1/0	1/0	-	-	-	-
Mass-Rear Leg	0/0	0/0	0/1	0/0	0/0	0/0	0/0	0/0
Mass-Pelvis	0/0	1/0	0/0	0/0	0/0	0/1	1/0	0/1
Mass-Inguinal Region	0/0	0/0	1/0	0/0	0/0	0/0	0/1	0/0
Mass-Abdomen	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/1

* = Observation during first 12 months/observation during last 6 months.
Data extracted from Tegeris Laboratories report, Tables T-4.2.1 and T-4.2.2 (report pages 79-82 and 83-89).

No lesions or signs observed during the study were considered to have been attributable to compound administration.

C. Body Weights: Group mean body weights ± S.D., at selected intervals, are presented in Table 3.

Table 3

Mean Body Weights of Mice Receiving AC 92,100 (Terbufos) for 18 Months

006352

Dose (ppm)	Males				Females			
	0	3	6	12	0	3	6	12
Week								
0	24.77[a]	24.14	23.90*	23.[illegible]	20.81	20.28	20.10	19.79*
	1.86[b]	1.52	1.91	2.00	1.67	1.87	1.76	1.68
	65[c]	65	65	65	65	65	65	65
1	26.49	26.36	25.10*	23.30*	22.48	21.64*	20.69*	19.08*
	2.27	1.63	1.89	1.86	1.64	1.44	1.64	1.79
	65	65	65	65	65	65	65	65
6	32.85	32.17	32.45	30.65*	27.39	26.89	27.60	25.24*
	2.35	2.14	2.52	2.13	2.84	2.23	2.11	2.04
	65	65	65	65	65	65	65	65
14	35.03	34.85	35.46	33.30*	29.60	29.43	30.55	29.20
	2.96	3.06	3.11	2.39	2.68	2.55	2.61	2.21
	64	65	65	65	65	65	65	65
22	36.60	37.02	37.38	34.78*	31.15	31.42	32.25	29.78*
	2.67	3.48	3.35	2.61	2.86	2.91	3.12	2.21
	63	65	65	64	65	65	64	65
30	37.43	37.98	38.43	34.60*	32.94	33.57	33.75	29.64*
	2.94	3.85	4.01	2.73	3.50	3.56	3.33	3.09
	63	65	65	63	63	64	63	65
38	38.33	38.74	38.94	35.38*	33.23	33.99	33.32	30.45*
	3.45	4.38	3.91	2.91	3.49	4.15	3.52	2.73
	63	65	65	60	62	64	63	63
46	38.35	39.09	39.53	35.99*	34.22	35.19	34.35	30.71*
	3.39	4.50	4.39	3.13	4.24	4.87	3.91	2.90
	63	65	65	59	62	64	62	61
54†	38.74	39.22	38.86	35.64*	33.89	34.41	34.45	30.41*
	3.87	4.96	4.43	2.89	3.81	4.24	3.57	3.30
	53	55	54	47	51	54	51	48
62	39.83	40.53	40.39	37.38*	34.87	33.90	34.90	31.21*
	4.11	5.30	4.92	3.15	3.90	5.46	3.82	3.50
	52	54	53	45	49	54	50	43
70	38.94	39.81	39.47	36.01*	34.55	35.33	34.17	30.44*
	4.43	5.40	5.23	3.37	4.81	7.00	3.86	3.85
	52	52	53	42	47	51	47	40
78	38.91	39.45	39.32	36.01*	34.46	35.02	34.18	30.75*
	3.68	5.10	5.00	3.51	4.65	5.83	4.30	3.37
	48	50	52	41	40	48	43	37

* = Statistically different from control at $p < 0.05$ using Dunnett's T Value.

† = 12 month scheduled interim sacrifice of 10 animals/sex/group.

Body weights stated to be identical to controls at time of randomization.

006352

a = group mean b = Standard Deviation c = number of mice

Data extracted from Tegeris Laboratories report, Table T-4.3.1 (pages 96-100) and Table T-4.3.2 (pages 101-105).

85

High-dose males and females had significantly lower body weights during the course of the study when compared to control values. There were statistically significant lower body weights at the start of the study in the 6 ppm male group and 12 ppm female group when compared to controls.

Dose (ppm)	Males				Females			
	0	3	6	12	0	3	6	12
Mean Body Weight (gm)								
Week: 0	24.77	24.14	23.90*	23.30	20.81	20.28	20.10	19.79*
Week: 78	38.91	39.45	39.32	36.01*	34.46	35.02	34.18	30.75*
Mean Body Weight Gain (gm)	14.14	15.31	15.54	12.71	13.65	14.74	14.08	10.96

* = Statistical significance from control, $p < 0.05$.

