6-7-77
RB

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Petition for the establishment of a tolerance of 0.10 ppm on Chlorpyrifos in/on Sweet-potatoes. Petition No. 6F1786.

DATE: 6/7/77

FROM: Toxicology Branch, Chan, S.L., Ph.D. Sin-Lam Chan

TO: Product Manager No. 12, Mr. Sanders, F.T. E/o OEP 6/8/77 File petition

Petitioner: Dow Chemical, U.S.A.
P. O. Box, 1706
Midland, Michigan 48640

Recommendations:

We defer to Chemistry Branch for the review of Chlorpyrifos residues in/on Sweet-potatoes.

The human exposure to Chlorpyrifos from the petitioned tolerance is very small compared to the exposure arising from the currently established tolerances. The MPI will not be exceeded with the addition of this tolerance. Toxicology Branch will, however, only recommend the granting of a conditional tolerance at the moment. Resubmission of the following deficient studies/clarifications within a period of a year will be required for consideration of the requested permanent tolerance.

(i) A new teratology study.
(ii) A new neurotoxicity study.
(iii) A clarification on the amount and nature of the major urinary metabolites in studies using ^{14}C and ^{36}Cl-Chlorpyrifos.

For a complete discussion of these deficiencies please refer to a recent review on Petition 6H5147 by Chan, S.L.

At a future time, the following studies will be required for the full establishment of tolerances for Chlorpyrifos.

(i) A second carcinogenicity study.
(ii) Mutagenicity studies required when EPA policy on these tests is finilyzed.

Note: Chemistry residue data are cleared by A. Smith, 10/21/76. Tox. branch conclusion is not affected.

Tox. branch.
SLC, 6/8/77

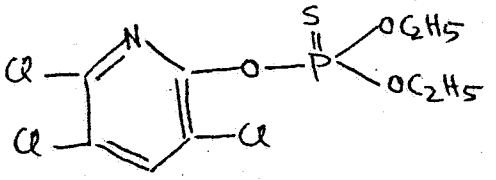
EPA Form 1320-6 (Rev. 6-72)

A. Substance Identification.

1. Chemical name: O,O-Diethyl O-(3,5,6-trichloro-2-pyridyl) phosphorothioate.

2. Synonyms: Chlorpyrifos, Lorsban, Dursban, Dowco 179 and ENT 27311.

3. Structural formula:



4. Other physical properties: See review on 6H5147.

B. Related petitions: 9F0817, 3F1306, 3F1370, 4F1445, 5G1595, 5H5080, 6H5147, 6F1380, 6F1777.

C. 1. Formulations:

(i) Lorsban 10G
(ii) Lorsban 15G
(iii) Lorsban 4E

(i) a Composition of Lorsban 10G, granular.

Chlorpyrifos (active)	10.0%
[redacted]	

(i) b Composition of Lorsban 10G, granular, alternate formulation

Chlorpyrifos (active)	10.0%
[redacted]	

INERT INGREDIENT INFORMATION IS NOT INCLUDED

(ii) a Composition of Lorsban 15G, granular

Chlorpyrifos (active)	15.0%
[redacted]	

(ii) b Composition of Lorsban 15G, granular, alternate formulation

Chlorpyrifos (active)	15.0%
[redacted]	

(ii) c Composition of Lorsban 15G, granular, alternate formulation

Chlorpyrifos (active)	15.0%
[redacted]	

(iii) a Composition of Lorsban 4E

Chlorpyrifos (active)	40.7%
[redacted]	

2. Inert Ingredients: Clearance

[redacted]	Cleared CFR 40 180.1001

INERT INGREDIENT INFORMATION IS NOT INCLUDED

D. Use proposed:

For the once per season, preplant broadcast application followed by incorporation 4-6" into the soil used for sweet-potatoe cultivation. Amount of Chlorpyrifos used = 2 lb./Acre.

E. Toxicological Review

(i) Acute toxicity studies with technical Chlorpyrifos.

See previous reviews and a recent review on 6H5147 by Chan, S.L.

(ii) Acute toxicity studies with formulations, Lorsban 10G, Lorsban 15G and Lorsban 4E.

