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

OCT - 5 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 2F02716. Fonofos. Request for Tolerance Increase for Fonofos on Potatoes

Tox. Chem. No. 454B
Project No. D217573
Submission No. S490706

TO: Beth Edwards, PM Team # 14
Registration Division (7505C)

FROM: Pamela M. Hurley, Toxicologist
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Pamela M. Hurley 9/5/95

THRU: Roger L. Gardner, Section Head
Section I, Toxicology Branch I
Health Effects Division (H7509C)

Roger Gardner 9/22/95

10/3/95

Background and Request:

Zeneca Ag Products has submitted a request to raise the tolerance for fonofos in or on whole potatoes from 0.1 ppm to 0.2 ppm. In addition, a feed additive tolerance is also proposed for 1.0 ppm in potato waste (peels). The Toxicology Branch (TB-I) has been asked to review and comment on the request.

Toxicology Branch Response:

TB-I has some difficulties with this request because there are data gaps for two major toxicological studies, the chronic dog study and the reproduction study in the rat. The two studies that the Agency currently has are classified as Core Supplementary and are insufficient for regulatory purposes. The current RfD is based on two co-critical studies, the chronic feeding study in the rat and the subchronic neurotoxicity study in the rat. The current RfD is 0.0075 mg/kg/day, based on a NOEL of 0.75 mg/kg/day and an uncertainty factor of 100. The data from the supplementary dog study indicate that the dog may be slightly more sensitive than the rat (the NOEL from the dog study is 0.2 mg/kg/day). A calculated RfD from this study using an uncertainty factor of 100 would be 0.002 mg/kg/day. Therefore, a new dog study could possibly change the RfD to a lower value than

the one currently published. Since this request is for increasing an existing tolerance, TB-I suggests that the chronic dietary exposure value be checked for fonofos before approving the request. In other words, what percentage of the RfD has been filled? If the percentage is relatively low and could tolerate a lower RfD in the future, then TB-I would be comfortable with raising the tolerance for potatoes. However, TB-I suggests that no new tolerances be approved without the chronic dog study and the reproduction study. The following profile summarizes the toxicology data base for fonofos.

Data Requirements (CFR 158.135):

Technical: Fonofos (Dyfonate)
Use Pattern: Broadcast, sprinkler, band applications
Action Type: Tolerance
Last Updated: 09/05/95

Guideline Study	Required	Satisfied
Acute oral LD_{50}	Yes	Yes
Acute dermal LD_{50}	Yes	Yes
Acute inhalation LC_{50}	Yes	Yes
Primary eye irritation	Yes	Yes
Primary dermal irritation	Yes	Yes
Dermal sensitization	Yes	Yes
Acute delayed neurotoxicity (hen)	Yes	Yes
Acute neurotoxicity screening (mammalian)	Yes	Yes
90-day subchronic oral		
rodent	Yes	Yes (comment 2)
nonrodent	Yes	No (comment 3)
90-day delayed neurotoxicity (hen)	Yes	Yes (comment 4)
Subchronic neurotoxicity screening (mammalian)	Yes	Yes
6-month dog (ocular effects)	Yes	No (comment 5)
Chronic feeding		
rodent	Yes	Yes
nonrodent	Yes	No (comment 3)
Oncogenicity		
rat	Yes	Yes
mouse	Yes	Yes

Guideline Study	Required	Satisfied
Teratology		
rabbit	Yes	Yes
mouse	Yes	Yes
2-Generation reproduction	Yes	No (comment 6)
Gene mutation	Yes	Yes
Chromosome aberration	Yes	Yes
Other genotoxic effects	Yes	Yes
Metabolism	Yes	Yes

Comments

1. This study has been requested in the FIFRA '88 requirements.

2. An acceptable chronic/oncogenicity feeding study in the rat is available. Therefore, the requirement for a 90-day oral study in the rat has been satisfied.

3. Although a 2-year chronic feeding study in dogs is available, it is not acceptable for regulatory purposes. Therefore, the requirement for a subchronic feeding study in dogs has not been satisfied.