Data calculated from Tegeris Laboratories report, Table T-4.3.1 (report pages 96 and 100) and Table T-4.3.2 (report pages 101 and 105).

When calculated as "body weight gain", there was a decrease in high-dose males of 10.1% and in high-dose females of 19.7%.

D. Food Consumption: There was a statistically significant ($p < 0.05$) decrease in food consumption (gm/mouse/week) in high-dose males at week one (control = 43.45 $\pm$ 6.45; high dose = 37.65 $\pm$ 5.53). This is not considered to be an unexpected finding during the first week (acclimation of animals to new medicated feed). Although there were 8/33 weighing periods where a statistically significant decrease in high-dose food consumption occurred, 5 of these intervals were at the 5 measurements during weeks 46-62 (consumptions were measured at 4-week intervals). In addition, the mean weekly food consumption (gm/mouse/week) for the four groups over the entire 18 month study period was: control = 39.43, 3 ppm = 40.34, 6 ppm = 39.70 and 12 ppm = 38.56 (a decrease in food consumption in the high dose of 2.2% of the control value). There was a statistically significant ($p < 0.05$) decrease in food consumption (gm/mouse/week) in high dose females at weeks one and two (week 1: control = 38.69 $\pm$ 4.71, high dose = 34.94 $\pm$ 6.61; week 2: control = 40.41 $\pm$ 4.27, high dose = 35.25 $\pm$ 3.85). These are not considered to be unexpected findings during the first week or two (acclimation of animals to new medicated feed). There were 15/33 weighing intervals when the high dose was significantly decreased from control values. In addition, at 29/33 intervals, the mean value for high-dose females was numerically less than the corresponding control value.

It is therefore concluded that in males, AC 92,100 had little or no effect on overall food consumption at any of the concentrations examined. In females, there was a slight decrease in food consumption at the high dose only.

E. Test Substance Analysis - Identification, Purity, Homogeneity and Stability: Data from all of these parameters were included as an Appendix to the Tegeris Laboratories report. Medicating solution, medicated diet preparation and sampling were performed at Tegeris Laboratories. Chemical analyses were performed at American Cyanamid Company, Princeton, NJ.

The concentration of AC 92,100 in initial samples were: 3 ppm = 3.02 to 3.11; 12 ppm = 11.3 to 11.8.

After 3, 7 and 14 days in mouse feeders (in the rodent room), concentrations were: 3 ppm = 2.97 $\pm$ 0.050 (S.D.), 2.94 $\pm$ 0.058 and 2.65 $\pm$ 0.056, respectively; 12 ppm = 11.3 $\pm$ 0.103, 10.9 $\pm$ 0.130 and 10.3 $\pm$ 0.200, respectively. Diets were prepared individually each week.

It appears that proper procedures were followed in order to assure that the mouse diets contained approximately the desired nominal concentration of compound.

F. Hematology: The following parameters were examined on 10 mice/sex/group at 12 months (scheduled interim sacrifice) and prior to terminal necropsy (18 months): Erythrocyte Count, Hematocrit, Hemoglobin, Differential Leukocyte Count, Total Leukocyte Count and Platelet Count.

There was no apparent effect of compound administration on any hematological parameters.

NOTE: Terminal Sacrifice, Female, 6 ppm, mouse no. 4930 - The number of leukocytes was reported as 65,400/mm^3. The percent of segmented neutrophils was 57. These values were greater than is usually noted (especially the number of leukocytes - up to 10 times usual). The reviewer feels that a comment should have been made in the report and that the leukocyte value should not have been included in the calculation of the mean $\pm$ S.D. values.

G. Twelve-Month Interim Sacrifice Organ Weights, Organ/Body Weight Ratios and Organ/Brain Weight Ratios: Mean absolute and organ-to-body weight ratios are presented in Table 4.

006352

Table 4

Organ Weights - 12 Month Interim Sacrifice†: Absolute and Organ-to-Body Weight Ratio of Mice Receiving AC 92,100 (Terbufos) for 18 Months

