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

001781

APR 20 1982

Casuall Nos: 8814 739

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Richard Mountfort, PM #23
Registration Division (TS-767)

THRU: Robert B. Jaeger, Section Head
Review Section #1
Toxicology Branch/HED (TS-769)

SUBJECT: Toxicological opinion on several proposed tolerance levels for 2,4,5-T and silvex.

Background:

The O.G.C. has obtained from the Registrant (Dow Chem. Co.) a request for tolerances of 2,4,5-T and Silvex, or Silvex alone on several racs. The O.G.C. has subsequently requested a toxicological opinion on the chemical (telephone communication with P. A. Roberts dated 4/1/82) without considering the presence of the possible contaminant, TCDD. The following opinion is in keeping with that request.

Conclusions and Recommendations:

1. TOX Branch considers the requested tolerances for silvex per se toxicologically supportable. (See deferral to RCB, below.

a. TOX Branch defers to RCB the question of the adequacy of the proposed tolerances in meat/fat and milk under uses proposed by the petitioner with the 700 ppm proposed residues in grasses.

2. TOX Branch notes an important data gap on 2,4,5-T, a chronic (long term) feeding study in a non rodent species (dog) has not been submitted for review. It is important since the target organs appear to include the liver and kidneys. Only a PADI should be considered, pending the outcome of a dog study.

176

3. TOX Branch would not consider a residue level of greater than 0.05 ppm in milk toxicologically supportable for infants on a whole milk diet without further information i.e., metabolites or parent chemicals exhibiting less toxicity to the liver or kidneys of young animals than older animals.

4. Particular formulations were not presented to determine if inerts have been cleared. Therefore, the Registrations cannot be approved by TB until the inerts are identified, and supporting acute TOX data on the formulation are submitted.

5. TOX Branch notes the possible presence of the 2,3,7,8 isomer of tetrachloro dibenzo-p-dioxin in both silvex and 2,4,5-T.

The low levels of dioxin have been tested in conjunction with the chemicals, silvex and 2,4,5-T. The direct effect of TCDD on the animals studied would not appear to indicate a direct oncogenic effect of the TCDD in those studies.

Data summary considered in request. Toxicity data used in this memo was extracted from the PD 1/2/3 on silvex and the PD 2/3 on 2,4,5-T dated July 9, 1979, and the hearing record.

2,4,5-T:

Teratology

Route	Species	Findings
Oral	Mouse	LEL = 35 mg/kg cleft palate NOEL = 20 mg/kg
Oral	Rat	LEL = 50 mg/kg fetal lethality NOEL = 25 mg/kg
Oral	Rat	NOEL = 50 mg/kg (purified) (only dose) LEL = 50 mg/kg + 0.06 ug/kg TCDD NOEL = 50 mg/kg + 0.03 ug/kg TCDD effect - fetotoxicity as rib abnormalities
Oral	Rabbit	LEL = 40 mg/kg feto toxicity-delayed OSS. NOEL = Not determined, 40 mg/kg lowest dose tested
Oral	Monkey	NOEL = 10 mg/kg (HDT)

2

Reproduction:

Route	Species	Findings
Oral	Rat	LEL = 10 mg/kg No reproductive effect but neonatal survival reduced NOEL = 3 mg/kg

Chronic Feeding:

Oral	2 year rat	LEL = 10 mg/kg liver metabolism copoporphrin NOEL = 3 mg/kg/day Not oncogenic at HDT (30 mg/kg)

Special Study:

in vitro	Young rat	Young rats have a much lower ability to excrete 2,4,5-T than adults.

Silvex:

Teratology

Route	Species	Findings
Oral	Rat Teratogenic	LEL = 75 mg/kg terata formation NOEL = 50 mg/kg
	fetotoxicity	LEL = 50 mg/kg feto cidal, decreased fetal wts.
	fetotoxicity	NOEL = 25 mg/kg (equivocal)
Oral (PGBE)	Rat	LEL = 100 mg/kg major terata NOEL = 50 mg/kg LEL for feto toxicity = 50 mg/kg NOEL for delayed ossification = 35 mg/kg

Chronic Feeding

Oral	2 year Rat	LEL = 7.9 mg/kg body wt. reduced NOEL = 2.6 mg/kg
Oral	2 year Dog	LEL = 2/6 mg/kg male liver degeneration NOEL = 0.9 mg/kg

3

A tolerance exists for silvex on pears at 0.05 ppm representing 0.04% of the ADI (0.009 mg/kg/day) based on a 2 year dog feeding study NOEL of 0.9 mg/kg/day.

In addition to published tolerances, the present action for silvex on sugarcane, rice, meat, milk and dairy products will result in a TMRC of 0.0387 mg/day of residue representing approximately 7.17% of the ADI.

The requested action for 2,4,5-T would allow total residues of 0.0385 mg/day (TMRC) and account for 2.14% of the PADI based on a NOEL of 3 mg/kg/day in the rat (a data gap of a nonrodent species, long term study exists).

Both compounds use a safety factor of 100 X.

Both compounds cause terata formation or are fetolethal in the rat at doses of 50 mg/kg or greater. The NOEL for fetolethality in the rat is 25 mg/kg. The NOEL in the mouse is 20 mg/kg; a NOEL for the monkey study was 10 mg/kg.

A possibly exaggerated scenario of a pregnant woman consuming 1 pound of meat, and 1 quart of milk in a day would roughly be equivalent to (0.09 mg/day) or 0.0015 mg/kg of silvex or 2,4,5-T residues. Using the NOEL of 10 mg/kg in the monkey a 6622 fold MOS would exist between exposure through those foods and the NOEL for the monkey study.

TOX Branch considers the MOS ratio an acceptable ratio to limit the likelihood of terata formation through this route of exposure.

Henry Spencer, Ph.D. 4/19/82
Review Section #1
Toxicology Branch/HED (TS-769)

TS-769:SPENCER:s11X73710:4/15/82 card 3

CFR 180.340 Silvex 4/7/82

001781

File last updated 4/7/82

ACCEPTABLE DAILY INTAKE DATA

Dog	NOEL	S.F.	ADI	MPI
mg/kg	PPM		mg/kg/day	mg/day(60kg)
0.900	36.00	100	0.0090	0.5400

Published Tolerances

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Pears(116)	0.050	0.26	0.00019

MPI	THRC	% ADI
0.5400 mg/day(60kg)	0.0002 mg/day(1.5kg)	0.04

****

Current Action IR1102

CROP	Tolerance	Food Factor	mg/day(1.5kg)
Sugarcane (214)	0.100	0.13	0.00005
Rice(137)	0.100	0.55	0.00003
Meat, reg(90)	0.100	10.81	0.01622
Milk&Dairy Products(93)	0.150	28.62	0.02146

MPI	THRC	% ADI
0.5400 mg/day(60kg)	0.0387 mg/day(1.5kg)	7.17

****

5

001781

[illegible] 4/6/82

File last [illegible] 4/6/82

ACCEPTABLE DAILY INTAKE DATA

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
mg/kg	[illegible]		mg/kg/day	mg/day(60kg)
.008	50.00	100	0.0300	1.2000

Current Action [illegible]

Crop	Tolerance	Food Factor	mg/day(1.5kg)
[illegible] (137)	[illegible]	0.55	[illegible]
[illegible] (94)	[illegible]	[illegible]	0.01622
Milk, Dairy Products(93)	.050	28.62	0.02146

[illegible]	[illegible]	% ADI
1.4400 mg/day(60kg)	[illegible] mg/day(1.5kg)	[illegible]

****

BEST AVAILABLE COPY

6