BD-515
TXR-2391

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

.002391

12/22/82

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Franklin Gee, Product Manager #17
Registration Division (TS-767)

SUBJECT: PP 2F2623 and FAP 2H5334. Request for a Tolerance for Cypermethrin on Cottonseed, and in Meat and Milk. EPA Registrations 10182-~~EUP~~-AL and 10182-~~EUP~~-AU for CYMBUSH 2E (preparation GFU-070) and CYMBUSH 3E (preparation GFU-061)

TOX Chem. No. 271DD

Background:

The ICI Americas, Inc. is requesting to establish tolerances as follows:

Proposed Tolerances

It is proposed that a tolerance be established for residues of (±)α-cyano-(3-phenoxyphenyl)methyl (±) cis,trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) in or on the following raw agricultural commodities:

0.5 ppm in or on cottonseed

0.05 ppm in the meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep.

0.05 ppm in milk

Proposed Food Additive Tolerance

It is proposed that 21 CFR be amended by the establishment of a food additive toleranccce for residues of (±)α-cyano-(3-phenoxyphenyl)methyl (±) cis, trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (cypermethrin) in or on the following agricultural commodity:

5 ppm in cottonseed oil.

Registration is also sought for CYMBUSH 2E (preparation GFU-070) and CYMBUSH 3E (preparation GFU-061).

1/33

002391

Recommendations:

1. Toxicology data referenced in support of this action includes a mouse oncogenesis study submitted by the ICI Americas, Inc. (EPA Acc. No. 071072) which shows that there were 13/60 females (21.7%) with alveologenic tumors in the high dose group versus only 8/121 females (6.6%) in the control groups. The low and mid dose female groups had 6/61 (9.8%) and 7/60 (11.7%) incidences of this tumor type. Toxicology Branch (TB) has not yet completed its review of this study (or other studies submitted September 1, 1982 and related to PP 2F2623).. However, since TB has established that the structurally related synthetic pyrethroid permethrin, caused increased incidences of alveologenic tumors in female mice, TB is concerned about the potential of cypermethrin to produce similar tumors. No further indoor uses or tolerances with cypermethrin will be approved by Toxicology Branch pending review of these studies and establishment of a policy for regulating permethrin.

2. Comments on the product CYMBUSH 2E. A product designated as CYMBUSH 2E was previously reviewed by Toxicology Branch (see review by J. D. Doherty dated September 8, 1980 for EPA File No. 10182-EUP-19). The product CYMBUSH 2E which accompanies this current action differs in its composition than the product which was previously reviewed. For example, the previous product was described as JFU-6670; the new preparation is described as GFU-070.

Five acute studies for the new preparation were submitted and reviewed (see review). The acute oral LD50 study was found to be Core Supplementary because no necropsy was performed. This is being made an issue because other studies with cypermethrin formulations have indicated that internal injuries may result from the ingestion of large quantities of this pesticide or its formulations (see J. Doherty review dated October 12, 1982, EPA Reg. No. 10182-EUP-GE). The acute oral LD50 study with CYMBUSH 2E (preparation GFU-070) must be repeated or the necropsy report from the study presented (ICI Labs CTL/P/630, dated July 16, 1981) must be submitted.

5. The other studies reviewed (see list) were found to be Core Minimum or better where the Core system was used. It should be noted that some of the mutagenesis studies did not include appropriate positive controls. Additional mutagenesis studies may be required when EPA policy is formalized.

6. Several studies were presented that demonstrated that cypermethrin is rapidly absorbed, metabolized and excreted by rats, mice and dogs. Only traces of the radioactivity derived from the parent compound were retained in the rat or mouse tissue.

12/12/82

John D. Doherty, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

Attachments:

12/12/82

OPP:HED:TOX: J.DOHERTY:sb 11/26/82 X73711 Rm 814 #m20

CYMBUSH 2E (preparation GFU-070) has the signal word WARNING consistent with acute oral LD50, eye irritation and dermal irritation data (Note: The acute oral LD50 study provided sufficient data to classify this product into Category II). The precautionary statement should be changed to read "May be fatal if swallowed".

The inerts in the formulation CYMBUSH 2E (preparation GFU-070) are cleared under 180.1001 b,c,d or e [redacted]

This inert ingredient(s) must be further identified for clearance.

3. Comments on the product CYMBUSH 3E. A product designated as CYMBUSH 3E was previously reviewed by TB (see J. Doherty review dated October 28, 1981 for EPA File No. 10182-EUP-19). The product CYMBUSH 3E which accompanies this current action differs in the composition than the product which was previously reviewed. For example, the previously reviewed product was described as GFU-034A; the new product is described as GFU-061.

Five acute studies for this new preparation were submitted and reviewed (see review). The acute oral LD50 study was found to be Core Supplementary (see discussion of CYMBUSH 2E above). The study must be repeated or a valid necropsy report submitted.

The product has the signal word DANGER consistent with the eye irritation toxicity data (corneal opacity not reversed in 7 days).

The inerts in this product CYMBUSH 3E preparation GFU-061) are cleared under 180.1001 b,c,d or e.

4. Of the several studies reviewed (see list below), the chronic feeding/oncogenesis study with rats was determined to be Core Supplementary and no conclusions were drawn related to the toxicity and/or oncogenic potential of cypermethrin. An additional 2-year chronic feeding/oncogenesis study with rats with cypermethrin has been submitted and review is pending as of December, 1982.

002391

STUDIES REVIEWED

Study	Results	Core Classification
Studies with technical material:		
Acute Oral LD_{50} - Mice	112 (90-137) mg/kg males 144 (112-233) mg/kg females (Tox Cat II)	SUPPLEMENTARY
Acute Oral LD_{50} - Guinea Pig	>4000 mg/kg - males	SUPPLEMENTARY
Acute Oral LD_{50} - Rabbit	959 (507-2218) mg/kg - female	SUPPLEMENTARY
Acute Intraperitoneal - Rat	~ 4000 mg/kg	SUPPLEMENTARY
Sensitization - Guinea Pig Magnusson and Kligman Test	Moderate Sensitizer	MINIMUM
Acute Oral LD_{50} - Rats with 3-phenoxybenzoic acid	LD_{50} >3000 mg/kg	SUPPLEMENTARY
2 Year Oncogenesis/Chronic feeding - rats	No conclusions drawn	SUPPLEMENTARY
3-generation reproduction - rats	NOEL = 500 ppm (HDT). Some weight loss (~3-4%) at 100 and 500 ppm in 21-day pups. Is not considered a definite toxic response	MINIMUM
Neurotoxicity - chickens	Not neurotoxic to chickens at 10 gm/kg (HDT)	GUIDELINES
21 day Subacute dermal-rabbits	NOEL = 20 mg/kg LEL = 200 mg/kg (HDT) liver necrosis, weight loss, testis weight changes without associated pathology	MINIMUM
Mutagenesis-Ames test	Not mutagenic in TA-98, TA-100, TA-1537, TA-1338, TA-1535 with and without metabolic activation	N/A (Study is of limited usefulness)
Mutagenesis - host mediated assay	Not mutagenic at 50 mg/kg	N/A

