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APR 2 1983

APRIL 27, 1983

Caswell No(s).

2A

To: Mr. Donald Stubbs, PM Team 41, RD/ERS (TS-767)

Registration No(s): 239-2418 (Orthene 75 S Soluble Powder) (75% a.i.)

Pesticide Petition No(s): 83-AZ-06 (Section 18)

Chemical(s): Acephate, formulated as Orthene 75 S Soluble Powder

→ Sec. 18 exemption for the use of acephate on grapes in Arizona. Expected

Requested Action(s): residue levels: fresh grapes, 3.0 ppm (of which no more than 0.3 ppm is Monitor) and raisins, 9.0 ppm (of which no more than 1.0 ppm is Monitor) (E. Zager, 4/26/83)

Recommendation: Approval cannot be presently recommended for the following reasons:

① Significant increase in TMRC (5.65% and 1.76% for acephate and Monitor residues respectively); and ② Acephate may pose health hazard to humans, because there

Inert(s) cleared 180.1001: Yes

% of ADI occupied: Existing: 35.50

Resulting: 37.22

Resulting % increase in TMRC: 5.65% (acephate residues) and 1.76% (Monitor residues).

Data considered in setting the ADI: 28-Month rat feeding / oncogenic study (inhibition of cholinesterase activity in brain, plasma and RBC). There is presently no ADI for Monitor.

Attached (?): ADI printout: YES/NO; TOX "one-liner": YES/NO; DER: YES/NO

Existing regulatory actions against registration: None

RPAR status: NO

New Data: 8 Mutagenic studies and a dermal sensitization study, all currently under review.

was an increased incidence of liver carcinomas in high-dose female mice and positive responses in several mutagenic studies.

Data gaps: Please see attachment.

Until this problem is solved, we are unable to recommend approval of regulatory action involving significant amounts of new residues, including emergency actions.

Risk assessment will be performed after the registrant submits additional (requested by TB) data. This action involves ① ground application only; ② PHI = 21 days; ③ 3489 acres; and ④ about 7850 lbs of acephate (a.i.). Secondary residues of

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Date:

Section Head: Edwin R. Budd 4/27/83

Branch Chief:

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acephate, attributed to this action, will be covered by the already established tolerances in milk, meat, etc.

File last updated 4/21/83

ACCEPABLE DAILY INTAKE DATA

FAT, Oiler NOEL	S.F.	ALI	MPI
mg/kg	ppm	mg/kg/day	mg/day/60kg
0.250	5.00	10	0.0250
			1.5000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Celery(28)	10.000	0.29	0.04292
Lettuce(84)	10.000	1.31	0.19622
Peppers(120)	4.000	0.12	0.00736
Beans(9)	3.000	2.04	0.09180
Cottonseed (oil)(41)	2.000	0.15	0.00450
Soybeans (oil)(148)	1.000	0.92	0.01377
Eggs(54)	0.100	2.77	0.00416
Milk&Dairy Products(93)	0.100	28.62	0.4292
Meat, inc poultry(89)	0.100	13.85	0.02077
All foods(197)	0.020	100.00	0.03000
Peanuts(115)	0.200	0.36	0.00107

MPI	TMRC	% ADI
1.5000 mg/day/60kg	0.4555 mg/day/1.5kg	30.37

Unpublished, Tox Approved 1G2550, 3E2770, 3G2790

CROP	Tolerance	Food Factor	mg/day/1.5kg
Avocados(6)	2.000	0.03	0.00090
Cranberries(44)	0.500	0.03	0.00023
Apples(2)	2.000	2.53	0.07590

MPI	TMRC	% ADI
1.5000 mg/day/60kg	0.5325 mg/day/1.5kg	35.50

Current Action Section 18 (83-AZ-06)

CROP	Tolerance	Food Factor	mg/day/1.5kg
Grapes, not raisins(67)	3.000	0.45	0.02024
Raisins(134)	9.000	0.04	0.00552

MPI	TMRC	% ADI
1.5000 mg/day/60kg	0.5583 mg/day/1.5kg	37.22

Increase in TMRC

① With regard to published tolerances: $\frac{0.02576 \times 100}{0.4555} = 5.65 \%$

② With regard to published and unpublished (Tox-approved) tolerances:
 $\frac{0.02576 \times 100}{0.5325} = 4.84 \%$

file last updated 2/9/83

ACCEPTABLE DAILY INTAKE DATA

DOg	NOEL	S.F.	ALI	MP1
mg/kg	ppm		mg/kg/day	mg/day (60kg)
\$\$\$\$\$\$\$\$	\$\$\$\$\$\$\$\$	\$\$\$	\$\$\$\$\$\$\$\$	\$\$\$\$\$\$\$\$

Published Tolerances

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Broccoli(19)	1.000	0.10	0.00153
Brussel Sprouts(20)	1.000	0.03	0.00045
Cabbage,sauerkraut(22)	1.000	0.74	0.01104
Cauliflower(27)	1.000	0.07	0.00107
Cucumbers,inc pickl(46)	1.000	0.73	0.01088
Eggplant(53)	1.000	0.03	0.00045
Tomatoes(163)	1.000	2.87	0.04312
Melons(92)	0.500	2.00	0.01502
Cottonseed (oil)(41)	0.100	0.15	0.00022
Potatoes(127)	0.00	5.43	0.00814
Lettuce(84)	1.000	1.31	0.01962
peppers(120)	1.000	0.12	0.00184
Beans(9)	1.000	2.04	0.03060
Celery(28)	1.000	0.29	0.00429
Sugar,cane&beet(154)	0.020	3.04	0.00109

