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

MAR 25 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Memorandum from Frank Davido (Exposure Assessment Branch/ HED) to William H. Miller (PM #16, Registration Division) Dated March 9, 1988 Concerning Reentry Data and TERBUFOS (Counter™ 15G). Caswell No. 131A.

FROM: Alan C. Levy, Ph.D.
Toxicologist, Review Section V
Toxicology Branch/HED (TS-769C)
Alan C. Levy 3/23/88

TO: James D. Adams, Ph.D.
Chemist
Field Studies and Special Projects Section #5
Exposure Assessment Branch, HED (TS-769)

and

William H. 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 3/24/88

and

Theodore M. Farber, Ph.D., D.A.B.T.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)
3/25/88

Registrant: American Cyanamid Company

Action Requested: Respond to the memorandum from Frank Davido (Exposure Assessment Branch/HED) to William H. Miller (PM #16, Registration Division) dated March 9, 1988 concerning reentry data and TERBUFOS: Recommendation of the Toxicology Branch.

Background Information: The above referred to memorandum (copy attached) addresses Agency concerns regarding the reentry of workers into fields which have been treated with TERBUFOS. Based on an oral four-week cholinesterase level study in dogs with a ChE NOEL of 0.00125 mg/kg, EAB calculated the Allowable Exposure Level and indicated that reentry is not safe even for 0.5 hours of work 7 days after TERBUFOS application. Because exposure to humans would be primarily by the dermal route, the Toxicology Branch feels that a dermal toxicity study in animals would be more appropriate for the establishment of allowable human exposure levels.

2 pages w/Attachment (14 pages)

Recommendation:

The Toxicology Branch recommends that a 21-day dermal study be performed following the protocol presented in FIFRA Guideline § 82-2. The preferred species is the rat because of the large data base available for comparison. Red blood cell and serum cholinesterase levels should be measured after the first dose and at study termination (21 days after the start of the study) in order to establish a cholinesterase NOEL. In addition, brain cholinesterase levels should be measured at the time of terminal sacrifice (21 days). Selection of dose levels is at the discretion of the registrant.

This recommendation should be appended to the Registration Standard Toxicology Chapter for TERBUFOS (memorandum of Alan C. Levy to William H. Miller dated October 9, 1987).

cc: R. Zendzian (TS-769C)
F. Davido (TS-769C)

Shaughnessy No.: 105001

Date Out of EAB: MAR 9 1988

To: William H. Miller
Product Manager 16
Registration Division (TS-767)

From: Frank Davido, Chief
Field Studies and Special Projects Section #5
Exposure Assessment Branch
Hazard Evaluation Division (TS-769C)

THRU: Paul F. Schuda, Chief
Exposure Assessment Branch/HED (TS-769C)

Attached, please find the EAB review of...

Reg./File # : 241-241

Chemical Name: Terbufos

Type Product : Insecticide

Product Name : Counter™ 15-G

Company Name : American Cyanamid

Purpose : Review of reentry data gathered after application to corn. Data includes exposure, dislodgeable residues, blood ChE levels, and urinary metabolite residues.

Date Received: 10/12/1987 Action Code: 400

Date Completed: 3/9/1988 EAB #(s) : 70985

Monitoring study requested: Total Reviewing Time: 21 days

Monitoring study voluntarily:

Deferrals to:

___ Ecological Effects Branch

___ Residue Chemistry Branch

X Toxicology Branch

REVIEW OF REENTRY DATA

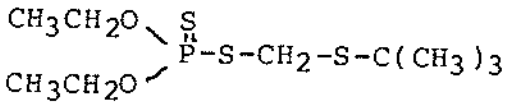
1. CHEMICAL:

Common name: Terbufos

Product name: COUNTER™ 15-G

Chemical name: O,O-Diethyl S-[(1,1-dimethylethyl)thio]methyl phosphorodithioate

Structure:



Other names: S-[(tert-Butylthio)methyl O,O-diethyl phosphorodithioate; CA 13071-79-9; RTECS # TD7200000; AC 92,100; Contraven™; COUNTER™; ST-100.