Study	Results	Core Classification
Mutagenesis, dominant lethal	Not mutagenic at 25 mg/kg (single dose) or 10.0 mg/kg (5 consecutive doses)	N/A
Mutagenesis, bone marrow cytogenics	Not mutagenic at 40 mg/kg	N/A
Metabolism - rats, mice and dogs	See review. [Cypermethrin is rapidly metabolized and the products are excreted in the urine. Only trace amounts of radioactivity are retained.)	MINIMUM
Studies with CYMBUSH 2E:		
Acute Oral LD_{50}-rats	0.35 (0.21-0.46) ml/kg-males 0.61 (0.43-0.77) ml/kg-females (Tox Cat II)	SUPPLEMENTARY
Acute dermal LD_{50}-rabbits	>2.0 ml/kg both sexes (Tox Cat III)	MINIMUM
Acute inhalation LC_{50}-rats	No conclusion	SUPPLEMENTARY
Primary dermal irritation-rabbits	PII = 4.00 (Tox Cat II)	MINIMUM
Primary eye irritation-rabbits	Corneal Opacity Reversed in 7 days (Tox Cat III)	GUIDELINES
Skin sensitization - guinea pigs (Magnusson and Kligman test)	Mild to moderate sensitizer	MINIMUM
Studies with CYMBUSH 3E:		
Acute Oral LD_{50}-rats	0.36 (0.20 - 0.73) ml/kg for males; 0.25 (0.14 - 0.55) ml/kg for females (Tox Cat II)	SUPPLEMENTARY
Acute Dermal LD_{50}-rabbits	>2.0 ml/kg both sexes (Tox Cat III)	MINIMUM
Primary Dermal Irritation-rabbits	PII = 5.08 Tox Cat II	GUIDELINES
Primary Eye Irritation-rabbits	Corneal Opacity persisting longer than 7 days (Tox Cat I)	GUIDELINES
Skin Sensitization-guinea pig (Magnusson and Kligman test)	(Laboratory conclusion is that product is a weak sensitizer)	INVALID

Cypermethrin (PP 383) = Acute oral toxicity, acute intraperitoneal toxicity and skin sensitization.

Central Toxicology Lab (ICI), CTL/P/570, Jan. 27, 1981, EPA Acc. No. 070565, TAB 45C.

In these experiments, rabbits, mice and guinea pigs were dosed with cypermethrin (91.5% pure, 53:47, cis/trans) in corn oil by the oral route. Rats were dosed intraperitoneally. The LD_{50}'s obtained (including the 95% confidence interval) are:

Mouse - males	112(90-137) mg/kg
Mouse - females	144(112-233) mg/kg
Guinea pig - male	>4000 mg/kg
Rabbit - female	959 (507-2218) mg/kg
Rat - male (intra-peritoneal	~4000 mg/kg

In mice, the most common signs of toxicity were subdued behavior, piloerection, urinary incontinence, excessive salivation and ataxia. The effects persisted in some survivors for up to 9 days. Note: 5 males and 5 females were dosed at each dose level. In guinea pigs none died, but the signs and symptoms were reported as persisting throughout the 14 day observation period. The symptoms included subdued behavior, urinary incontinence and staining of the ventral surface. In rabbits, some of these same signs and symptoms plus fecal incontinence were reported as persisting for 5 days.

Following intraperitioneal dosing to rats, the symptoms of subdued behavior, piloeretion, dehydration, urinary and fecal incontinence, ungroomed appearance and abnormal/defective gait were noted to persist throughout the 14 day observation period. No rats dosed with 2000 mg/kg died. 3/5 rats dosed with 4000 mg/kg died.

No detailed tables showing the behavioral responses or gross necropsy results were reported. It is not known if gross necropsy was performed. These studies are CORE SUPPLEMENTARY.

The sensitization aspects of this study were conducted using the method of Magnusson and Kligman. Twenty test guinea pigs and 8 controls were utilized. The induction phase consisted of intradermal injections of 0.1 ml of 5% (w/v) cypermethrin in maize oil. The challenge phase consisted of applying cypermethrin (undiluted) to the test area by using filter paper and keeping in place for 48 hours.

After challenge by cypermethrin, 16/19 guinea pigs (one was sacrificed because of poor health) developed signs of mild to severe redness. Only 2 control guinea pigs showed mild redness. The conclusion of the laboratory was that cypermethrin is a moderate sensitizer. Note: challenge with 50% cypermethrin confirmed that this chemical is a sensitizer. This study is CORE MINIMUM.

002391

R41207 (3-phenoxybenzoic acid): Acute oral toxicity to rats.

Central Toxicology Lab. (ICI); CTL/P/627, April 2, 1981, EPA Acc. No. 070565, TAB 44C

Groups of 5 male and 5 female rats were fasted for 16-20 hours and then dosed by gavage with 500, 1000, 2000, or 3000 mg/kg of 3-phenoxybenzoic acid (a cream colored powder which is a metabolite of cypermethrin and permethrin) as a suspension in 0.5% Tissaton AC. The rats were observed for 14 days.

Two high dose group males died, 1 mid and 1 high dose group female died. Thus, the LD_{50} is $\geq$3000 mg/kg for both sexes.

Signs of toxicity were evident within 24 hours and persisted for up to 7 days. These signs included subdued behavior, piloerection, urinary incontinence, dehydration and stained fur. These signs were reported as being only barely evident in the lower dose group.

SUPPLEMENTARY DATA. No necropsy was performed or not reported if performed.

Cypermethrin Technical: Subacute Dermal Toxicity Study in Rabbits. 002391

Central Toxicology Laboratory, ICI, Study No. LB0019, Feb. 4, 1981, EPA Acc. No. 070564[illegible], TAB # 17C

Four groups of 10 male and 10 female New Zealand White rabbits which were 77-119 days of age at the start of the experiment were prepared by clipping and half from each group were further abraded. Additional clippings and abrasions were made during the experiment. The rabbits were dosed with 0, 2, 20 and 200 mg/kg/day of cypermethrin (91.5% purity, 53/47 cis/trans) dissolved in polyethylene glycol. The dose was administered at 1 ml/kg and kept in contact for six hours by means of occlusive dressings. A total of 15 applications were made during the 21 day exposure period (a series of three 5 consecutive application were made).

Results:

1. Clinical observations - Feçal incontinence and subdued behavior were noted but the data do not indicate clearly if the test animals were more adversely affected than the controls. The rabbits showed signs of local dermal irritation which was most severe in the high dose test group. The low dose group was slightly affected.

2. Body weight - The female high dose test group was shown to be adversely affected (less body weight gain). The abraded females were affected to a greater degree and only this group attained statistical significance.

3. Organ weights (the liver, kidney, adrenal, heart, gonads, thyroid and pituitary were weighed). Of these organs, only the high dose male group testes were apparently affected. For example, the absolute weight was 19% lower and the relative weight was 15% lower.

