2-15-72

ENVIRONMENTAL PROTECTION AGENCY

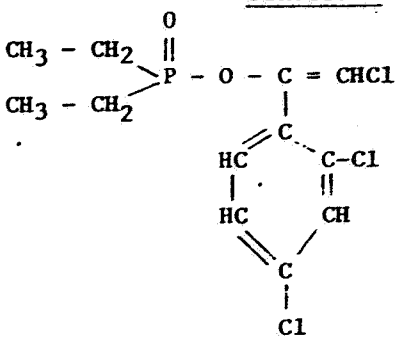
Dr. Parkin

003255

DATE: February 15, 1972

Request for tolerances of 2-chloro-1-(2,4-dichlorophenyl) vinyl diethyl phosphate (Birlane)(Supona)(Chlorfenvinphos), an insecticide, of 0.05 ppm in or on whole washed turnips and rutabagas as exported from Canada to the United States.

STRUCTURE



Mr. Drew M. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 2E1206

Shell Chemical Company
1700 K Street, N.W.
Washington, D.C. 20006

Related Petitions: PCB Ref. No. 66-11, 0F0991, 1E1082

TOXICOLOGICAL REVIEW

I. Summary of previously submitted toxicity data.

All data submitted in the present petition were submitted previously in one or more of the three earlier petitions with the exception of the acute oral and percutaneous study in rats to the currently marketed Birlane formulations.

A. PCB Ref. No. 66-11; Dr. G.E. Whitemore (4/8/66)

1. A 90 day feeding study in rats at dosage levels of 0, 10, 30, 100, and 300 ppm Birlane depressed ChE activity at all levels but produced no systemic toxicity.

2. A 90 day feeding study in rats at dosage levels of 0, 1, and 3 ppm demonstrated no ChE inhibition at the 1 ppm level.

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3. A 2 year dog feeding study at 0, 30, 200, and 1000 ppm produced abnormal ChE activity at all levels but no other effects. A no-effect level was not demonstrated.

4. A three generation rat reproduction study at 0, 30, 100, and 300 ppm gave evidence of a no-effect level at 30 ppm for 2 generations but not in the third generation.

Dr. Whitemore concluded that the data supported a No Residue registration for use on agricultural premises: barns (including dairy barns), feed lots, around feed troughs, manure piles, and poultry houses.

B. 0F0991; Mr. D.L. Ritter (6/23/71)

1. A three generation rat reproduction study at 0, 1, 5, and 15 ppm produced no effects at any level.

2. A 2 year rat feeding study at 1, 10, 30, 100, and 300 ppm produced a no-effect level based on erythrocyte ChE at 10 ppm and based on systemic toxicity at 30 ppm.

3. Acute oral LD_{50}

rats	24 mg/kg
male rats	13.3 mg/kg
mice	117 mg/kg
chicks	37 mg/kg
hens	23 mg/kg

4. Acute intravenous LD_{50} dogs 50.4 mg/kg

5. one of 2 Brahman cattle orally dosed with 20 mg/kg Birlane died while the other experienced a very severe whole blood ChE depression.

6. Transient conjunctivitis (cleared by day 4) was noted in 2/6 adult male albino rabbits inoculated in the right eye with 0.1 ml 4 lb/gal E.C.

7. Spraying of cattle once a week for 12 weeks or twice a week for 6 weeks with a 0.1% emulsion resulted in a depression of whole blood ChE (Michel).

Mr. Ritter concluded that the data supported the proposed tolerances for meat, fat and meat by-products of cattle, and milk of 0.002 ppm and eggs- meat, fat, and meat by-products of poultry of 0.001 ppm.

C. 1E1082; Mr. D.L. Ritter (in preparation)

1. Acute oral LD_{50}

Species	Material	Vehicle	LD_{50} mg/kg
Rat	Technical	Propylene glycol	10.85-13.3
	Technical	Peanut oil	9.66-39
	Technical	Dimethyl sulfoxide	10-15
	Technical	Polyethylene glycol	23.8
Mouse	Technical	Peanut oil	133-155
	Technical	Dimethyl sulfoxide	150-200
	Technical	Polyethylene glycol	117
Rabbit	Technical	None	500-1000
	Technical	Peanut oil	300-324
Guinea-pig	Technical	10% aqueous suspn.	125-250
Dog	Technical	None	>5000
	Technical	Propylene glycol	>12000

2. Acute oral LD_{50} (Birlane isomers)

Birlane Isomer Content	Acute oral LD_{50}
7% cis plus 90% trans	39 and 25 mg/kg
86% cis plus 14% trans	35 mg/kg

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3. Acute dermal LD_{50}

Species	Material	Vehicle	LD_{50} mg/kg
Rat	Technical	Xylene	92 - 108
	Technical	(Not stated)	31
Rabbit	Technical	(None)	417*
	Technical	(None)	1250 - 2500
	Technical	(None)	3200 - 4700

* Birlane was rubbed into the skin for three minutes with a glass rod which may account for the differences in toxicity.