2. TEST MATERIAL:

COUNTER™ 15-G was applied aerially. Data of interest for this reentry-data review include foliar (corn) dislodgeable residues, dermal and inhalation exposures, blood cholinesterase levels, and urinary metabolite concentrations.

3. STUDY/ACTION TYPE:

Submission of data in response to the Registration Standard.

4. STUDY IDENTIFICATION:

Reg. File No. 241241. Accession No. 252762. Record No. 204093. MRID #137760 American Cyanamid Report # C-2370, dated 2/24/84; "COUNTER* terbufos (CL 92,100/15-G): Farm Worker Exposure Study with Aerial Application of Counter 15-G (AER; NE, 1983)", by R. Peterson.

5. REVIEWED BY:

James D. Adams, PhD
Chemist
Field Studies and Special Projects Section #5

James D. Adams

3/9/1988

6. APPROVED BY:

Frank Davido, Chief
Field Studies and Special Projects Section #5
Exposure Assessment Branch, HED (TS-769)

Frank L. Davido

3/9/1988

7. CONCLUSIONS:

Not all of the data in this submission are acceptable for the assessment of the hazard of fieldworkers to residues of terbufos upon reentry into treated fields. The data that are available and acceptable indicate that exposure of corn scouts should not be permitted without personal protective equipment. That equipment should consist of chemically resistant gloves, long-sleeved shirt, long pants, and shoes with socks. It is possible that a dermal penetration factor would obviate this requirement.

Even more important is exposure of detasselers in the propagation of seed corn. That work is usually done by high school students and involves exposures for 8 or more hours/day.

8. RECOMMENDATIONS:

The Registrant should be required to submit dermal penetration data for Terbufos, and until that data is submitted and reviewed, the label should state that the scouts must wear at least chemically resistant gloves, long-sleeved shirt, long pants, and shoes. Use of Terbufos on seed corn should not be allowed until the dermal penetration data is submitted and reviewed.

The Registrant should also submit a disslodgeable residue dissipation study to be conducted in California if Terbufos is to be registered in the Southwestern States, i.e. where rainfall is less than 25 inches/year.

9. BACKGROUND:

This data was previously reviewed by Harold R. Day, Chemist, of the Exposure Assessment Branch and is being reviewed here to incorporate new toxicology data and to attempt to resolve the fieldworker protection issues for this registration with the existing data.

This submission contains data to satisfy 3 major guideline requirements. These are drift of Counter 15-G during aerially application, exposure of loaders and flaggers to the pesticide, and exposure of fieldworkers (in this case scouts) to residues of the pesticide after application to corn. The only part of the data treated in this review is reentry, i.e. exposure of the corn scouts.

The exposure data, in turn, contains several types of data, not all of which are required under 40 CFR § 158.140 and guidelines Subdivision K. The data include foliar disldgeable residues on corn, acetyl-cholinesterase and pseudo-cholinesterase levels in scouts' blood, residues in fieldworkers' urine and dermal exposure levels calculated from residues on patches, and hand rinses.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

A. MATERIALS AND METHODS

Pesticide Application:

COUNTER® 15-G Soil Insecticide-Nematicide was applied aerially July 9, 1983 to corn in York County, Nebraska at 6.7 lbs/acre which is equivalent to 1.0 lb active ingredient per acre.

Foliar Dislodgeable Residues (FDRs):

Whole leaves from the top, middle, and bottom thirds of 2 corn plants were removed on days 0, 3, and 7 post application. The protocol stated that sampling would continue on days 10 and 14, but there are no sample numbers, analytical data, nor calculations for those dates. Leaves were traced to determine the leaves' areas and then cut into jars to be sealed for storage until analysis.

Fieldworker Dermal Exposure:

Fieldworker-exposure determination is an alternate method that is allowed under Subdivision K for the establishment of reentry intervals. Measurement of scouts' exposures to foliar residues was determined by a modification of the methods of Durham and Wolfe (1962) and Franklin et al. (1981). This was done concurrently with sampling for FDR determination, with FDR sampling not done by scouts during measurement of their exposure.

Dermal exposure was measured by placing 12, 40 cm^2, gauze pads on each individual. Pads were pinned on both the inside and outside of the workers' clothes at the ankle and below the knee of one leg, on the forearm and upper arm of the preferred arm, mid-point on the chest, and between the shoulder blades. Hand exposure was measured by washing each hand with 200 ml of ethanol at the end of the exposure period.