4. Biochemical analyses - Samples were taken from the central ear artery before the first application and 18 hours after the final application. Plasma urea, glucose and triglycerides, aspartate transaminase, alanine transaminase, and alkaline phosphatase, Ca++, Mg++, phosphorous, total protein, albumin, cholesterol, Na+, and K+ were determined using laboratory test kits.

   No consistent adverse effects on these parameters were noted.

5. Hematology - Samples were taken from the ear artery before the first application and 18 hours after the final application. Hemoglobin, hematocrit, total white cell count, red cell count, mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentrate were measured by a Coulter counter. Platelet count was determined by an "auto counter."

   With the exception of apparent decreases in total white blood cell counts in the high dose groups (in females) and, in particular, decreases in lymphocytes at all dose levels (-30% maximum) in females, there were no other apparent effects of cypermethrin on the blood.

6. Gross Pathology - (No table summarizes the results, they are presented in the individual animal pathology sheets). No increases in gross necropsy observations noted, except for possible increases in miscellaneous changes in the liver in the mid and high dose group rabbits.

7. Histopathology - Lesions of various kinds were reported in the adrenals, brain, heart, skin, uterus, subcutaneous tissue, fallopian tube, kidneys, liver, lungs, thyroid, and thymus.

   Of these tissues, the liver was reported as having increased incidences of necrosis in the high dose groups only and abraded rabbits were more frequently affected than the nonabraded. The heart may also have been affected with higher incidences of myocardial fibrosis. There were an insufficient number of test rabbits at each dose level to conclude formally that these organs were adversely affected by these commonly occurring lesions.

Conclusion - This study is CORE MINIMUM.

A NOEL of 20 mg/kg/day is assigned.

The effects at 200 mg/kg include liver necrosis and some loss in weight gain and possible decreases in testes weight without associated pathology. The dermal irritation effects are not included in the NOEL but their presence is indicated. The differences noted in decreases in white blood cell counts are not considered by this reviewer to be a response to the test chemical, chiefly because there is no dose response and this type of reaction is not characteristic of pyrethroids.

Toxicity studies on the insecticide WL 43467: A three generation reproduction study in rats.

002391

Shell Toxicology Laboratory (Tunstall) TLGR 0188.78, February 1979, EPA Acc. No. 070564, TAB 22c.

The experiment was started (F_0 generation) with 4 groups of 30 male and female Wistar SPF rats (Shell Toxicology Lab, Tunstall) which were dosed for five weeks at either 0, 10, 100, or 500 ppm of cypermethrin (batch no. 30, 98% pure). After five weeks, a single male was placed with a single female to produce the F_1A and later the F_1B generations. Litter F_1A was sacrificed at weaning (21 days). One male and one female from each of the F_1B litters were selected and paired to produce the F_2A and F_2B generations.. Similarly, the F_3A and F_3B generations were produced from the F_2B generation.

Results:

1. Reproductive performance - No adverse effects were noted on the general health or behavior of the rats at any dose. There were no adverse effects on the fertility index (number of pregnancies/number of matings), the gestation index (pregnancies resulting in live litters), viability index or lactation index.

2. Litter parameters - The following data were collected on each litter: date born, number of pups born alive, number of pups born dead, sex of pups at weaning, total litter weight on days 1, 4, 7, 14, and 21, individual pup body weights on day 21.

   Of the several parameters measured, the only parameter which appeared to be affected in a dose related manner was the mean pup weight at 21 days. The following table illustrates the differences noted.

	Males		Females	
Dietary Concentration (ppm)	Number of observations (N)	Mean male pup weight (g)	Number of observations (N)	Mean female pup weight (g)
0	681	48.2	661	46.6
10	681	48.5	672	46.9
100	704	46.7** (-3%)	666	45.6** (-2%)
500	687	46.3** (-4%)	652	44.7** (-4%)
Standard deviation of a single observation		6.99		6.75

** $P \leq 0.01$ - Significance of the difference between treatment and control means using Williams t test.

These data contain the weights of all pups. When the individual generations are considered (F_1A, F_2B, etc.) the statistical significance is not readily apparent.

3. Pathology - There were no consistent histopathological changes reported for either the pups when born or the parental rats.

Conclusion - This study is CORE MINIMUM. Only two pups (a male and female) from each litter were examined histologically. The data are in summary form only and individual data are not presented. A NOEL of 500 ppm (HDT) is assigned for adverse effects on reproduction. A NOEL of 10 ppm is assigned for systemic effects. However, the small depressions in pup weight (~3%) noted at 100 ppm are not considered of sufficient magnitude to require that the level of 100 ppm be used in ADI determinations for cypermethrin. (Note: decrease in pup weight is a characteristic of other pyrethroids in three generation reproduction studies.)

00239

The acute oral toxicity (LD50) and neurotoxic effects of cypermethrin to the domestic hen.

Huntingdon Research Centre, July 3, 1981, Study No. CTL/C/1077 and ICI 345 NT/8178, EPA Acc. No. 070564 (TAB 16c)

Part 1 - LD_{50} Determination

Six groups of 5 hens (Gallus, gallus domesticus, adults of 12 months of age) were dosed with either 0, 4,096, 5,120, 6,400, 8,000 or 10,000 mg/kg of cypermethrin (batch no. P25, 53:47 cis/trans ratio and of 87.8% purity). The hens were observed for 14 days.

Results:

No hens died. Thus, the LD_{50} is greater than 10,000 mg/kg for hens. No signs of ill health were reported. There were some indications of reduced body weight gain for the higher dose groups, but this was an initial and not a lasting response. SUPPLEMENTARY data.

Part 2 - Neurotoxicity Study

Five groups of 10 hens were dosed at 500 mg/kg TOCP (positive control groups), 0, 2,500, 5,000 and 10,000 mg/kg of cypermethrin. The hens were observed for 21 days for signs of ataxia or other behavior changes. After 21 days the birds were sacrificed and their spinal cord and sciatic nerves examined.

Results:

No signs of ataxia developed in the cypermethrin treated birds. Histopathology did not reveal lesions in the birds treated with cypermethrin that were in excess of expected control ranges. TOCP, the positive control, gave the expected positive result for both ataxia and histopatholgoy.

This study is CORE GUIDELINES. Cypermethrin is shown by this experiment not to produce the delayed type neurotoxicity characteristic of organophosphates.

Toxicity studies on the insecticide WL 43467: A two year feeding study in rats. 002391

Shell Toxicology Laboratory, TLGR.0189.78, Feb. 1979, EPA Acc. No. 070564, TAB 23c.

Five groups of male and female Wistar rats SPF obtained from the Shell Breeding Labs were dosed with 0, 1, 10, 100 and 1,000 ppm of cypermethrin (cis/trans ratio 1:1 from batch #30 and 98% purity). There were 96 control males and females and 48 test group males and females for each dose level. The experimental protocol required that interim sacrifices of 12 male and female controls and 6 males and females from each dose group be sacrificed at 6, 12, and 18 months. Thus, there were 48 controls of each sex and 24 test group rats of each sex for each dose level scheduled to receive the test diet for the two year period.