4. A 90-day delayed neurotoxicity study is available in the hen. This study is classified as Core Minimum because it is based on the old neurotoxicity testing guidelines. The Office of Pesticide Programs (OPP) is in the process of finalizing new guidelines for neurotoxicity testing. The 90-day hen study published in OPP's previous guidelines is missing the assays for acetylcholinesterase (AchE) and neuropathy target esterase (NTE). This assay is included in the new guidelines for hen studies. Therefore, the 90-day hen study will apply to the previously published OPP neurotoxicity testing guidelines. TB-I notes that the Registrant has added the AchE and NTE assays in the acute delayed neurotoxicity study in the hen.

5. This study has been requested in the FIFRA '88 requirements. The Agency has approved a deferral for ocular effects testing until further guidance can be provided.

6. This study has been rereviewed and has been reassessed as Core Supplementary. It does not satisfy the regulatory requirements for a reproduction study.

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Guide-line #	Study Identification and Classification	Results
81-1	Acute Oral Toxicity in Rats Lab: Stauffer Chemical MRID 00078777 Report # T-6461 Date: 2/12/79 Acceptable	LD_{50}: 24.5 (21.4-28.0) mg/kg (males) LD_{50}: 10.8 mg/kg (9.6-12.2) (females) TOXICITY CATEGORY: I Tremors, salivation, diarrhea, lacrimation & labored breathing.
81-2	Acute Dermal Toxicity in Rabbits Lab: Stauffer Chemical MRID 00078777 Report # T-6461 Date: 2/12/79 Acceptable	LD_{50}: 159 (40-615) mg/kg TOXICITY CATEGORY: I Tremors, salivation, diarrhea, rapid breathing and miosis.
81-3	Acute Inhalation Toxicity in Rats MRID 419359-01 Lab: ICI Central Tox. Lab Report # HR2047 Date: 04/11/91 Acceptable	LC_{50}: 51.0 (33.5-77.7) µg/l (males) LC_{50}: 17.9 (8.6-37.0) µg/l (females) (Four hour exposure) TOXICITY CATEGORY: I Median lethal concentration was based on atmospheric concentrations. Clinical signs of toxicity and cholinesterase inhibition were evident and were consistent with the combination of neurological and irritancy effects which are typical of those seen following exposure to organophosphorus compounds.

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Guide-line #	Study Identification and Classification	Results
81-4	Primary Eye Irritation in Rabbits Lab: Stauffer Chemical MRID: 00078777 Report # T-6461 Date: 2/12/79 Acceptable	Primary Irritation Score: Not given in DER. TOXICITY CATEGORY: IV Moderate irritation for 1/6 animals. 0.01 ml tested because in other studies with technical dyfonate, all animals died with a dose of 0.1 ml with no irritation. 0/6 died in this study.
81-5	Primary Dermal Irritation in Rabbits Lab: Stauffer Chemical MRID: 00078777 Report # T-6461 Date: 2/12/79 Acceptable	Primary Irritation Score: Not given. TOXICITY CATEGORY: IV 2/6 animals died. No irritation. 0.05 ml given as a dose. The required dose is 0.5 ml. However, all animals had died with a previous dose of 0.5 ml of the 93% Technical with Aliquot 335. The Tox. Category was I in the previous study.
81-6	Dermal Sensitization in Guinea Pigs Lab: ICI Central Toxicology Laboratory MRID: 428426-01 Report # CTL/P/3195 Date: 12/05/90 Acceptable	Fonofos (94.9% pure) was tested for skin sensitization potential using a version of the maximisation test of Magnusson and Kligman. Formaldehyde was used as a positive control and elicited a positive response. Fonofos is considered to be a weak to mild sensitizer under the conditions of the study.

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Guide-line #	Study Identification and Classification	Results
81-7	Acute delayed neurotoxicity - chickens Lab: Woodward Research MRID: Not available Report # Not available Date: 1/10/69 Core Grade: Minimum (original assessment).	NOEL: 6.32 mg/kg LOEL: 20 mg/kg Effects: Dose levels tested: 2, 6.32, 20 mg/kg. Slow locomotion, curling under of toes, head lowering, squatting, loss of equilibrium, possible demyelination of peripheral nerve for 1 chicken. Study not currently acceptable for regulatory purposes.