Fieldworker Inhalation Exposure:

Concentrations of the pesticide residues in air were determined by trapping residues on XAD-2 resin contained in 15 cm by 8 mm stainless steel tubes. Air was drawn through the tubes at 1.5 l/min during the exposure period with tubes located in the breathing zone (at the neck). This means that the air was monitored for only 30 minutes (the scouts' exposure period).

Blood Cholinesterase Levels:

Three pre-exposure blood samples were collected from each scout, and blood samples were also collected at the end of each reentry day and each day following a reentry. The blood samples were analyzed for serum cholinesterase and red blood-cell cholinesterase levels.

Residues in Fieldworkers' Urine:

Pre-exposure, 0-24 hr, 24-48 hr [24-hour] urine samples were collected from each of the 3 scouts in this study. The urine was analyzed for the di-ethyl phosphoric acid metabolite of Terbufos and for creatinine. Creatinine analysis was done as a check on the completeness of the daily samples.

B. REPORTED RESULTS

Dislodgeable Residues:

I have gone through several calculations using the analytical data. All of the Registrant's calculations that I checked were correct. Since some of the factors in the submission's equation do not vary, it is possible to simplifiy that equation to:

$$\text{Residues, ng/cm}^2 = \frac{R_{(SAMP)} \times V_3 \times 10^4}{R_{(STD)} \times A}$$

The data is summarized in the following table along with means and standard deviations that I calculated from the data. The Registrant had also performed these calculations.

TABLE 1

FOLIAR DISLODGEABLE RESIDUE LEVELS

Days from Application	Leaf Area, cm^2	V_3, ml	GC Responses Std	GC Responses Sample	FDRs, ng/cm^2 Sample	Avg.	Std Dev.
-1	6114	2	7	80	0.29		
0	6076	50	70	77	74.8		
0	6954	100	130	82	228		
0	5466	50	21	53	36.2		
0	6690	25	59	54	40.8		
						95.0	90.3
3	7336	25	15	58	8.81		
3	5538	10	30	62	8.74		
3	5610	10	115	60	34.2		
3	7386	10	30	48	8.46		
						15.1	12.8
4	6740	5	125	51	18.2		
4	6020	5	80	56	11.9		
4	6028	5	72	51	11.7		
4	4984	20	45	54	33.4		
						18.8	10.2
7	7306	5	122	57	14.6		
7	7646	5	27	53	3.33		
7	7458	5	75	58	8.67		
7	7638	5	105	57	12.1		
						9.7	4.9

Fieldworker Dermal Exposure:

Analytical data from patches on the outside of scouts' clothing is summarized below in Table 2. The data in the table is not exactly as presented by the Registrant. The variance occurs because the Registrant assumes that there is no exposure if there is not a detectable level of residues, and I have used the more commonly accepted assumption that the exposure is equal to one-half of the detection limit. This is especially indicated as the best assumption in the light of the small exposure times involved.

Analytical data from patches on the inside of scouts' clothing is summarized below in Table 3. Here again the data is not exactly as presented by the Registrant since it now contains exposure estimates based on half of the non-detectable level where appropriate.

Analytical data, in ug, from rinsing of scouts' hands are:

	Scout A	Scout B	Scout C	Mean	Standard Deviation
Day 3	7.1	9.6	14.6	10.4	3.82
Day 7	3.8	3.7	3.5	3.67	0.15

The Registrant has converted the reported analytical data to exposure doses per body area by using surface areas calculated from Figure 5 of Popendorf and Leffingwell (1982). This assumes a 50 percentile man is 175 cm (5 ft, 8.8 in.) tall, weighing 78 Kg (172 lb) with 1.92 m^2 of body surface.

Wearing of normal work clothing tends to reduce dermal exposure of clothed body parts, and that occurs with the submitted data. The Registrant used unexposed body area (from patches inside clothing) where appropriate and exposed areas estimated from hand rinses and patches adjacent to the exposed areas. Values calculated assuming half of detectable limit, where appropriate, are summarized in Table 4. The sums of the means of body-part exposures gives estimated, total, dermal exposure rates of 488 ug/hr and 309 ug/hr at 3 and 7 days after application, respectively.