Results:

1. Clinical observations - No behavioral effects of this test chemical were noted or reported. The clinical observations reported were stated as being in all dose groups and not related to the presence of the test chemical.

2. Body weight and food consumption - A NOEL for depression of body weight is set at 100 ppm although only minor depressions (<10%) were noted at 1,000 ppm. The high dose group also showed signs of reduced food intake in the first year of the study.

3. Survival - The following table shows the survival rate for each group and includes only those rats which were scheduled for the 24 month interval.

	Males	Females
Controls	33/48 (69)*[1]	20/48 (42)
1 ppm	12/24 (50)[1]	8/24 (33)
10 ppm	13/24 (54)	9/24 (38)
100 ppm	17/24 (71)	10/24 (42)
1000 ppm	17/24 (71)	12/24 (50)

* Survivors/starters (%)
[1] Toxicology Branch calculation differs slightly from the report (Table 3).

Although survival is usually 50% or greater (except for the 1 and 10 ppm group females), the number of survivors is less than the desirable 25 individuals for each sex at each dose level.

4. Clinical Chemistry - Assayed at 6, 12, 18 and 24 months. Parameters measured were protein, urea, alkaline phosphatase, aspartate amino transferase, alanine amino transferase and Na^+, K^+ and Cl^-.

No consistent dose related deviations were noted. Occasional deviations in urea, Na^+, K^+, and Cl^- were noted but these changes could not be definitely linked to ingestion of cypermethrin.

Not all of the parameters currently recommended for assay were determined for this study.

002391

5. Hematology - Assayed at 6, 12, 18 and 24 months. Parameters measured included Hb, HCT, RBC, WBC, mean cell volume, mean cell hemoglobin prothrombin time and KCCT time. WBC counts included differential leucocytes, absolute value of neutrophils and lymphocytes.

   No consistent dose related deviations were noted for these parameters.

6. No urinalysis data were presented. (The protocol did not require urinalysis.)

7. Organ Weights - Determined at 6, 12, 18 and 24 months for the brain, heart, liver, spleen, kidneys, and testes (no ovaries).

   No consistent dose related deviations were noted. Occasional deviations in the testes, kidneys, heart and liver weights, but the magnitude and inconsistency of these variations is not considered to be of toxicological concern.

8. Gross Necropsy - The summary of the findings reports that there were no compound-related gross necropsy changes noted. <u>This report is unsubstantiated</u> by a listing of the gross observations or a tabulation for each group.

9. Pathology - Microscopic examination was performed on all rats in the 24 month group, but on only those rats in the 0, 100, and 1,000 ppm groups (except those dying spontaneously) for the interim sacrifice groups. The following lists the tissues for analysis.

   <u>Tissues examined microscopically</u>

   Brain* (cerebrum, cerebellum, mid brain, medulla)
   Heart* - ventricles
   Liver*
   Spleen*
   Kidneys*
   Testes*
   Ovaries
   Stomach
   Pancreas
   Mesenteric lymph nodes
   Prostate or uterus
   Thyroid/parathyroid with oesophagus and trachea
   Thymus (if present)
   Eye and lachrimal glands
   Lungs
   Pituitary
   Adrenals

Small intestine (3 levels)
Large intestine (2 levels)
Salivary glands (sub-maxillary)
Urinary bladder
Sciatic nerves
Any other macroscopic lesions in any tissue

Tissues stored for reference

Knee joint and femur
Muscle (femoral)
Mammary gland (posterior site with skin)
Seminal vesicles
Spinal cord (thoracic)
Tongue
Bone marrow smear from femur

Non-neoplastic findings were not tabulated but are presented with each animal.

Neoplastic Findings

1. 6 month group - No neoplasia reported.

2. 12 month group - Four control female rats, 2 - 100 ppm group and 0 - 1,000 ppm group rats developed tumors. Males were reported as being unaffected. No test chemical effect is obvious.

3. 18 month group - Among the males there were 7, 2, and 2 rats affected with tumors for the control, 100 and 1,000 ppm test groups. Among the females there were 19, 10, and 7 rats affected with tumors for the control, 100 and 1,000 ppm test groups. No effect due to treatment was evident. Of the 36 rats with neoplasia among the females, 35 were pituitary neoplasms. The distribution for pituitary adenomas was 19/24, 9/12 and 7/12 for the control, 100 and 1000 ppm groups.

4. 24 month group - The following table lists the tumors (of any kind) reported in each group for those rats which lived after 18 months or longer.

	Males	Females
Controls	25/48*	54/48
1 ppm	9/24	28/24
10 ppm	14/24	37/24
100 ppm	9/24	27/24
1000 ppm	13/24	27/24
Total	70	143

* Tumors/number of rats available.

Among the males, there were 25 (36%) rats with pituitary adenomas, 12 (17%) rats with tumors in the skin. All other neoplasms were scattered among the different organs and were of low frequency (2 or less per group). No indication of an oncogenic effect was noted in males.

Among the females, there were 114 pituitary adenomas (66%). For example, there were 39/48, 19/24, 23/24, 16/24 and 17/24 females affected for the control, 1, 10, 100 and 1000 ppm groups. The mammary glands had a total of 25 neoplasms (14%). All other neoplasms (34 incidences) were isolated occasions (<2 per group). No evidence of a neoplastic effect of cypermethrin was evident.

Lungs - There were 3 incidences of lung adenocarcinoma, one in the male (high dose group) and two in the female test groups (1 control and 1 in the 100 ppm group).

Liver - There was a single incidence of liver adenoma (10 ppm female group).

Thyroid - No adenomas were reported. There were two incidences of parafollicular carcinoma reported, one among the males (10 ppm group) and one among the females (10 ppm group).

Conclusion - This sudy is CORE SUPPLEMENTARY and cannot be used to satisfy either the chronic feeding or oncogenesis in rats data requirements. The following is a list of deficiencies.

1. Insufficient number of rats surviving for 24 months.

2. No tabulation of gross necropsy observations.

3. No parallel table of gross necropsy information with microscopic findings (i.e., individual pathology reports).

4. No tabulation of non-neoplastic findings.

5. Not all parameters for blood chemistry determinations were measured and no urinalysis was conducted.

002391

An examination of cypermethrin for potential mutagenicity using the Salmonella/microsome reverse mutation assay.

Central Toxicology Lab, # CTL/P/595, November 13, 1980, EPA Acc. No. 070564, TAB 19c

Technical grade cypermethrin (91.5% pure with a cis/trans ratio of 53:47, sample # 1B24331/79) was tested in five strains of Salmonella typhimurium (TA-1535, TA-1537, TA-1538, TA-98 and TA-100) at dose levels of 4, 20, 100, 500, and 2,500 ug/plate with and without metabolic activation (S9). Three separate experiments were conducted. The following positive controls were used. For TA-1535: 1,3-propane sulfone (+S9), none (-S9); for TA 1537: 9-aminoacridine (+S9), none (-S9); for TA 1538: acetylaminofluorene (+S9), none (-S9); for TA 98: acetylaminofluorene (+S9), none (-S9); for TA 100; 1,3-propane sulfone (+S9), none (-S9).