Dose (ppm)	Male				Female			
	0	3	6	12	0	3	6	12
Terminal Body Weight	38.599	39.950	38.910	35.040	33.890	33.800	33.660	30.150
± S.D.	2.789	4.616	3.160	3.323	3.773	5.193	4.994	2.918
Brain: Weight gm	0.508	0.516	0.512	0.499	0.524	0.529	0.503	0.507
S.D.	0.036	0.024	0.025	0.018	0.029	0.036	0.042	0.027
Organ to B.W.	13.208	13.101	13.243	14.384	15.628	15.096	15.203	16.937
S.D.	1.174	1.891	1.289	1.661	1.917	2.639	2.359	1.645
Adrenals: Weight gm	0.008	0.008	0.007	0.008	0.016	0.015	0.014	0.011
S.D.	0.003	0.003	0.003	0.003	0.009	0.005	0.005	0.004
Organ to B.W.	0.224	0.216	0.217	0.254	0.457	0.430	0.412	0.374
S.D.	0.092	0.088	0.086	0.116	0.257	0.173	0.138	0.116
Gonads: Weight gm	0.255	0.261	0.260	0.255	0.043	0.045	0.056	0.056
S.D.	0.044	0.018	0.047	0.045	0.020	0.029	0.064	0.017
Organ to B.W.	6.594	6.618	6.725	7.298	1.270	1.222	1.534	1.904
S.D.	0.922	0.862	1.415	1.172	0.629	0.689	1.478	0.697
Heart: Weight gm	0.241	0.265	0.241	0.249	0.203	0.186	0.193	0.162*
S.D.	0.028	0.029	0.026	0.032	0.033	0.023	0.039	0.021
Organ to B.W.	6.223	6.659	6.216	7.187*	5.966	5.263	5.779	5.372
S.D.	0.501	0.678	0.618	1.221	0.544	0.720	1.082	0.621
Kidneys: Weight gm	0.801	0.832	0.784	0.772	0.608	0.561	0.535	0.528
S.D.	0.073	0.097	0.074	0.047	0.080	0.058	0.114	0.056
Organ to B.W.	20.788	20.887	19.992	22.261	18.045	15.851*	15.856*	17.541
S.D.	1.574	1.825	2.100	3.181	2.283	2.016	2.011	1.285
Liver: Weight gm	2.356	2.441	2.241	2.085	1.994	1.987	2.015	1.651*
S.D.	0.255	0.414	0.313	0.248	0.296	0.326	0.348	0.240
Organ to B.W.	60.960	60.947	57.624	59.596	58.941	55.676	60.008	55.116
S.D.	3.960	5.706	7.240	5.474	6.451	6.130	6.564	9.186
Lungs: Weight gm	0.317	0.384	0.336	0.333	0.305	0.266*	0.260*	0.275
S.D.	0.063	0.091	0.082	0.099	0.039	0.035	0.032	0.031
Organ to B.W.	8.194	9.808	8.727	9.530	9.083	7.500*	7.801	9.208
S.D.	1.522	3.092	2.649	2.765	1.362	1.126	0.942	1.508
Pituitary: Weight gm	0.003	0.003	0.003	0.004	0.004	0.004	0.003	0.003
S.D.	0.000	0.001	0.001	0.001	0.001	0.001	0.002	0.001
Organ to B.W.	0.086	0.078	0.087	0.100	0.122	0.109	0.076	0.107
S.D.	0.015	0.013	0.022	0.037	0.043	0.027	0.034	0.043
Spleen: Weight gm	0.094	0.103	0.111	0.085	0.120	0.120	0.116	0.111
S.D.	0.016	0.026	0.040	0.012	0.022	0.027	0.034	0.025
Organ to B.W.	2.416	2.624	2.951	2.447	3.557	3.408	3.439	3.697
S.D.	0.326	0.797	1.360	0.466	0.682	0.889	0.811	0.931
Thyroids: Weight gm b	0.009	0.008	0.007	0.007*	0.010	0.009	0.007*	0.007
S.D.	0.002	0.001	0.002	0.003	0.002	0.003	0.003	0.003
Organ to B.W.	0.240	0.206	0.186	0.192	0.281	0.255	0.197	0.240
S.D.	0.047	0.033	0.049	0.066	0.057	0.075	0.063	0.090

† = 10/sex/group, a = Body Weight, b = with parathyroids, * = Statistical Significance: $p < 0.05$

Organ-to-Body Weight = gm organ weight ÷ 1000 gm body weight.

Data extracted from Tegeris Laboratories report, Table T-4.6.1 (report pages 125 - 128 and 131 - 134).

There were sporadic instances of statistically significant differences of absolute (gm) or relative (organ-to-body weight ratio) organ weights: in males at the high dose, an increase in relative heart and a decrease in absolute thyroid weights; in females, a decrease in absolute heart, liver and thyroid weights in high dose, as well as a decrease in absolute lung and relative kidney at low and mid dose and relative lung at low dose.

H. Eighteen-Month Terminal Sacrifice Organ Weight, Organ/Body Weight Ratios and Organ/Brain Weight Ratios: Mean absolute and organ-to-body weight ratios are presented in Table 5.

The only statistically significant value was an increase in the absolute liver weight in low-dose males. It is therefore considered that the administration of AC 92,100 did not have an effect on terminal sacrifice organ weights.