Fieldworker Inhalation Exposure:

There were no detectable levels of airborne Terbufos, and the estimate of scouts' inhalation exposure is, therefore, undefined.

Blood Cholinesterase Levels:

There were no statistically significant decreases in the scouts' blood cholinesterase levels.

TABLE 2.

TERBUFOS RESIDUES ON DERMAL PATCHES OUTSIDE CLOTHING

Worker	Chest	Back	Upper Arm	Lower Arm	Upper Leg	Lower Leg
Day 3						
Scout A	16.3	2.5*	27.3	59.5	112.4	52.1
Scout B	6.5	2.5*	2.5*	35.3	108.0	17.6
Scout C	9.2	2.5*	2.5*	2.5*	61.8	6.5
Mean	10.7	2.5	10.8	32.4	94.1	25.4
S. Dev.	5.06	NA	14.3	28.6	28.0	23.8
Day 7						
Scout A	11.9	2.5*	49.6	30.4	10.3	5.2
Scout B	5.3	18.1	16.2	48.1	14.5	5.5
Scout C	16.8	2.5*	43.3	48.5	14.0	5.4
Mean	11.3	7.7	36.4	42.3	12.9	5.4
S. Dev.	5.8	9.0	17.7	10.3	2.3	0.2

* Half of the detection limit [Residues were non-detectable.]

TABLE 3.

TERBUFOS RESIDUES ON DERMAL PATCHES INSIDE CLOTHING

Worker	Chest	Back	Upper Arm	Lower Arm	Upper Leg	Lower Leg
Day 3						
Scout A	2.5*	2.5*	2.5*	2.5*	44.9	2.5*
Scout B	2.5*	2.5*	2.5*	2.5*	2.5*	2.5*
Scout C	2.5*	2.5*	2.5*	15.6	69.9	2.5*
Mean	2.5	2.5	2.5	6.9	39.1	2.5
S. Dev.	NA	NA	NA	7.6	34.1	NA
Day 7						
Scout A	2.5*	2.5*	2.5*	58.8	8.7	5.0
Scout B	2.5*	2.5*	10.5	5.4	10.9	5.3
Scout C	2.5*	2.5*	2.5*	33.1	11.5	5.0
Mean	2.5	2.5	5.2	32.4	10.4	5.1
S. Dev.	NA	NA	4.6	26.7	1.5	0.2

* Half of the detection limit [Residues were non-detectable.]

Residues in Fieldworkers' Urine:

There were no detectable levels of Terbufos metabolites in the scouts' urine, and the amount of absorbed Terbufos is undefined.

C. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES

Foliar Dislodgeable Residues (FDRs):

"Dislodgeable residues on the corn leaves decreased from 3 to 7 days after treatment. This was similar to the observed decrease in the estimated total dermal exposure values of the scouts."

Fieldworker Dermal Exposure:

The Registrant's Table VII (on p 16 of the submission) contains "Estimated Total Dermal Exposures" ranging from 118.5 to 524.3 ug/hr with an average of 380.6 ug/hr on day 3 and 187.1 to 303.6 ug/hr with an average of 249.9 ug/hr on day 7. An "Estimated % Toxic Dose/hr" is also calculated and reported for days 3 (0.44 %/hr) and 7 (0.29 %/hr) based on the dermal LD_{50}.

Fieldworker Inhalation Exposure:

"Air monitoring showed CL 92,100-related compound levels to be < 0.25 mcg, the sensitivity of the method, for all samples collected." ["mcg" means micrograms]

Blood Cholinesterase Levels:

"Results of the urinary alkyl phosphate analyses were all negative indicating no significant absorption of CL 92,100."

Residues in Fieldworkers' Urine:

"Plasma and red blood cell cholinesterase values of exposed workers showed no significant decrease in activity when compared to pre-exposure samples, indicating no adverse physiological effects from the exposure."