4. Intravenous LD_{50}

Species	Material	Vehicle	LD_{50} mg/kg
Rat (m)	Technical	Emulsion in 'Lipomul'	6.6
Dog (mongrel)	Technical	Emulsion in 'Lipomul'	50.4

5. Intraperitoneal LD_{50}

Species	Material	Vehicle	LD_{50} mg/kg
Rat (f)	Technical	Polyethylene glycol	8.5
Mouse (m)	Technical	Polyethylene glycol	37
Mouse (m)	Technical	Not Stated	89.3

6. Subcutaneous LD_{50}

Guinea pigs Technical Birlane 500 mg/kg

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7. Respiratory studies (14 days)

Species	Material	Concentration	Deaths
10 rats, 10 mice	Technical	2.0 mg/l (290 ppm)	8 rats, 4 mice
	48% w/v Birlane	2.0 mg/l	1 rat, 0 mice
	24% w/v Birlane	2.4 mg/l	-- --

8. Acute oral and dermal LD_{50} of Birlane formulations

(See next page for chart)

9. Dermal irritation and sensitization
Birlane is a primary skin irritant at levels of 0.5% Technical and above in tests conducted on guinea pigs.

10. Demyelination tests conducted in 16 month old white Leghorn hens inoculated i.p. for 10 days with 0, 100, 150, 200, and 300 mg/kg were negative.

11. Mixtures of Birlane with Diazinon, Malathion, Methyl parathion, and Ronnel (fenchlorphos) showed strong potentiation while Gusathion (azinphos) was mildly potentiated. Seventeen other insecticides showed no ability for potentiation with Birlane.

12. Calves (12 wk old) and yearling cattle may safely ingest 10 mg/kg body weight of Birlane while it may safely be applied topically at 0.1% concentrations on calves and 0.15% on yearling cattle.

8. Acute oral and dermal LD_{50} of Birlane formulations

Formulation	Oral LD_{50} Value in Rat		Dermal LD_{50} Value in Rat	
	mg/kg active ingredient	mg/kg total formulation	mg/kg active ingredient	mg/kg total formulation
24% EC	11.5	46.7	27	110
35% liquid seed-dressing	9.2	30.8	32	107
40% powder seed-dressing	7.1	17.8	(2000 M)* (1600 F)	(5000 M) (4000 F)
25% WP	5.2	20.8	(2000 M) 26 (97 F)	(8000 M) 140 (388 F)
10% Granules	--	--	(800)	(8000)
5% FSD	7.2	144.0	32	640
20% EC - [redacted]	12.1	52.8	32	140
20% EC - [redacted]	7.9	34.4	17.3	74
20% EC - [redacted]	15	77.8	38.5	186

* Figures in brackets denote values obtained by applying the formulation in the dry state

** Solvents

INERT INGREDIENT INFORMATION IS NOT INCLUDED

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13. Toxicity in Brahman and European cattle

Formulation	Dosage	Route	Cattle type	No. treatment	No. showing clinical symptoms of intoxication	Average cholinesterase (% of normal)
25% W.P.	10 mg/kg	Oral	Brahman	1	–	45
25% W.P.	10 mg/kg	Oral	European	2	–	63
25% W.P.	20 mg/kg	Oral	Brahman	2	2	13
25% W.P.	20 mg/kg	Oral	European	2	–	28
25% W.P.	0.25%	Topical	Brahman-Cross	2	–	45
25% W.P.	0.25%	Topical	European	3	–	85
24.1% E.C.	0.15%	Topical	Brahman-Cross	1	–	73
24.1% E.C.	0.15%	Topical	European	4	–	85

14. Dipping sheep in 0.2% and 0.08% Birlane resulted in a depression of blood cholinesterase.

15. Repeated dipping of the hands and forearms of 2 volunteers in 0.05% Birlane in water resulted in a 45 - 50% reduction of plasma ChE (Michel); rbc ChE unaffected.

16. Birlane applied to the forearms of 9 volunteers at 5 - 10 mg/kg for up to 4 hours failed to produce unequivocal alterations.

17. When a dust or wettable powder formulation were applied to the forearms of 9 volunteers, amounts in excess of 10 mg/kg were required to elicit rbc and plasma ChE inhibition.

18. Route of elimination of Birlane

Species	Administered	Urine (24 hr)	Urine (96 hr)	Feces (96 hr)	Expired Gases (96 hr)	Milk (24 hr)
Rats	Oral	67.5%	87.2%	11.2%	1.4%	--
Dogs	Oral	86.0%	89.4%	4.73%	--	--
Man	Oral	94.0%	--	--	--	--
Cow	Topical	17.6%	26.7%	1.48%	--	--
Cow	Intramuscular	--	--	--	--	0.2%

19. Acute oral LD_{50} of Birlane metabolites

Metabolite		Species	LD_{50} mg/kg
2,4-dichloroacetophenone	III	Rat	>2,600
2 chloro-1- (2',4' dichlorophenyl) vinyl ethyl hydrogen phosphate	IX	Rat	>1,000
2,4-dichlorophenacyl chloride	II	Rat	1,450
2,4-dichloromandelic acid	VI	Rat	>1,000

20. Fish LC_{50}

Species	2 hours	96 hours
Harlequin Fish	3 - 10 ppm	0.3 ppm
Guppies	3 ppm	0.3 ppm
Mosquito Fish	100% mortality at 24 hr. at levels of 0.015 ppm and above.	