I. Gross Pathology:

1. Mice Found Dead or Sacrificed Moribund: Incidences for the time intervals of "first 12 months" and "month 13 to termination" are presented in Table 6.

During the first 12 months, 4/8 high-dose males examined had dilated renal pelves (1/2 in male controls and none in any female group). Urinary bladder distended (hemorrhagic) was reported in 3/8 high-dose males but in no other males or in any females. In high-dose females, 2/8 had pale liver compared with 1/4 control and none in any male group. Also, in high-dose females, 2/8 had fluid filled (blood) uteri compared with 0/4 controls and 0/5 in the other two dose groups. It is not considered that any of these findings are compound related.

There were no observations made during the interval of month 13 to termination which were considered to be compound related.

006352

Table 5

006352

Organ Weights - Terminal Sacrifice (18 Months)†: Absolute and Organ-to-Body Weight Ratios of Mice Receiving AC 92,100 (Terbufos) for 18 Months

Dose (ppm)	Male 0	Male 3	Male 6	Male 12	Female 0	Female 3	Female 6	Female 12
Terminal Body Weight	38.150	40.570	37.180	37.720	33.760	35.340	33.580	30.990
± S.D.	3.636	5.459	3.242	5.215	2.999	4.509	4.311	2.464
Brain: Weight gm	0.468	0.478	0.484	0.484	0.515	0.488	0.507	0.488
S.D.	0.040	0.045	0.021	0.021	0.062	0.028	0.030	0.032
Organ to B.W.[a]	12.312	11.941	13.092	12.995	15.352	13.984	15.276	15.823
S.D.	0.973	1.658	1.041	1.494	2.292	1.828	1.697	1.394
Adrenals: Weight gm	0.009	0.010	0.011	0.007	0.012	0.016	0.028	0.012
S.D.	0.003	0.007	0.009	0.002	0.004	0.004	0.052	0.004
Organ to B.W.	0.233	0.266	0.287	0.188	0.351	0.454	0.839	0.396
S.D.	0.089	0.173	0.213	0.070	0.130	0.105	1.562	0.116
Gonads: Weight gm	0.296[c]	0.231	0.210	0.181	0.310	0.270	1.007	0.135
S.D.	0.061	0.028	0.061	0.057	0.399	0.355	2.185	0.133
Organ to B.W.	5.728	5.790	5.705	4.855	8.982	6.801	29.985	4.169
S.D.	1.710	1.085	1.724	1.684	11.434	8.482	65.695	3.804
Heart: Weight gm	0.232	0.255	0.244	0.250	0.218	0.195	0.220	0.187
S.D.	0.041	0.049	0.048	0.024	0.014	0.022	0.059	0.037
Organ to B.W.	6.097	6.365	6.524	6.771	6.497	5.632	6.574	6.030
S.D.	0.927	1.522	0.913	1.291	0.557	0.684	1.432	1.151
Kidneys: Weight gm	0.801	0.918	0.819	0.800	0.594	0.566	0.566	0.460
S.D.	0.100	0.147	0.135	0.141	0.117	0.104	0.103	0.158
Organ to B.W.	21.042	22.801	21.995	21.514	17.673	15.980	16.882	14.802
S.D.	2.107	3.539	2.666	4.200	3.447	1.988	2.306	4.866
Liver: Weight gm	2.161	2.869*	2.333	2.122	2.191	2.438	2.259	1.859
S.D.	0.206	1.147	0.371	0.227	0.316	0.384	0.532	0.183
Organ to B.W.	56.856	69.468	62.824	56.804	64.949	68.958	67.178	60.035
S.D.	5.316	19.971	9.328	6.748	7.842	5.769	13.161	4.445
Lungs: Weight gm	0.418	0.503	0.379	0.380	0.367	0.352	0.322	0.333
S.D.	0.076	0.332	0.158	0.109	0.091	0.049	0.069	0.071
Organ to B.W.	11.123	13.167	10.082	10.269	10.861	10.123	9.655	10.815
S.D.	2.604	10.559	3.554	3.208	2.458	2.018	2.118	2.592
Pituitary: Weight gm	0.004	0.003	0.004	0.003	0.004	0.007	0.004	0.004
S.D.	0.001	0.001	0.001	0.001	0.002	0.009	0.001	0.001
Organ to B.W.	0.102	0.081	0.097	0.093	0.103	0.175	0.115	0.131
S.D.	0.037	0.037	0.020	0.027	0.057	0.215	0.027	0.049
Spleen: Weight gm	0.084	0.154	0.098	0.107	0.164	0.164	0.175	0.124
S.D.	0.025	0.164	0.037	0.087	0.068	0.066	0.097	0.063
Organ to B.W.	2.239	3.728	2.648	2.690	4.842	4.650	5.305	3.925
S.D.	0.698	3.610	1.075	1.625	1.896	1.702	3.027	1.807
Thyroids: Weight gm	0.010	0.008	0.009	0.007	0.009	0.007	0.008	0.008
[b] S.D.	0.003	0.004	0.003	0.002	0.004	0.002	0.003	0.003
Organ to B.W.	0.259	0.206	0.236	0.190	0.255	0.202	0.244	0.253
S.D.	0.077	0.107	0.074	0.066	0.121	0.077	0.081	0.100