D. REVIEWER'S DISCUSSION AND INTERPRETATION OF STUDY RESULTS

Pesticide Application:

Application of the pesticide in Nebraska and, thus, the environmental conditions of the study place a limitation on utility of the data. The consensus is that environmental conditions and especially rainfall, humidity, and dew have a strong influence on the rate of dissipation of pesticides. This is especially true for organophosphorus pesticides such as Terbufos. This means that the data cannot be used to estimate fieldworker exposure in California and the rest of the arrid southwest. It can be used for all other parts of the United States. The pesticide application is acceptable in all other respects.

Foliar Dislodgeable Residues (FDRs):

The leaves were extracted with a solvent. This is not the FDR Procedure of Gunther et al. (1973) or Iwata et al. (1977) that are cited/suggested on page 32 of Guidelines Subdivision K as acceptable for FDR quantification. However, it appears that this procedure would give higher residue levels than the FDR procedure; and this part of the procedure is acceptable.

The FDR data in Table 1 are highly variable but not more so than is common in other submissions and publications of FDR data for other pesticide and crop combinations. The mean (Avg.) values are plotted in the attached figure.

In general, FDRs decline most rapidly on the day of application to arrive at much lower rates of residue loss on later days. That also occurs with this data.

Fieldworker Dermal Exposure:

The submitted dermal exposure data are unacceptable, primarily, because of the methodology used for assessing hand exposure. The method for predicting exposure suggested in Subdivision K is to use FDR data with a correlation of FDR levels versus dermal exposure. That procedure will be used here. Nevertheless, it is instructive to consider the dermal exposure data submitted.

The reported "Estimated % Toxic Dose/hr" are also unacceptable. Acceptable reentry levels must be based on No Observed Effect Levels (NOELs) and not on percent of toxic doses such as LD_{50}.

Use of hand-rinse data is not allowed under Subdivision K. It has been reported that hand-rinse gives much lower values than dosimetry with gloves; and residues penetrated into the skin may not be retrievable by rinsing. Hand exposure is frequently the major point of dermal exposure so this is not a trivial point. Averages of the hand-rinse residues in this submission were 20.8 ug/h on day 3 and 7.34 ug/h on day 7.

The Registrant's reported residue levels on individual patches assumes that a non-detectable amount is equal to zero. It is more common to assume that the actual level is one-half of the detection limit. I have applied that rule for the data shown in Tables 2, 3, and 4. Lack of detectable residue levels does not mean that there is no exposure. It means that that exposure is undefined although it is less than the level of dectectability.

Table 4 is a summary of the dermal exposure doses that I have calculated from means of residue levels listed in Tables 2 and 3 and from areas of body parts listed in Table 1-7 of Subdivision U of the Guidelines for Pesticide Assessment. The individual dermal exposure doses listed in Table 4 are similar to the

Table 4

Average Dermal Exposures to Terbufos Residues During Scouting Treated Corn

in micrograms/hour (ug/h)

Exposure		Unexposed Areas (Inside Patches)					Exposed Areas			Total Dermal Exposure
Day no.	time, hrs	Chest (3550)	Back (3550)	Thigh (3820)	Lower leg (2380)	Upper Arm (2910)	Lower Arm (1210)	Hands (820)	Head (1300)	
3	0.5	17.8	17.8	298.7	11.9	14.6	78.4	20.8	27.8	488
7	0.5	17.8	17.8	79.5	24.3	30.3	102.4	7.34	29.4	309

individual values in Table VII of the submission with the exception being those where residues were non-detectable. The doses reported in Table 4 are based on the data for protected areas where appropriate, on hand-rinse data, and on data extrapolated from adjacent chest patches in the case of head-face-neck exposure.

The Registrant should have followed the methodology suggested in Subdivision K. With that methodology, it is possible to predict fieldworker exposure rates with only FDR values. The FDRs in combination with surrogate data predict that exposure would be 118 ug/hr on day 3 after pesticide application and 73 ug/hr on day 7. These values do not differ significantly from the exposure levels reported by the Registrant. That is, combinations of the submitted exposure and FDR data lie within the range of our surrogate data.

Fieldworker Inhalation Exposure:

The submitted inhalation exposure data are unacceptable. At 1.5 L/min, 30 min is not sufficient time for most pesticides to be detected/quantified in air. The volume of air trapped only amounts to 45 liters so it is not surprising that no airborne residues were detected/quantified.