MP1	TMRC	% ADI
\$\$\$\$\$\$\$\$ mg/day (60kg)	0.1494 mg/day (1.5kg)	0.00

unpublished,Tox Approved 9G2151,2G2696,3E2770

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Peanuts(115)	0.100	0.36	0.00054
Soybeans (oil)(148)	0.050	0.92	0.00069
Cranberries(44)	0.100	0.03	0.00005

MP1	TMRC	% ADI
\$\$\$\$\$\$\$\$ mg/day (60kg)	0.1507 mg/day (1.5kg)	0.00

Current Action Section 18

CROP	Tolerance	Food Factor	mg/day (1.5kg)
Grapes, not raisins(67)	0.300	0.45	0.00202
Raisins(134)	1.000	0.04	0.00061
			<u>0.00263</u>

MP1	TMRC	% ADI
\$\$\$\$\$\$\$\$ mg/day (60kg)	0.1533 mg/day (1.5kg)	0.00

Increase in TMRC

① With regard to published tolerances: $\frac{0.00263 \times 100}{0.1494} = 1.76 \%$

② Including unpublished (Tox-approved) tolerances: $\frac{0.00263 \times 100}{0.1507} = 1.75 \%$

Studies with Orthene 75 S Soluble Powder (Orthene 75 S)

Study	Results	Toxicity Category	Core (Other Grade)
Acute Oral LD50, (rabbit)*	LD50 = 707 mg/kg; M	-	Acceptable
Acute Dermal LD50, (rabbit)	LD50 = > 10 g/kg; M+F	IV	Minimum
Acute Inhalation LC50 (rat)	LC50 = > 12.1 mg/l; M+F	III	Minimum
Primary Dermal Irritation (rabbit)	PIS = 0	IV	Minimum
Primary Eye Irritation (rabbit)	No irritation on day 7.	III	Minimum
Dermal Sensitization (rabbit)	Not a sensitizer. Scores for days 1 thru 16 were 0-0.8. Challenge score (Draize) was 0.25.	-	Minimum

- * There is no acute oral LD50 rat study with Orthene 75 S, containing 75% acephate. The following values were obtained in an acute oral LD50 study with Orthene 85, a formulation containing 85% acephate: LD50 = 1490 mg/kg (male rat) and LD50 = 739 mg/kg (female rat).

Existing Toxicity Data Bank for Acephate:

Acephate is currently undergoing an active Registration Standards Review. The toxicity data baseline, derived from that review, is as follows:

Study	Results	Core (Other) Grade
Acute Delayed Neurotoxicity (hen)	Not observed (no leg paralysis) at the 375 mg/kg level.	Supplementary
Subchronic (90-day) feeding: cholinesterase activity (rat)	NOEL = 5 ppm (0.25 mg/kg), based on the inhibition of cholinesterase activity in plasma, RBC and brain; M+F	Minimum
Subchronic (37-73 days) oral dosing (human)	NOEL = 0.02 mg Monitor + 0.18 mg Acephate/kg (M) and 0.03 mg Monitor + 0.27 mg Acephate/kg (F), based on the inhibition of plasma cholinesterase activity and systemic effects.	Acceptable as Supplementary Data
Chronic (2-year) feeding (dog)	NOEL = 30 ppm (0.75 mg/kg), based on the inhibition of plasma, RBC and brain cholinesterase activity; M & F. NOEL = > 100 ppm (2.5 mg/kg), for systemic toxicity; M+F.	Minimum
Chronic 28-months feeding/oncogenic (rat)	NOEL = 5 ppm (0.25 mg/kg), based on the inhibition of cholinesterase activity in plasma, RBC and brain; M+F. (Not yet finalized).	Minimum for the chronic feeding part and Supplementary ^{Minimum} for the oncogenic part.*
Oncogenic: Interim Report (mouse)	Incomplete data	Supplementary
Teratogenic (rabbit)	Not fetotoxic or teratogenic at the 10 mg/kg (highest tested). Slight maternal toxicity was observed at this level.	Minimum

* Acephate was not oncogenic to male and female rats under the conditions of this study. The highest level of acephate tested was 700 ppm (35 mg/kg).

K. Locke 2/8/83

Teratogenic (rat) Not teratogenic at the 200 mg/kg level (highest tested) Slight maternal toxicity was observed at this level. Minimum

Mutagenic Acephate is capable of inducing point mutations and can damage DNA in yeast cells, mammalian cells in culture and human cells in culture. No chromosomal effects were found. Acceptable

Please see attachment for results with other mutagenic studies. R.K. Locke 4/4/82

Metabolism (rat) Acephate was excreted essentially unchanged in urine, in 6 hours after dosing. Did not accumulate in tissues and was not converted to Monitor. Minimum

Reproduction Study is still missing as far as the Agency is concerned. According to Chevron Chemical Company, this study was just completed (March, 1982) in England.

Oncogenic: Final Report (mouse)

Female CDI mice, fed 1000 ppm of Techn. acephate (highest level tested), had a higher incidence of hepatocellular carcinomas (HC) and hyperplastic nodules (HN) than did the controls. The incidence of HC and HN in the high-dose females was 15.8% and 19.7%, respectively. The values for the corresponding controls were 1.3% and 2.7%, respectively. All of these HC and most of the HN (14.5%) were observed at the terminal sacrifice. The incidence of HC in the historical controls (females) ranged from 0 to 6%. The incidence of hepatocellular adenomas was very low in this study. (R.K. Locke 4/21/83)

TOXICITY DATA GAPS FOR ACEPHATE

The following studies are either missing or are incomplete

(supplementary) and require replacement:

Study	Missing	Supplementary
Dermal Sensitization ●		✓
Acute Delayed Neurotoxicity		✓
21-Day Dermal	✓	
Reproduction	✓	
Mutagenic ●		✓

● These studies have been submitted and are currently under review.

Krystyna B. Locke 4/21/83