These studies have been adequately reviewed previously. Lorsban 10G and Lorsban 15G belong to toxicity category III and Lorsban 4E belongs to toxicity category II. They are classified for general use in non-domestic applications.

(iii) Subacute, chronic and special studies with the active ingredient, Chlorpyrifos.

The review of the following studies has been presented recently on 6H5147 by Chan, S.L. Only a brief summary is re-stated below:

(a) 90-Day rat feeding study

RBC AChE NEL = 0.03 mg/kg/day
Systemic NEL = 100 ppm.

(b) 180-Day rat feeding study

RBC AChE NEL = 0.15 mg/kg/day
Systemic NEL > 0.75 mg/kg/day

(c) 2-Year rat feeding study

RBC AChE NEL = 0.1 mg/kg/day
Systemic NEL > 3.0 mg/kg/day
Carcinogenic potential - none

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(d) 2-year dog feeding study

RBC AChE NEL = 0.1 mg/kg/day
Systemic NEL > 3.0 mg/kg/day

(e) 3-generation reproduction study

RBC AChE NEL = 0.1 mg/kg/day
Systemic NEL > 1.0 mg/kg/day
reproduction NEL > 1.0 mg/kg/day

teratogenic test - not acceptable

(f) Neurotoxicity study with laying hens

Study is not acceptable.

(g) Metabolism of ^{36}Cl-Chlorpyrifos and ^{14}C-Chlorpyrifos in rats.

A clarification will be required on the discrepancy over the nature of the major urinary metabolite(s).

(iv) Acute toxicity studies with 3,5,6-trichlorc-2-pyridinol (TCP), the major plant and animal metabolite.

(a) Acute oral LD_{50} of TCP in rats.

No. of rats per group = 10M & 10F
No. of dose levels = 5
LD_{50} for male rats = 794 mg/kg (709-889 mg/kg)
LD_{50} for female rats = 870 mg/kg (758-1009 mg/kg)
Toxic signs = paralysis, dyspnea, mild salivation and death. 14 days observations.

This study is acceptable.

(b) Acute oral LD_{50} of TCP in mice.

No. of mice per group = 15M & 15F
No. of dose levels = 5
LD_{50} for male mice = 384 mg/kg (333-433 mg/kd)

LD_{50} for female mice = 415 mg/kg (367-469 mg/kg)
Toxic signs: tremors, paralysis, dyspnea and death.
14 days observation.

This study is acceptable.

(c) Acute oral LD_{50} of TCP in dogs.

No LD_{50} was obtained because of emesis. Single oral dose of 500 mg/kg and multiple doses of 50, 500 or 1000 mg/kg induced emesis in the dogs. Toxic signs: emesis, salivation, diarrhea, transient mydriasis and depressed gag reflex.

This study is acceptable.

(v) Subacute studies with TCP.

(a) 90-Day rat feeding study with TCP.

Protocol: 10M & 10F per group were fed diet containing 0, 100, 300, 1000, 3000, and 10,000 ppm of TCP. Observations and tests included body weight gain, food consumption, hematology, partial hemachemistry, organ weight and gross and histopathology.

Results: No treatment related effects for rats (M & F) fed 1000 ppm of TCP and lower.

For rats on 3000 ppm TCP - Duiresis.
For rats on 10,000 ppm TCP - growth rate retardation and driresis.

Evaluation: NEL = 1000 ppm.

This study is acceptable.

(b) 90-Day dog feeding study with TCP.

Protocol: 3-4 dogs/sex/group were fed 0, 1, 3, 10 and 30 mg/kg/day of TCP. Observations and tests included toxic signs, body weight gain, hematology, hemachemistry, urinalyses, organ weight, gross and histopathology.

Results: Treatment related toxic effects were only seen in the highest dose level, 30 mg/kg for which the SGOT, SGPT and AP were elevated without any extensive liver damage.

Evaluation: NEL = 10 mg/kg/day.

This study is acceptable.

(c) 3-Week cataractogenicity study of TCP on Pekin Ducklings.

Protocol: 10 ducklings per group were placed on dose levels of 0, 0, 1, 3, 10, 30, 60, 100, 300 and 1000 ppm of TCP for 3 weeks.