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Guide-line #	Study Identification and Classification	Results
81-7	Acute delayed neurotoxicity - hens Lab: Huntingdon Res. Cntr. MRID: 431613-01 Study # ISN 316/931844 Date: 11/8/93 Core Grade: Guideline	NOEL: N/A Effects: Technical fonofos (94.2%) administered by gavage at 143 mg/kg. Most birds died in the first group. Second group, atropine injected both prior to and after dosing. Vehicle control & 500 mg/kg TOCP tested concurrently. Fonofos treated birds displayed unsteadiness, inability to stand and subdued behavior which disappeared by day 6 in surviving birds. No clinical evidence of delayed neurotoxicity (ataxia) in treated birds and levels of NTE similar to vehicle controls. 51% reduction in AChE levels in brain for treated birds when compared to vehicle controls. Trace axonal degeneration observed in spinal cord and peripheral nerves of 5/6 of vehicle controls. 4/6 birds in positive controls showed minimal axonal degeneration in spinal cord and 1/6 in the proximal sciatic nerve. In addition, trace axonal degeneration observed in cerebellum of 3/6 birds. In fonofos treated birds, trace axonal degeneration observed in spinal cord and peripheral nerves of 6 birds and in cerebellum of 1 bird. In one bird, significant axonal degeneration (moderate or marked) observed in distal sciatic and tibial nerves on right side only. Since no clinical evidence of acute delayed neurotoxicity, no evidence of decrease in NTE activity fonofos birds, positive controls displayed unusually weak response and no evidence of delayed neurotoxicity in

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Guide-line #	Study Identification and Classification	Results
		the 90-day study, this finding considered to be equivocal.
81-8	Acute mammalian neurotoxicity - rats Lab: Zeneca Central Toxicology Lab MRID: 427778-01 Report # AR5434;CTL/P/3946 Date: 3/17/93 Core Grade: Guideline	NOEL: 4 mg/kg LOEL: 7 mg/kg Effects: Alpk:APfSD rats at 0, 2, 4 or 7 mg/kg. 10/sex/dose in corn oil by gavage at 1 ml/100 g bw. 7 mg/kg: 1 ♀ displayed reduced foot withdrawal reflex, shaking, signs of urinary incontinence, tip toe gait and upward curvature of the spine 6 hours after dosing. Recovery observed by 24 hours. Positive control data provided.
82-5	90-day delayed neurotoxicity study in hens Lab: Stauffer Chemical Company MRID: 401501-20 Report # T-6237 Date: 11/8/78; reformatted and reissued: 3/24/87 Core Grade: Minimum	NOEL for inhibition of plasma cholinesterase: < 2.0 mg/kg/day (LDT). NOEL for other acute neurotoxic effects: < 2.0 mg/kg/day. Effects: Dose levels tested: Administered orally to adult hens for 90 days at 2, 4 and 8 mg/kg/day. Positive control group administered tri-o-cresyl phosphate (TOCP). No evidence of delayed neurotoxicity observed in any of the treated hens. Treated animals exhibited significant weight loss in high dose group, clinical signs of toxicity in mid- and high dose groups (possibly the low dose group), inhibition of plasma cholinesterase in all dose groups and impaired egg production in all dose groups.

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Guideline #	Study Identification and Classification	Results
82-7	90-day mammalian neurotoxicity study in rats Lab: Zeneca Central Toxicology Lab MRID: 427926-01 Report # PRO889;CTL/P/3879 Date: 4/27/92 Core Grade: Guideline	NOEL: 50 ppm LEL: 125/150 ppm NOEL for ChE inhibition: 15 ppm LEL: 50 ppm Effects: Alpk:APfSD rats at 0, 15, 50 or 125/150 ppm (0, 0.75, 2.5, or 6.25/7.5 mg/kg/day) in diet for 90 days. Highest dose level changed from 125 ppm to 150 ppm at week 5. 12 rats/sex/dose. 15 ppm: ↓ erythrocyte cholinesterase activity (♂+♀) & plasma ChE activity (♀). 50 ppm and above:↓ ChE observed (♂+♀) for all 3 parameters. 125/150 ppm: ♀: upward curvature of spine, tiptoe gait, signs of urinary incontinence, pinched in sides, reduced splay reflex, splayed gait, eye bulging and shaking; ↓ motor activity. No microscopic indications of neurotoxicity. LEL for ChE inhibition based on ↓ ChE for all 3 parameters at 50 ppm.