Since there were no detectable levels of airborne Terbufos, the scouts' inhalation exposure is undefined. However, it can be calculated to be less than 20 ug/hr as follows:

1) The sensitivity of the method is 0.25 ug per sample at 45 l/sample which is then equal to 5.5556×10^{-3} ug/l;
2) During hard work, the inhalation rate is 60 l/min or 3600 l/hr; and
3) $(5.5556 \times 10^{-3}$ ug/l)(3600 l/hr) = 20 ug/hr.

The Registrant's comment that the levels were "< 0.25 mcg" applies only to the samples as taken and not to fieldworker exposure rates.

Blood Cholinesterase Levels:

Even though both of these enzymes hydrolyze acetylcholinesterase, they characteristically do not respond equally to a given cholinesterase inhibitor. So it is appropriate that both enzymes should be analyzed.

The levels are quite variable. This characteristically occurs with blood cholinesterase levels even when no inhibition is involved. The fact that the levels do not exhibit significant levels of enzyme inhibition is probobly a matter of the exposure time involved and is meaningless for longer exposure times. Also, the high day-to-day variability of blood cholinesterase levels make substantial inhibition necessary for the results to

be statistically significant. The data are not unacceptable, but they are limited in value because the exposure time was so short. This data is not useful for the establishment of dermal penetration or estimation of a reentry interval.

Residues in Fieldworkers' Urine:

The sampling, handling of samples, and analytical procedures are accetable, but it is not surprising that the metabolites of Terbufos were not detected in urine. Here again it is a problem of the length of exposure. A 30-minute exposure may well not have caused a detectable amount of Terbufos to be absorbed to then be excreted in the urine. That is, the lack of detectable Terbufos metabolites in the urine in this data does not mean that Terbufos does not penetrate human skin. The data does indicate that a scout who only enters a treated corn field for 30 minutes/day would have non-detectable and, therefore, low levels of absorbed Terbufos. This data is not useful for the establishment of dermal penetration or estimation of a reentry interval.

The Reentry Level (RL):

For determination of a reentry interval, a reentry level must first be estimated from the Allowable Exposure Level (AEL) and the surrogate data base. The AEL in turn must be calculated from toxicity data. The pertinent toxicity is a No Observed Effect Level (NOEL) of 0.00125 mg/Kg for cholinesterase inhibition from a dog feeding study. The calculation is as follows:

$$AEL = \frac{(NOEL)(Body\ Weight)}{(SF)(DP)(8\ hr/day)}$$

where;

SF = the Safety Factor (10)
DP = Dermal Penetration Factor [100% is assumed for lack of data]

$$= \frac{(1.25 \times 10^{-3}\ mg/Kg/day)(78\ Kg)}{(10)(1)(8\ hr/day)} = 0.00122\ mg/hr$$

$$= 1.22\ ug/hr$$

When this AEL is compared to the measured or predicted exposure rates (cf Table 4), it indicates that reentry is not safe even for 0.5 hours of work 7 days after pesticide application. Also, during the height of the growing season, a scout might have to reenter a number of treated fields per day.

There are 2 other reentry situations that are expected to be more hazardous than this. These are reentry where Terbufos has been applied to foliage in an arrid environment such as California and the Southwestern States. That should be addressed with an additional Foliar Disslodgeable Residue dissipation study to be conducted in the San Joaquin, Imperial, or Coachella valleys of California. The second situation is detasseling of corn for production of hybrid seed. I suspect that, given the very low NOEL, reentry would not be allowable even in the Midwest.

11. COMPLETION OF ONE-LINER:

Not applicable.

12. CBI APPENDIX:

Not Applicable.

REFERENCES

Durham, W. F. and H. R. Wolfe. (1962) Bull. World Health Org. 26:75-91.

Franklin, C. A.; R. A. Fenske; R. Greenhalgh; L. Mathieu; H. V. Denley; J. T. Leffingwell; and R. C. Spear. (1981) J. Tox. Environ. Health. 7:715-731.

Popendorf, W. J. and J. T. and Leffingwell. (1982) Residue Reviews 82:125-201.

Dissipation of Terbufos Foliar Residues