a = Body Weight b = With Parathyroids c = Unreadable middle digit

Organ-to-Body Weight = gm organ weight ÷ 1,000 gm body weight.

006352

* = Statistical Significance: $p < 0.05$

† = Organs weighed for 10 mice/sex/group.

Data extracted from Tegeris Laboratories report, Table T-4.6.7, 4.6.8, 4.6.10, and 4.6.11 (report pages 137-140 and 143-146).

Table 6

Gross Pathology Findings of Mice Receiving AC 92,100 (Terbufos) for up to 18 Months*

Mice Found Dead or Sacrificed Moribund

	Males				Females			
Dose (ppm)	0	3	6	12	0	3	6	12
FIRST 12 MONTHS								
Number of Mice Examined	2	0	1	8	4	1	4	8
Kidneys-Renal Pelves Dilated	1	-	0	4	0	0	0	0
Urinary Bladder-Distended, Hemorrhagic	0	-	0	3	0	0	0	0
Thymus-Enlarged	0	-	0	0	2	0	1	0
Liver-Pale	0	-	0	0	1	0	0	2
Uterus-Fluid Filled, Blood	-	-	-	-	0	0	0	2
MONTH 13 TO TERMINATION								
Number of Mice Examined	5	6	3	7	12	7	8	11
Skin-Ear Lesion/Crusty/Foci	2	0	1	0	0	0	1	0
Liver-Nodule, Dark/Red	0	0	2	0	0	0	0	0
Kidneys-Pale/Yellow	0	0	0	0	1	0	2	0
Lungs-Nodules, White	0	0	0	0	1	3	0	0
Thoracic Cavity-Fluid, White/Clear	0	1	0	0	0	0	2	0
Spleen-Enlarged	0	0	1	0	3	3	1	0
Lymph Nodes-								
Mesenteric, Enlarged/Pale	0	1	1	1	2	4	1	0
Mesenteric, Red/Dark	0	1	1	1	0	2	0	1
Cervical, Enlarged	0	0	0	0	0	2	1	0
Ovaries-Cyst(s)/Fluid, Clear	-	-	-	-	3	4	3	4
Cyst(s)/Fluid, Red	-	-	-	-	1	0	0	2
Nodule(s), White	-	-	-	-	0	0	0	3
Enlarged	-	-	-	-	0	0	0	2
Uterus-Mass, Horn	-	-	-	-	2	0	1	0
Horn(s) Enlarged	-	-	-	-	2	0	0	2

* = Findings listed only when the incidence was greater than 1 mouse/sex/group

006352

- = Not examined

Data extracted from Tegeris Laboratories report, Tables T-4.7.3 (report pages 157-158) and T-4.7.4 (report pages 159-163).

006352

2. Twelve-Month Scheduled Interim Sacrifice (10 mice/sex/group): The only tissues which had more than one mouse/group exhibit a finding were in females and are shown below:

Dose (ppm)	0	3	6	12
Uterus - Horns Enlarged	4	3	2	0
Ovaries - Cyst(s)	5	5	5	7

None of the above findings are considered to be compound related.

3. Eighteen-Month Terminal Sacrifice: Those tissues in which more than one mouse in a group was observed to have a finding are presented in Table 7.

Enlarged lymph nodes were reported in more dosed males and females than in control groups. Microscopic findings in females indicated lymphoid hyperplasia of the mesenteric lymph nodes in 0, 1, 3 and 3 mice of the control, 3, 6 and 12 ppm groups, respectively (males - 2, 2, 4 and 1 for the same dose groups). The only neoplasm noted was one lymphosarcoma in a mid-dose male. As there is a high degree of subjectivity involved in using the term "enlarged" (no lymph nodes were weighed) and no definitive microscopic findings were described, it is not felt that it can be concluded that the administration of AC 92,100 was responsible for the enlargements described.

J. Microscopic Pathology:

1. Mice Found Dead or Sacrificed Moribund: Table 8 presents the neoplastic (benign and malignant) findings from mice found dead or sacrificed moribund.