Results:

Cypermethrin did not cause consistent increases in the mutation of these strains of Salmonella under the conditions of these assays. In one test an apparent effect was noted (strain TA-98, twice background) but this could not be confirmed in a repeat test.

Conclusion - Cypermethrin is shown not to be a mutagen in this study. It is important to note that no positive controls were included for studies which did not include the S9 activation system.

Toxicity studies with agricultural chemicals: mutagenicity studies with Ripcord in microorganisms in vitro and in the host mediated assay. 002391

Shell Toxicology Laboratory, Report TLGR.80.059, June 1980, EPA Acc. No. 070564, TAB 18c.

This report describes the procedures and results of three experiment-types to determine if cypermethrin (RIPCORD, batch 30, 98% pure) is mutagenic. The experiments consisted of Ames type mutagenesis with strains of Salmonella typhimurium TA-1535, TA-1537, TA-1538, TA-98, and TA-100. Strains of E. coli WP_2 and WP_2 uvrA were also tested. The microbial assays were tested with and without metabolic activation with rat liver S9 microsomal fraction.

A second approach was to test for mutagenesis in the yeast Saccharomyces cerevisiae JDI in vitro with and without metabolic activition. For this study, 4-nitroquinoline-N-oxide and cyclophosphamide were included as positive controls.

The third approach was the host-mediated assay using mice treated with cypermethrin at 25 and 50 mg/kg and then inoculated with the yeast Saccharomyces cerevisiae. After 5 hours, the yeast were harvested and examined for the presence of mutations. Ethylmethane sulfonate was used as a positive control.

Results

Part 1 - Bacterial Tests. Cypermethrin when tested at 0, 0.2, 2.0, 20, 200 or 2,000 ug/plate with and without metabolic activation did not show evidence of causing mutations in either the Salmonella or E. coli strains. It should be noted that for strains TA-1538, TA-98 and TA-100 the positive control benzo (a) pyrene produced only a small response above background for the assay without metabolic activation. Also, for the E. coli studies, the same agent (4-nitro- quinoline-N-oxide) was used as a positive control for the studies with and without metabolic activation.

Part 2 - Saccharomyces gene conversion assay. Cypermethrin when tested at 0, 0.01, 0.1, 0.5, 1.0 and 5.0 mg/ml did not induce evidence of mitotic gene conversion. The positive controls 4-nitroquinoline-N-oxide (direct acting) and cyclophosphamide (indirect mutagen) produced the expected positive responses at both the histidine and tryptophan loci.

Part 3 - Host mediated assay. The rate of mitotic gene conversion in S. cerevisiae JDI which were harvested from the mice treated with cypermethrin were not different from the controls. The positive control ethyl methanesulfonate gave the expected positive result.

Conclusion - Cypermethrin was not shown to be a mutagen in these assays.

Toxicity studies with WL 43467: Dominant lethal assay in male mice after single oral doses of WL 43467. 002391

Shell Toxicology Laboratory, TLGR.0042.77, December 1977, EPA Acc. No. 070564, TAB 21c

Part 1 - Five treatment groups of male CDI (Charles River) mice were dosed with 0 (36 mice), 6.25, 12.5, or 25 mg/kg in a single dose or 2.5 or 5.0 mg/kg/day for five daily doses. The control group was given the vehicle, DMSO. Following dosing, each male was caged with 3 females and allowed to copulate. Each week for 8 weeks, a new set of females was presented to the mice. The following parameters were examined: non-pregnant females, early foetal deaths, live foetuses, and late foetal deaths.

Results:

The mice dosed for 5 consecutive days with cypermethrin at 2.5 or 5.0 mg/kg day showed an indication of a possible dominant lethal effect as indicated in the following table.

Group	Mean Total Fetuses Per Pregnant Female
DMSO	12.2
6.25 mg/kg cypermethrin	12.1
12.50 mg/kg cypermethrin	12.4
25.0 mg/kg cypermethrin	12.8
2.5 mg/kg cypermethrin*	11.0
5.0 mg/kg cypermethrin*	10.9

* dosed for 5 consecutive days.

This result suggested that cypermethrin may have some potential as a dominant lethal agent and a second experiment was initiated.

Part 2 - 4 treatment groups of 12 and a control group of 36 male CDI mice were dosed with 0, 2.5, 5.0, 7.5 or 10.0 mg/kg of cypermethrin for five consecutive days. The controls received the carrier solvent DMSO. Following dosing, each male was caged with 3 females and 4 days later an additional group of 3 females were presented to the males.

In addition to this main group, 5 groups of 8 males were dosed with 0, 2.5, 5.0, 7.5 or 10.0 mg/kg of cypermethrin for five consecutive days. Four mice from each group were sacrificed on days 1 and 7 after the last dose and their testes were removed together with the head and tail of the epididymis.

Results:

6 mice died but there was no clear relationship between the dose level and the deaths.

No consistent effect of cypermethrin was noted on any of the parameters used to indicate a dominant lethal effect.

There was no evidence that the testes or the epididymis was affected by cypermethrin as indicated by histopathology.

Conclusion - The initial observation that cypermethrin may induce a small degree of dominant lethality noted in the first study was not repeated in the second experiment which used higher dose levels.

002391

Toxicity studies with WL 43467: Chromosome studies on bone marrow cells of Chinese hamsters after two daily oral doses of WL 43467.

Shell Research Ltd., TLGR.0136.77, December 1977, EPA Acc. No. 070564, TAB 20c

48 male and 48 female Chinese hamsters (Shell Turnstall Labs) were grouped into units of 6 hamsters each and were dosed orally with cypermethrin (batch number 30) at 0, 20 or 40 mg/kg, or 100 mg/kg of cyclophosphamide in water or DMSO on two successive days. The test chemicals were given 8 or 24 hours prior to sacrifice. 90 minutes before sacrifice, each hamster was injected with colcemid (intraperitoneally).

The following parameters were measured: polyploidy, chromatid gaps, chromatid breaks, exchange figures, acentric fragments, multiple chromatid breakage, % polyploid cells, % cells showing gaps, % showing aberrations, mean % polyploidy per animal, mean % gaps per animal and mean % aberrations per animal.

There was no consistent effect of cypermethrin on any of these parameters. The positive control gave the expected positive result. Thus, under the conditions of this assay when cypermethrin was tested at about 25% of the LD_{50}, there was no evidence that cypermethrin caused chromosome damage or aberrations.

Metabolism and pharmacokinetics of 14C labelled cypermethrin in rats, mice and dogs.

11 studies dealing with the metabolism and pharmacokinetics in rats, mice and dogs were presented for review and are listed below. For the purposes of this review, the results are summarized in terms of identification of metabolites, half life of the chemical in the body following administration, and tissue retention of the radioisotope.

For these studies, 4 isomers of cypermethrin were synthesized with the label in either the benzyl or cyclopropyl moiety. There were 4 isomers because of the cis and trans property of cypermethrin. The radiolabeled chemicals were synthesized in the company research laboratories.