Results: The body weight gain was depressed for ducklings fed 1000 ppm TCP. Some ducklings in this group had a prolonged prothrombin time. There was no opacification of lens in any test group.

Evaluation: TCP is non-cataractogenic.
NEL = 300 ppm.

This study is acceptable.

(vi) Subacute and special studies with Chlorpyrifos.

These studies are of supplementary value in support of this petition. They have been adequately reviewed previously in related petitions. A review of these studies is presented in a brief summary below:

(a) 21-Day rat inhalation study:

Rats were exposed to 7 hr. Chlorpyrifos at a concentration of 0.007 µg/ℓ for 21 days without any effect on cholinesterase activity or toxic signs.

(b) 90-Day dog feeding study:

RBC AChE NEL = Not obtained, depression for all levels test, i.e. 20 & 60 ppm.
Systemic NEL < 20 ppm.
Toxic signs: Elevated SGPT and retardation of male growth rate.

(c) Subacute dog feeding to obtain a NEL on Cholinesterase activity.

Feeding time = 9-35 days.
Plasma ChE NEL = 1 ppm.
RBC AChE NEL = 60 ppm (fed only for 9 days).

(d) 90-Day dog feeding study.

2M & 2F per group per dose at levels of 0, 0.01, 0.03, 0.1, 0.3 and 1.0 mg/kg/day.
Plasma ChE NEL = 0.01 mg/kg/day (30 days feeding).
RBC AChE NEL = 0.03 mg/kg/day (90 days feeding).

(e) 21-Day oral administration of Chlorpyrifos to humans.

4 persons per group were given daily doses of 0, 0.014, 0.03 and 0.1 mg/kg of Chlorpyrifos. Observations and tests included plasma and RBC cholinesterase, urinalyses, urinary metabolites, hematology and hemachemistry.

Evaluation: Plasma ChE NEL = 0.014 mg/kg/day.
RBC AChE NEL > 0.10 mg/kg/day.
No other treatment related effects.

(f) Study on Cholinesterase activity in Humans and Rabbits exposed to Chlorpyrifos.

The dermal study is summarized below:

No. Applications	Duration, each Application (hr)	Dosages mg/kg	ChE% Depression Rabbit Pla	Rabbit RBC	Human Pla	Human RBC
1	12	50	60	45	0	0
3	12	25	>90	>80	≤55	0
4	12	10	>90	>90	10	0
20	12	5	>90	>80	≤40	0

4 humans and 4 rabbits were exposed to Chlorpyrifos, 61.5% in xylene, 25' from a ULV fogger for 5 minutes.

Human plasma and RBC ChE = No depression.
Rabbit plasma ChE = 30% depression.
Rabbit RBC AChE = No depression.

For a comparable Chlorpyrifos exposure, the human cholinesterase activity is less affected than that of rabbits.

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(g) Potentiation studies of Dursban with Ruelene and Malathion

	LD_{50} g/kg	
Dursban	0.245	
Ruelene	1.020	
Malathion	1.370	
Dursban + Malathion (50/50)	0.420	Calculated.
Dursban + Malathion "	0.135	Actual.
Dursban + Ruelene "	0.398	Calculated.
Dursban + Ruelene "	0.373	Actual.

i.e. A 3 fold potentiation between Dursban and Malathion.

(h) Potentiation study of Chlorpyrifos with Vapona

	LD_{50} g/kg	
Chlorpyrifos	118	(77-181)
Vapona	59	(38-91)
Chlorpyrifos + Vapona (50/50)	79	- Calculated.
Chlorpyrifos + Vapona "	135	(97-188) Actual.

i.e. No potentiation between Chlorpyrifos and Vapona.

(i) Metabolism studies of Chlorpyrifos in rats.

C^{14}- Chlorpyrifos and residues in various organs extracted with benzene, n-butano and ethanol/ether mixture were low and very variable.

Urinary recovery of ^{14}C-Chlorpyrifos metabolites was low and variable. The major metabolite, trichloro-2-pyridinol recovered amounted to only about 10% of Chlorpyrifos intake. Chlorpyrifos itself was absent in the urine.