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21. Acute toxicity of birds

Species	Material/Vehicle	Route	LD_{50} mg/kg
Chicken			
wk. old	Technical/Polyethylene glycol	Oral	3€.3
1 wk. old	Technical/Polyethylene glycol	intra-peritoneal	23.1
Rhode Island Red Hens: 2 years	Technical/Polyethylene glycol	Oral	approx. 240
White Leghorns 2 months	Technical/Undiluted	Oral	44 – 62.5
Japanese Quail	Technical/Undiluted	Oral	27.0
Pheasant	Technical/Undiluted	Oral	100.0
Pigeon	Technical/Undiluted	Oral	13.8

22. Subacute and chronic toxicity of birds

Species	Dose	Duration	Results
Hens	0.08%	1 year	No significant effects
Pheasants	0.08%	3 months	No significant effects

Mr. Ritter concluded that the data supported the proposed tolerances of 0.03 ppm in the flesh of cattle and sheep and of 0.15 ppm in the fat of cattle and sheep

II. New toxicity data.

The Acute Oral and Percutaneous Toxicities to Rats of Some Currently Marketed Birlane Formulations (Tunstall Laboratory; TLGR.0016.70)

A. Procedure

Four specific-pathogen free 12-13 week old Carsworth Farm E strain rats/sex/dosage level were observed for toxic signs for 10 days following treatment by the oral or percutaneous route with various Birlane formulations. For the oral studies, the Birlane was administered intraesophageally. In the percutaneous test the Birlane formulation was applied to the shorn dorso-lumbar area, covered

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24 hours, and then washed away with weak detergent solution.

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Methods of application of the formulations tested

Formulation	Oral	Percutaneous
24% emulsifiable concentrate	1% a.m.* aqueous dilution	Undiluted
35% liquid seed dressing	1% a.m. dilution in Dimethylformamide	Undiluted
25% wettable powder	1% a.m. aqueous suspension	1. Dry 2. 3% a.m. aqueous suspension
5% field strength dust	1% a.m. aqueous suspension	1. Dry 2. 3% a.m. aqueous suspension
40% powder seed dressing	1% a.m. aqueous suspension	Dry
10% granules	--	Dry

* a.m. = active material

B. Results

1. The acute oral toxicity values of five Birlane formulations to rats.

Formulation	Oral LD_{50} values (mg/kg active material)	Oral LD_{50} values (mg/kg total formulation)
24% emulsifiable concentrate	11.5	46.7
35% seed dressing	9.2	30.8
5% field strength dust	7.2	144
25% wettable powder	5.2	20.8
40% powder seed dressing	7.1	17.8

Formulation	LD_{50} values (mg/kg active material)	LD_{50} values (mg/kg total formulation)	LD_{50} values (mg/kg active material)	LD_{50} values (mg/kg total formulation)
24% emulsifiable concentrate	27	110	--	--
35% liquid seed dressing	32	107	--	--
25% wettable powder	26	104	Male >2,000 Female 97	Male >8,000 Female 388
5% field strength dust	32	640	Male >800 Female 400	Male >40,000 Female 20,000
40% powder seed dressing	--	--	Male >2,000 Female 1,600	Male >5,000 Female 4,000
10% granules	--	--	>800	>8,000

CONCLUSIONS

ie rat is the most sensitive animal to Birlane (Supona) toxicity. n the 2 year feeding study a no-effect level, based on rbc ChE, = 10 ppm was determined. With a 10-fold safety margin, a dietary ntake of 1 ppm or 0.05 mg/day would be safe in man.

rnips constitute 0.03% of the diet while rutabagas are present ly in trace amounts. At a proposed tolerance of 0.05 ppm Birlane n or in these foods, man would be expected to ingest 0.000025 mg/day. total of 0.004625 mg/day of Birlane would be anticipated when the ximum residues on sheep and beef fat and sheep and beef mea. (see .L. Ritter memo, in preparation, PP# 1E1082) are also considered. is is far below the maximum daily intake which is regarded as being fe for man.

ie proposed usage of this pesticide is specifically for turnips for port and direct human consumption, so it is not reasonably expected r residues of Birlane to occur in the edible tissues and by-products animals.

RECOMMENDATIONS

ised on the toxicology data submitted, the proposed tolerance of 05 ppm of 2-chloro-1-(2,3-dichlorophenyl) vinyl diethyl phosphate irlane)(Supona)(Chlorfenvinphos) in or on whole washed turnips and tabagas as exported from Canada to the United States is safe.

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