Listed below are the studies reviewed.

Studies in Rats

A. Cypermethrin: The kinetics of cypermethrin in the blood of rats following a single oral dose.

Shell Toxicology Laboratory, TLER.80.073, August 1980, EPA Acc. No. 070564, TAB 24c

B. Cypermethrin: Excretion and retention of cypermethrin and its metabolites in rats following a single oral dose (CA 200 mg/kg).

Shell Toxicology Laboratory, TLER.80.083, October 1980, EPA Acc. No. 070565, TAB 25c

C. Cypermethrin: Bioaccumulation study in the rat (70 days)

Central Toxicology Lab (ICI), CTL/P/599, June 5, 1981, EPA Acc. No. 070565, TAB 27c

D. (^{14}C)-Cypermethrin: A study to determine the bioaccumulation of radioactivity in the rat following repeated oral administration (up to 28 days)

Hazelton Labs (Europe) # 2487-72/201, October 1980, EPA Acc. No. 070565, TAB 26c

Studies in Mice

E. The elimination of radioactivity by mice following oral dosing with ^{14}C-cis and ^{14}C-trans WL-43467 (cypermethrin.)

Shell Toxicology Laboratory, TLGR .0079. 78, October 1978, EPA Acc. No. 070565, 32c

F. The metabolites of cis and trans cypermethrin (WL 43467) in mice.

Shell Toxicology Laboratory, TLGR .0102. 78, June 1978, EPA Acc. No. 070565, 34c

G. The elimination of residues from the fat of mice following the oral administration of (^{14}C-benzyl) W2 43487 (Cis WL-43467).

Shell Toxicology Laboratory, TLGR .0080.78, June 1978, EPA Acc. No. 070565, TAB 33c

H. Taurine conjugation in the metabolism of 3-phenoxybenzoic acid and the pyrethroid insecticide cypermethrin (WL-43467) (in mice).

Shell Toxicology Laboratory, TLGR .0135.77, Dec. 1977, EPA Acc. No. 070565, TAB 35c

Studies in Dogs

I. The metabolism of cypermethrin (WL-43467) in mammals. The fate of single oral doses of cis and trans (^{14}C-benzyl) cypermethrin in the dog.

Shell Toxicology Laboratory, TLGR .0011.79, April 1979, EPA Acc. No. 070565, TAB 36c

J. The metabolism of cypermethrin (WL-43467) in mammals. The fate of a single oral dose of (^{14}C-cyclopropyl) cypermethrin in the dog.

Shell Toxicology Laboratory, TLGR .79.029, April 1979, EPA Acc. No. 070565, TAB 38c

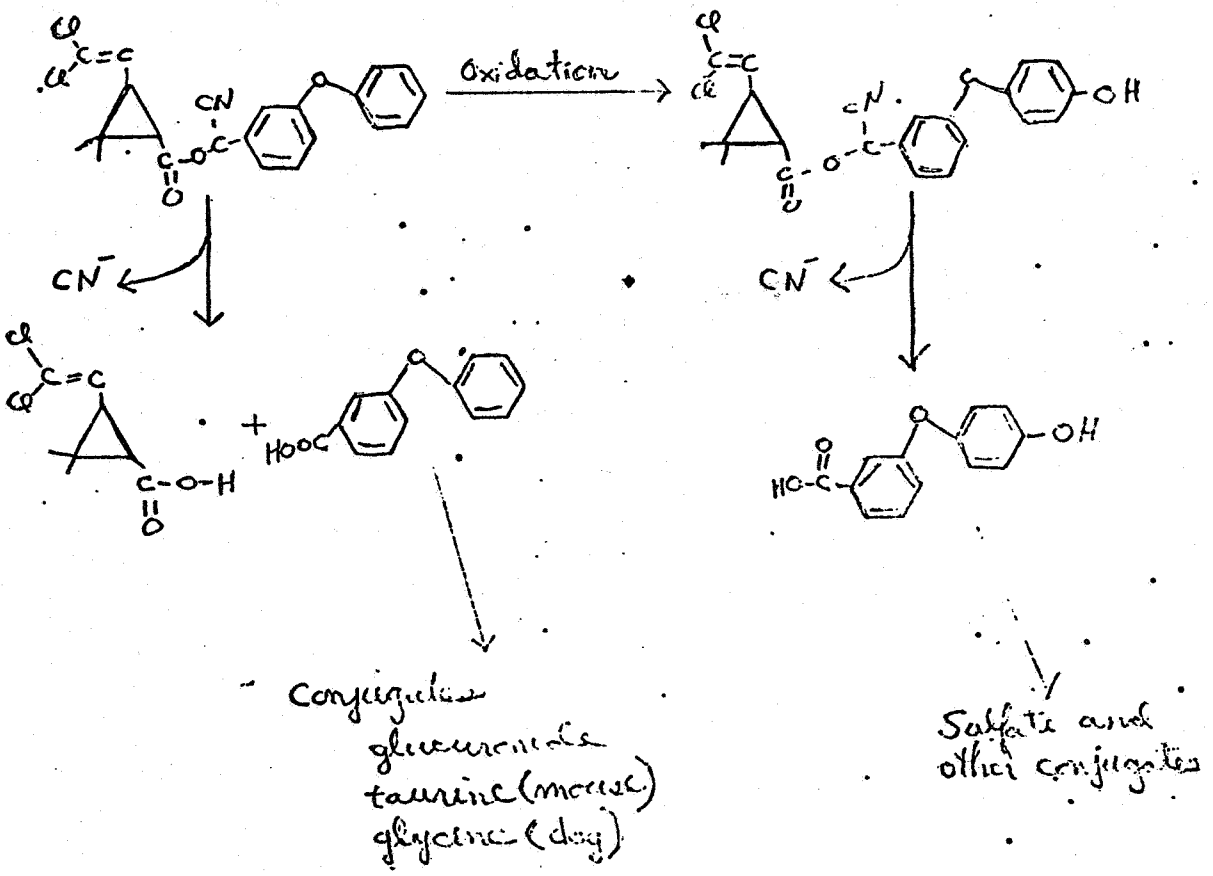
K. The metabolic fate of the cis and trans isomers of WL-43467 (cypermethrin) and of 3-phenoxybenzoic acid in dogs.

Shell Toxicology Laboratory, TLGR..79.012, April 1979, EPA Acc. No. 070565, TAB 37c

Part I: Identification of metabolites

002391

The metabolic fate of cypermethrin following absorption was shown to be nearly the same in all three species with regard to the major metabolic pathway. In all three species cypermethrin is hydrolysed to cyclopropane carboxylic acid and 3 phenoxybenzoic acid. The principle pathway as derived from urinary metabolites is as shown:



Other minor metabolites were also demonstrated.

Note: None of these studies discussed the fate of cyanide once liberated from the parent compound.

In all three species, the radioactivity recovered in the feces was mostly unchanged cypermethrin.