F. Evaluation of ADI.

1. Prior Tolerances for Chlorpyrifos.

CFR 40, § 180.342 Chlorpyrifos; tolerances for residues.

Tolerances are established for combined residues of the pesticide chlorpyrifos (0,0-diethyl 0-(3,5,6-trichloro-2-pyridyl) phosphorothioate and its metabolite 3,5,6-trichloro-2-pyridinol in or on the following raw agricultural commodities:

Commodity:	Parts per million
Bananas (whole)	0.25
Bananas, pulp with peel removed	0.05
Beans, lima	0.05
Beans, lima, forage	1
Beans, snap	0.05
Beans, snap, forage	1
Cattle, fat	1.5
Cattle, mbyp	1.5
Cattle, meat	1.5
Corn, field, grain	0.1
Corn, fresh (inc sweet K + CWHR)	0.1
Corn, fodder	0.1
Corn, forage	0.1
Cottonseed	0.5
Eggs	0.01
Goats, fat	0.1
Goats, mbyp	0.1
Goats, meat	0.1
Hogs, fat	0.1
Hogs, mbyp	0.1
Hogs, meat	0.1
Horses, fat	0.1
Horses, mbyp	0.1
Horses, meat	0.1
Milk, fat [0.01 ppm (N) in whole milk]	0.25
Peaches	0.05
Poultry, fat (exc turkeys)	0.01
Poultry, mbyp (exc turkeys)	0.01
Poultry, meat (exc turkeys)	0.01
Sheep, fat	0.1
Sheep, mbyp	0.1
Sheep, meat	0.1
Turkeys, fat	0.2
Turkeys, mbyp	0.2
Turkeys, meat	0.2

2. Pending Tolerances for Chlorpyrifos and Metabolites

(i) 0.05 ppm in or on Almonds, apples, pears, plums and prunes (Petition No. 6F1777)

(ii) 0.75 ppm in or on Sorghum grain, 1.50 ppm in or on Sorghum forage and fodder (Petition No. 6F1830).

(iii) <0.025 ppm in or on food (food additive tolerance for the use of insecticidal strips) (Petition No. 6H5147).

3. ADI Determination

2-year rat feeding study:

RBC AChE NEL = 0.1 mg/kg/day.

2-year dog feeding study:

RBC AChE NEL = 0.1 mg/kg/day.

A safety factor of 10 is used since Chlorpyrifos is an organophosphate acetylcholinesterase inhibitor.

ADI = 0.01 mg/kg/day.
MPI = 0.60 mg/day for a 60 kg man.

4. Exposure from present and pending tolerances.

(a) From present tolerances:

Source	PPM	Intake (gm)	Chlorpyrifos (mg)
Bananas, Beans, snap & lima, peaches	0.05	62.5	0.0031
Beef	1.50	110.0	0.1650
Beef fats	1.50	11.0	0.0165
Beef by-products	1.50	22.9	0.0344
Other meat by-products	0.10	10.0	0.0010
Other meat & poultry	0.10	150.0	0.0150
Other animal fats	0.10	11.0	0.0011
Corn	0.10	31.6	0.0032
Dairy product	0.01	515.1	0.0052
Eggs	0.01	57.0	0.0006
		Total daily exposure =	0.240 mg

(b) From pending tolerances

Source	PPM	Intake (gm)	Chlorpyrifos (mg)
Almonds, apples, pears, plums, prunes	0.05	44.4	0.0023
Sorghum grain	0.75	0.6	0.00045
Food additive tolerance	0.025	1500.0	0.0375
		Total daily exposure =	0.0403 mg

5. Exposure from the petitioned tolerance of 0.10 ppm in or on sweet-potato.

For a daily intake of 4.0 gm of sweet-potato, the exposure level is

= 0.1 x 0.004 mg

= 0.0004 mg of Chlorpyrifos.

6. The MPI for Chlorpyrifos = 0.60 mg/person/day.
The exposure from established tolerance = 0.240 mg/day.
The exposure from pending tolerance = 0.040 mg/day.
The exposure from this petition = 0.0004 mg/day.

It is seen that the exposure from this petition is very small. The MPI for Chlorpyrifos will not be exceeded.