Table 9 indicates instances of disagreement within the report pertaining to the number of found dead/sacrificed moribund animals examined (individual necropsy sheets vs gross pathology vs mortality table). It is considered that none of these differences has any impact on the validity of the study.

There are no apparent compound related effects on neoplastic findings. Other microscopic observations did not reveal an indication of compound induced changes.

006352

Table 7

Gross Pathology Findings of Mice Receiving AC 92,100 (Terbufos) for up to 18 Months*

18 Month Terminal Sacrifice

	Males				Females			
Dose (ppm)	0	3	6	12	0	3	6	12
Number of Mice Necropsied	48	49	51	40	39	47	43	36
Skin-Foci, Crusty/Ulcerated	3†	3	2	1	1	0	1	0
Mass, Subcutaneous/Red	0	0	1	0	0	0	0	2
Liver-Mass(es)	6	6	8	4	0	1	0	0
Mass(es), Red/Tan	2	5	1	0	0	0	0	0
Nodule(s), Clear/Grey	1	3	2	0	0	0	0	0
Cyst, Fluid Filled Clear	2	0	1	0	0	1	0	1
Pale	0	0	0	2	0	0	2	0
Kidneys-Dilated Renal Pelvis	4	1	0	2	0	0	1	0
Stomach-Glandular Portion Thickened	0	3	0	1	0	2	0	0
Urinary Bladder/Ureter-Distended/ Fluid Filled	2	0	0	0	0	0	0	0
Lungs-Mass(es)	0	3	0	0	1	1	0	0
Foci, Red/Dark	9	7	7	5	6	6	6	4
Foci, White/Grey	2	2	2	0	0	4	0	1
Nodule(s),Clear/Tan/Grey/White	2	4	3	2	5	3	2	0
Consolidated Lobe/Red	0	0	0	0	0	0	2	0
Pituitary-Enlarged	0	0	0	0	3	1	0	0
Spleen-Enlarged	1	3	1	2	0	1	1	0
Lymph Nodes-								
Mesenteric, Enlarged	0	2	3	4	1	5	4	3
Mesenteric, Red/Dark/Pale	0	2	3	4	1	4	2	2
Sublumbar Enlarged	0	0	0	0	0	2	0	0
Cervical, Enlarged	2	6	8	2	0	1	2	1
Eyes-Opaque	2	1	2	2	3	2	1	2
Cornea, Cloudy/Rough	2	0	3	0	0	2	4	3
Thymus-Enlarged	0	2	1	0	2	1	2	2
Mesentary-Cyst, Fluid Filled Clear	1	2	0	0	0	0	0	0
Pelvic Fat-Foci Hemorrhagic	0	0	0	0	0	2	0	0
Ear/Pinna-Pinna Absent	1	3	1	0	0	0	0	0
Lesion, Ulcerated/Cavity	0	0	2	1	0	0	0	0
Seminal Vesicles-Enlarged	0	3	0	0	-	-	-	-
Ovaries-Cyst(s), Fluid Filled	-	-	-	-	20	22	28	23
Cyst(s), Fluid Filled, Red/Dark	-	-	-	-	2	7	6	4
Uterus-Mass(es), Horns	-	-	-	-	0	3	0	1
Horns Enlarged/Thickened	-	-	-	-	1	4	1	2
Horns, Cyst(s)/Clear Fluid	-	-	-	-	3	9	5	5
Horns, Nodule(s)	-	-	-	-	2	1	2	2
Enlarged/Swollen/Thickened	-	-	-	-	2	1	0	0
Horns, Tortuous	-	-	-	-	8	5	3	2

* = Findings listed only when the incidence was greater than 1 mouse/sex/group
† = Number of mice showing finding.
Data extracted from Tegeris Laboratories report, Table T-4.7.2 (report pages 151 - 156).

Table 8

Neoplastic Findings for Mice Receiving AC 92,100 (Terbufos) for up to 18 Months - Found Dead or Sacrificed Moribund