Part II: Tissue Retention

In the rat, following a single oral dose (200 mg/kg of labelled cyclopropyl or benzyl cypermethrin) there were significant levels of label remaining in the tissue 7 days after dosing. In this experiment, the blood, liver, fat, muscle, brain, ovaries/testes, bone, heart, spleen, kidney, intestines, skin and residual carcass were analyzed by combustion.

In the males:

1. Following treatment with ^{14}C benzyl cypermethrin, the fat (21.16 ug/gm), skin (3.02 ug/gm), intestines (2.05 ug/gm), liver (1.08 ug/gm), and kidney (1.02 ug/gm) showed evidence of retaining at least some of the radioactivity (the data were presented as mg equivalents of cypermethrin/gm of tissue). The other tissues had less than 1.00 ug/gm.

2. Following treatment with ^{14}C cyclopropyl cypermethrin, the fat (14.97 ug/gm), intestines (11.30 ug/gm), liver (4.91 ug/gm), carcass (2.50 ug/gm), skin (2.61 ug/gm) and kidney (1.49 ug/gm) showed evidence of retaining the label. Other tissues were less than 1.0 ug/gm.

In the females:

1. The pattern of retention was similar to the male except that the ovaries retained 4.66 ug/gm of the label derived from the ^{14}C benzyl labelled material and 2.99 ug/gm of the label derived from the ^{14}C cyclopropyl labelled material.

The tissue residues in the rats dosed with 200 mg/kg of cypermethrin were subjected to methanol extraction. From 24 to 99% of the label was extracted by this solvent. The tissues which retained most of the label following extraction were the liver, bone, heart and, to a lesser extent, the skin and spleen, blood, brain and kidney depending on the location of the label in the parent compound.

Two experiments were conducted to determine the bioaccumulation of ^{14}C following daily oral (by gavage) doses of ^{14}C cypermethrin 50:50 cis/trans at the level of 2.0 mg/kg/day. The first experiment included 9 male and female rats of each sex to be dosed for 28 days and the rats were sacrificed 24 hours after the last dose. The fat (4.1 ug/gm), skin (636 ug/gm), liver (.566 ug/gm) and ovaries (.710 ug/gm) had the highest levels of radioactivity.

The second experiment included dosing 60 female rats with ^{14}C benzyl-labelled cypermethrin (50:50 cis/trans) with 2 mg/kg for up to 70 days. Groups of 3 treated and 1 untreated rat were sacrificed at days 1, 4, 7, 14, 21, 28, 35, 42, 49, 56, 63 and 70 days following dose administration. Following the last dose (day 70), the remaining 24 treated rats were sacrificed on days (2 treated rats and 1 control) 3, 8, 15, 22, 29, 36, 43 and 50 days post dosing. Samples of liver, kidney, body fat, blood, plasma, skin, and ovaries (carefully trimmed of fat) were disected out and analyzed for residues of ^{14}C. The fat and skin accumulated the most radioactivity (peaks of 3.91 ug/gm and 1.86 ug/gm respectively). These tissues also showed the slowest rate of decline of radioactivity following cessation of dosing. The

laboratory stated that the differences in the 28 day preliminary experiment (above) with respect to ^{14}C residues in the ovaries was due to carefully trimming away fat from the organ. Peak radioactivity in the liver, kidneys, blood, and plasma was always less than 1 ug/gm. The ovaries and the sciatic nerve were always less than .04 or .03 ug/gm with the controls showing a level based on background radiation of .01 ug/gm. These data also showed that cis cypermethrin was the predominant form of the residue in the fat.

In the mouse, the tissue retention of ^{14}C-benzyl labelled WL-43481 (cis cypermethrin) was studied. 10 male mice (CF strain) were dosed with 8.8 mg/kg and were sacrificed on days 8, 14, 21, 30 and 42 post dosing (2 mice on each sacrifice day). Following sacrifice, fat samples were removed and computed and analyzed for radioactivity.

The results showed that the residual ^{14}C in the fat had a half life of 15 days (10-20 days). Analysis of the fat samples by GLC showed that virtually all of the extracted radioactivity was accounted for as unchange cis cypermethrin.

No studies were presented to demonstrate the tissue retention of cypermethrin in the dog.

002391

Part III: Absorption and Excretion of Labelled Cypermethrin

In all three species, (rat, mouse and dog) most of the radioactivity was excreted in the urine following ingestion. The respiratory and bile routes are of minor (if any) significance.

In the rat, studies were presented repeating the results with single oral doses of 2.0 mg/kg and 200 mg/kg for both the ^{14}C benzyl and ^{14}C cyclopropyl labelled isomers (each preparation was approximately 50% cis and 50% trans). For the low dose group, the half lives based on periodically sampling the blood were reported to be:

Isomer	Sex	t 1/2
14-benzyl	Males	2.78 hr.
	Females	4.63 hr.
14-cyclopropyl	Males	4.30 hr.
	Females	4.79 hr.

For the low dose groups, sampling of the blood 3 hours or more after dosing revealed that from <1.0% to as much as 9.0% of the radioactivity remaining was as the parent compound. The rest of the radioisotope was as metabolites. The benzyl labelled material showed a higher percentage of parent compound than the cyclopropyl label.

The amount of radioactivity recovered following a single oral dose of 200 mg/kg of either ^{14}C Cyclopropyl or ^{14}C benzyl cypermethrin is shown in the following table.

Percentage of Radioactivity Recovered in 7 Days (Total)

		u	Urine	Feces	Total Recovered*
^{14}C benzyl	Males	5	28.6 ± 2.5	55.3 ± 4.6	86.7
	Females	5	32.9 ± 4.9	59.0 ± 7.3	93.9
^{14}C cyclopropyl	Males	3	41.3 ± 4.6	45.9 ± 8.2	91.4
	Females	3	55.8 ± 5.2	34.1 ± 4.3	93.4

*Total recovered is the sum of urine, feces, and including the amount in the tissues.

Following a single oral dose of 8.0 mg/kg to mice of ^{14}C benzyl cypermethrin (50% cis/50% trans) the distribution of the radioactivity is shown below (as obtained from male mice).

Isomer	% of dose recovered		
	Urine	Feces	Total
Cis	41.1	51.1	85.2
Trans	66.2	24.7	90.9

As indicated above, the absorption of isotope from the benzyl labelled material is greater than that from the cyclopropyl labelled material.

Absorption and excretion studies with dogs were somewhat limited in their usefulness because only 1 or 2 animals were used in each experiment. Thus, varying amounts of ^{14}C were recovered in the urine or the feces. Consistent with studies in other species, the cis isomer is recovered in somewhat greater quantities in the feces.

Cymbush 2E Formulation

Cypermethrin formulation (GFU070): Acute toxicity and local irritation.

ICI Lab: CTL/P/630, July 16, 1981. EPA Acc. No. 070557.

1. Acute Oral LD_{50} - rats

Groups of five male and five female fasted (16-20 hours) rats were dosed by gavage with cypermethrin 2E formulation at levels of 0.21, 0.31, 0.42, 0.63, 0.73, and 0.83 ml of formulation/kg of body weight and observed for death and behavioral changes. 14 days after dosing, the following LD_{50}'s were determined.