Dose (ppm)	Males				Females			
	0	3	6	12	0	3	6	12
BENIGN								
Lungs-Adenoma, Bronchoalveolar	0/7[a]	0/6	0/4	2/15	1/15	2/9	1/11	0/19
Stomach-Adenoma	0/3	0/4	0/2	1/6	0/8	0/6	1/7	0/10
Hardarian Gland-Adenoma	0	0	0	0	2	1	0	0
Adrenals-Adenoma, Medullary	0/3	0/5	0/3	1/6	0	0	0	0
Subcutaneous-Hemangioma	0	0	0	1	0	0	0	0
MALIGNANT								
Subcutaneous-Lymphosarcoma	0	0	1	0	0	0	0	0
Liver-Hepatocellular Carcinoma	0/4	0/5	2/3	0/7	0	0	0	0
Hepatocellular Adenocarcinoma	1/4	0/5	0/3	0/7	0	0	0	0
Hemangiosarcoma	0/4	1/5	0/3	0/7	0	0	0	0
Adrenals-Medullary Adenocarcinoma	1/3	0/5	0/3	0/6	0	0	0	0
Thymus-Lymphosarcoma	0/1	1/3	0/2	0/4	2/11	1/5	1/9	0/6
Skin-Osteosarcoma	0	0	0	0	0/11	0/7	0/7	1/11
Mammary Gland-Carcinoma	0	0	0	0	0/8	1/5	0/3	0/7
Invasive Carcinoma	0	0	0	0	0/8	0/5	0/3	1/7
Liver-Sarcoma, Multiple	0	0	0	0	1/11	0/7	0/8	0/11
Spleen-Lymphosarcoma	0	0	0	0	0/10	1/7	0/7	0/11
Stomach-Adenocarcinoma	0	0	0	0	1/8	0/6	0/7	0/10
Mesenteric Lymph Nodes-Lymphosarcoma	0	0	0	0	2/10	0/6	0/4	0/9
Uterus-Sarcoma Leiomyosarcoma	0	0	0	0	1/10	0/7	1/8	0/10
Ovaries-Lymphosarcoma	0	0	0	0	0/11	1/7	0/8	0/10
Lung-Adenocarcinoma, Bronchoalveolar	1/5	0/6	0/3	0/7	0	0	0	0

a = No. with finding/No. examined

Data exctracted from Tegeris Laboratories report, Table T-4.8.3.3 (pages 226 - 236) and Table T-4.8.4.3 (pages 248 - 258).

Table 9

Mice Dosed with AC 92,100 for 18 Months -
Gross Necropsy Findings for Found Dead/Sacrificed Moribund Animals
Agreement/Disagreement within Report for Number of Mice Examined

Dose (ppm)	Males				Females			
	0	3	6	12	0	3	6	12
1st TWELVE MONTHS								
Individual Necropsy Sheets	2[a]	0	0	7	4	1	3	6
Gross Pathology (Page 157)	2	0	1	8	4	1	4	8
Mortality Table (Page 93)	2	0	0	7	4	1	3	6
MONTH 13 to TERMINATION								
Individual Necropsy Sheets	5	6	4	8	11	7	9	13
Gross Pathology (Page 159)	5	6	3	7	12	7	8	11
TOTAL								
Individual Necropsy Sheets	7	6	4	15	15	8	12	19
Gross Pathology (Pages 157 & 159	7	6	4	15	16	8	12	19
Mortality Table (Page 95)	7	5	3	15	15	8	12	19
DISAGREEMENT:								
1st 12 Months								
Necropsy VS Gross Pathology	-	-	X[b]	X	-	-	X	X
Necropsy VS Mortality Table	-	-	-	-	-	-	-	-
Gross Pathology VS Mortality Table	-	-	X	X	-	-	X	X
Month 13 to Termination								
Necropsy VS Gross Pathology	-	-	X	X	X	-	X	X
Total								
Necropsy VS Gross Pathology	-	-	-	-	X	-	-	-
Necropsy VS Mortality Table	-	X	X	-	-	-	-	-
Gross Pathology VS Mortality Table	-	X	X	-	X	-	-	-

a = Number of mice reported to have been examined.
b = X is disagreement within report.

006352

2. Twelve-Month Scheduled Interim Sacrifice (10 mice/sex/group): Table 10 shows benign neoplastic lesions observed in the animals sacrificed at 12 months.

There were no apparent compound related effects on benign neoplastic lesions and no malignant lesions reported. Other microscopic findings did not reveal any compound induced effect.

3. Eighteen-Month Terminal Sacrifice: Table 10 presents the benign neoplastic lesions and Table 11 shows those lesions reported to be malignant.

There were no benign, malignant or other microscopic findings at the terminal sacrifice which appeared to be compound related.

IV. Conclusions:

Under the conditions of this study, there was no apparent indication that AC 92,100 had an oncogenic effect at any of the concentrations examined (HDT = 12 ppm) in CD-1 mice.

The suggestion of a possible slight increase in mortality was observed in both sexes (especially males) at the high dose of 12 ppm. There was a slight, but statistically significant, decrease in body weight gain throughout the 18 months in both sexes at the high dose. Body weight gains were 10.1% below controls for males and 19.7% below controls for females. There was little or no effect on food consumption in males and a slight decrease in females of the high-dose group.

It is therefore concluded that a slight degree of toxicity was observed in male and female high-dose (12 ppm) mice, but not at the lower doses of 6 or 3 ppm.