0.35 (0.21-0.46) ml/kg for males
0.61 (0.43-0.77) ml/kg for females

Signs of toxicity included ataxia, excessive salivation, chromodaccryorrhea, urinary incontinence, subdued behavior and piloerection. These symptoms were reported as occuring in the first 4 days but three rats had some effects evident at the end of the 14 day observation period.

This study is CORE SUPPLEMENTARY. No necropsy was performed or reported. Note: necropsy data in acute LD_{50} determinations with other cypermethrin containing products have revealed that there is evidence of long lasting internal injuries which need further definition. The product is Toxicity Category II.

2. Acute Dermal LD_{50} - Rabbits

One group of 5 male and 5 female rabbits were prepared and dosed with 2 ml of cypermethrin 2E formulation/kg and the test material was kept in place for 24 hours by means of occlusive dressing. The rabbits were observed for 14 days. No rabbits died. Signs of toxicity included downward curvature of the spine, subdued behavior and fecal incontinence. Control animals did not show these signs. The skin of the rabbits (treated and untreated areas) were examined histologically and it was noted that the skin showed inflammation and necrosis. This study is CORE MINIMUM. No necropsy was performed. Sufficient data have been generated to classify this product into Toxicity Category III by the dermal route.

3. Primary Dermal Irritation - Rabbits

Application of 0.5 ml of cypermethrin 2E formulation to the backs of rabbits prepared for the assay resulted in a PII of 4.00. This study is CORE MINIMUM. Toxicity Category II (some signs of irritation including desquamation in 6 of the test rabbits were present 9 days after the application.)

4. Primary Eye Irritation - Rabbits

0.1 ml of undiluted test material cypermethrin 2E formulation were instilled into one eye of each of 9 female rabbits. The eyes of 3 of

these rabbits were washed with 175 ml of lukewarm water 20-30 seconds after instillation. Some corneal opacity was noted (described as slight) and this was reported as being reversed by the 3rd day. There was also conjunctiva irritation which was mostly reversed by the 7th day. The eyes of rabbits which were washed following administration of test material did not develop corneal opacity.

This study is CORE GUIDELINES. The product is Toxicity Category III.

5. Skin Sensitization - Guinea Pigs

The skin sensitization properties of cypermethrin 2E formulation were assessed by using the maximization test of Magnusson and Kligman. Intradermal injections of 0.1 ml volume of 0.1% cypermethrin formulation were made for the induction phase. One week later, a topical application of the formulation (0.2-0.3 ml) was made. The challenge application was made two weeks after the topical application. The challenge consisted of dosing with a 50% dilution of the test material. Other challenges were made with 5% and 15% dilutions on different areas of the guinea pigs back.

There was evidence of a sensitization reaction for all dose levels of test material applied. The testing laboratory regarded this product as a mild to moderate sensitization product. This study is CORE MINIMUM.

6. Cypermethrin Formulation GFU070: 4 hour vapor inhalation exposure in rats.

ICI Labs, CTL/P/639, December 14, 1981

Two groups of 10 rats (5 males and 5 females) (Wistar derived) was selected. One group served as a control group, the second served as the test group. The test chemical was introduced into the chamber by placing 10 ml of cypermethrin formulation GFU070 into a 50 ml sintered glass bubbler. The atmospheres were generated by blowing 9 liter/minof air through the test substance. A fresh 10 ml was used for each hour of exposure. The rats were exposed to this atmosphere as generated for 4 hours. The control group was exposed to air alone.

Results:

1. The results of analysing the atmosphere within the chamber revealed that no cypermethrin was introduced into the chamber by this method.

2. No rats died, there were some signs of irritation which were believed to be in response to the organic solvent in the formulation.

3. There were no real differences reported for the exposed and control rats with regard to lung and liver weights or necropsy.

This study is SUPPLEMENTARY. Data for the toxicity of the solvents only was generated (nominal concentration of solvent = 5.37 mg/l). Additional inhalation data may be required if this product is to be used as a spray mist.

Cymbush 3E Formulation

Cypermethrin 3E Formulation (GFU061): Acute Toxicity and Local Irritation.

ICI Labs CTL/P/584, March 19, 1981. EPA Acc. No. 070556.

1. Acute Oral LD_{50} - Rats

Groups of 5 male and 5 female fasted (16-20 hours) rats were dosed with cypermethrin 3E formulation and observed for death and behavior responses for 14 days. The LD_{50}'s of:

.36 (.20 to .73) ml formulation/kg for males
.25 (.14 to .55) ml formulation/kg for females

Signs of toxicity included subdued behavior, ataxia, urinary incontinence, signs of dehydration, excessive salivation, respiratory difficulties, stained fur and piloerection. Some survivors had symptoms at the end of the 14 day observation period.

SUPPLEMENTARY DATA. No necropsy was performed. Other studies with cypermethrin indicated long lasting internal injuries and this must be evaluated for each cypermethrin formulation. Submission of a necropsy report may allow upgrading this study to CORE MINIMUM. Sufficient data to classify this product to Toxicity Category II have been generated.

2. Acute Dermal LD_{50} - Rabbits

A single dose level of 2.0 ml/kg of undiluted cypermethrin 3E formulation was applied to the prepared backs of 5 male and 5 female rabbits. None of the males, but a single female died. The LD_{50} was thus determined to be >2.0 ml/kg (2.02 gm/kg). Signs of toxicity included respiratory difficulties. Necropsy did not reveal definite test chemical related pathology. This study is CORE MINIMUM. Toxicity Category III.

3. Primary Dermal Irritation - Rabbits

a. Undiluted material - following application of 0.5 ml of cypermethrin 3E formulation to the prepared backs of six female rabbits, a PII of 5.08 was determined. The testing laboratory described this product as a severe irritant. Toxicity Category II. This study is CORE GUIDELINES.

b. Maximum spray strength dilution (1.0 ml of formulation diluted to 2.54 ml with distilled water). Following application of 0.5 ml of this preparation to the prepared backs of six female rabbits a PII of 2.92 was determined. SUPPLEMENTARY information.

4. Primary Eye Irritation - Rabbits

a. Undiluted material - 0.1 ml of test material was instilled into the eye (left) of each of 9 female rabbits. 3 of the rabbits were irrigated for 1 minute 20-30 seconds following instillation. Corneal

opacity developed which was not reversed in all of the rabbits by the 7th day. Rinsing the eyes 20-30 seconds after instillation greatly prevented the opacity from forming. Toxicity Category I. GUIDELINES.

b. Maximum Spray Strength Dilution: 0.1 ml of diluted 3E formulation (1 ml to 2.54 ml) resulted in milder corneal opacity which was reversed by the 7th day.

5. Skin sensitization - guinea pigs. This test is considered INVALID because unhealthy guinea pigs were used. In spite of the INVALID rating, the test indicates that cypermethrin 3E formulation is a "weak sensitizer" (laboratory conclusion). Other studies with cypermethrin indicate that this chemical is associated with sensitization. An additional study is not required for this product. The product must contain a warning of possible skin sensitization for some users.