V. Core Classification: <u>Core Minimum Data</u>.

Oncogenic potential is negative up to and including a dose level of 12 ppm (HDT).

Table 10

Benign Neoplasms Observed in Mice Having Received AC 92,100 (Terbufos) for up to 18 Months

006352

Dose (ppm)	Male 0	Male 3	Male 6	Male 12	Female 0	Female 3	Female 6	Female 12
12 MONTH INTERIM SACRIFICE*								
Liver-Hepatocellular Adenoma	0	1	0	0	-	-	-	-
Lungs-Bronchoalveolar Adenoma	0	0	2	0	0	0	0	1
NO MALIGNANT NEOPLASMS REPORTED								
18 MONTH TERMINAL SACRIFICE								
Number of Mice Sacrificed	48	49	51	40	39	47	43	36
Lungs-Bronchoalveolar Adenoma	3	8	4	5	4	4	1	1
Bronchoalveolar Adenoma/Multi	0	1	1	0	-	-	-	-
Parathyroid-Adenoma	1	0	0	0	-	-	-	-
Seminal Vesicle-Adenoma	0	0	1	0	-	-	-	-
Hardarian Gland-Adenoma	4	4	1	2	2	1	0	1
Papillary Adenoma	0	0	1	0	1	0	0	0
Preputial Gland-Adenoma	0	0	1	0	-	-	-	-
Liver-Hepatocellular Adenoma	0	1	0	0	-	-	-	-
Adrenals-Medullary Adenoma	-	-	-	-	1	0	0	0
Cortex Adenoma	-	-	-	-	0	0	1	0
Thyroid-Follicular Adenoma	-	-	-	-	0	0	2	0
Testes-Interstitial Cell Tumor	1	0	0	0	-	-	-	-
Uterus-Leiomyoma	-	-	-	-	1	1	2	1
Endometrial Polyp	-	-	-	-	1	0	0	0
Ovaries-Cystadenoma	-	-	-	-	0	0	0	1
Theca-Cell Tumor	-	-	-	-	0	0	1	0
Pelvic Fat-Hemangioma	-	-	-	-	0	0	1	0
Skin-Pilomatricoma	-	-	-	-	0/40	0/47	0/43	1/36

006352

* Month scheduled interim sacrifice: 10 mice/sex/group

Data extracted from Tegeris Laboratories report, Tables T-4.8.3.1, T-4.8.3.2, T-4.8.4.1 and T-4.8.4.2 (report pages 215-219, 220-225, 237-241 and 242-247).

006352

Table 11

Malignant Neoplasms Observed in Mice Having Received AC 92,100 (Terbufos) for 18 Months

18 Month Terminal Sacrifice

Dose (ppm)	Male				Female			
	0	3	6	12	0	3	6	12
Lung-Carcinoma, Bronchoalveolar PAP	0/48*	1/49	0/51	0/40	-†	-	-	-
Thymus- Lymphosarcoma	0/36	2/34	2/44	0/31	2/37	2/43	1/40	1/32
Liver-Hepatocellular Carcinoma	0/48	3/48	1/51	0/40	-	-	-	-
Reticulum Cell Carcinoma	0/48	0/48	0/51	1/40	-	-	-	-
Kidneys-Sarcoma	0/48	1/49	0/51	0/40	-	-	-	-
Lymphosarcoma	-	-	-	-	0/40	0/47	1/43	0/36
Stomach-Carcinoma, Invasive	0/48	1/49	0/51	0/40	-	-	-	-
Adenocarcinoma	-	-	-	-	0/40	1/47	0/43	0/36
Mesenteric Lymph Nodes- Lymphosarcoma	0/45	0/47	1/50	0/40	-	-	-	-
Thyroid-Lymphosarcoma	0/46	1/48	0/51	0/40	-	-	-	-
Bone-Fibrosarcoma, Invasive	1/48	0/48	0/51	0/40	-	-	-	-
Prepuce-Sarcoma	1[a]	0	0	0				
Adrenals-Cortical Carcinoma	-	-	-	-	0/40	0/46	1/43	0/36
Mesentary-Lymphosarcoma	-	-	-	-	0	0	0	1[a]
Granulocytic Leukemia - Spleen	0	0	0	1[a]				

* = Number of mice with observations/number of mice examined.
† = No mention of observation in report.
a = Number of mice with observation; no mention of number of mice examined.

Data extracted from Tegeris Laboratories report, Table T-4.8.3.2 (report pages 220-225) and Table T-4.8.4.2 (report pages 242-247).

006352

Terbufos toxicology review dated 10/7/87

Page _____ is not included in this copy.

Pages 99 through 106 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.