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Guideline #	Study Identification and Classification	Results
83-1	Chronic feeding study in dogs Lab: Woodward Research MRID: 00082233 Report # T-2153? Date: 1/10/69 Core Grade: Supplementary	NOEL: Cholinesterase NOEL: 8.0 ppm LOEL: 16.0 ppm (dose level lowered to 8.0 ppm at week 14). Systemic NOEL: 16.0 (8.0) ppm. LOEL: 60 ppm Effects: Dose levels tested: 0, 16(8.0), 60 and 240 ppm for 2 years. 240 ppm: deaths, clinical signs, decrease in body weight, increase in serum alkaline phosphatase, possible liver effects (organ weights and histopathology) and acute tissue congestion; at 60 ppm: a few clinical signs, liver weight increases and some possible body weight decreases, however, there were no major systemic effects. Quality of study not sufficient for regulatory purposes.
83-2 (a)	Oncogenicity study in mice Lab: Stauffer Chemical MRID: 401501-21 Report # T-11995 Date: 3/12/87 Core Grade: Guideline	NOEL: 5 ppm LOEL: 25 ppm Effects: Dose levels tested: 0, 5, 25, 100 ppm for 18 months. Cholinesterase inhibition (brain, erythrocyte and serum). Hyperplasia and hypertrophy of duodenum, reductions in body wt. gain & food consumption in high dose males.

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Guide-line #	Study Identification and Classification	Results
83-3	Teratology Study in Rabbits MRID 401501-22 Lab: Wil Research Labs Report # WIL-27027 Date: 2/23/87 Core Grade Minimum	Maternal NOEL: 1.5 mg/kg/day (HDT) Effects: Dose levels tested: 0, 0.2, 0.5, 1.5 mg/kg/day. Tested at sufficiently high dose level because in range-finding study at: 0 - 10.0 mg/kg/day, maternal toxicity observed at 2.0 mg/kg/day and above (death). Developmental NOEL: 1.5 mg/kg/day (HDT). NOEL borderline because there was a non-statistically significant increase in number of resorptions/doe in high dose group. Increase within historical control range & standard deviation for measurement was large.
83-3	Teratology Study in Mice Lab: Stauffer Chemical MRID: 420576-01 Report # T-I0192 Date: 4/2/92 Core Grade Minimum	Maternal NOEL: 6 mg/kg/day Maternal LOEL: 8 mg/kg/day Effects: Dose levels tested: 0, 2, 4, 6, 8 mg/kg/day. Some symptoms of neurotoxicity, including tremors, chromodacryorrhea. Developmental NOEL: 4 mg/kg/day Developmental LEL: 6 mg/kg/day Effects: Sternebral malalignment & slight dilation of 4th cerebral ventricles.

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Guideline #	Study Identification and Classification	Results
83-4	Multigeneration Reproduction Toxicity in Rats MRID 00082234 Lab: Woodward Research Report # Not given Date: 1/10/69 Core Grade Supplementary	NOEL: Could not be determined. Effects: Dose levels tested: 0, 10 or 31.6 ppm. No effects observed. Reproductive NOEL: Could not be determined due to deficiencies in study.
83-5	Chronic/oncogenicity feeding study in rats Lab: ICI Americas, Inc. MRID: 406179-01 Report # T:11997 Date: 05/02/88 Core Grade: Minimum	NOEL: 15 ppm LOEL: 60 ppm Effects: Dose levels tested: 0, 4, 15, 60 ppm for 2 years and 120 ppm for 12 months. Not oncogenic. Cholinesterase inhibition (brain, serum and erythrocyte). Decreases in body weight gain in females at 120 ppm.
84-2 (a)	Gene Mutation Assay (Ames Test) Lab: ICI Central Toxicology Lab MRID: 417692-01 Report # CTL/P/3153 Date: 12/21/90 Acceptable	Dose levels tested: Tested with and without activation at 0.32, 1.6, 8.0, 40, 200, 1000, 5000 µg/plate. Tested up to levels of cytotoxicity. Results negative when compared to vehicle (DMSO) and absolute controls.

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Guide-line #	Study Identification and Classification	Results
84-2 (b)	Structural Chromosomal Aberration Assay: In vitro cytogenetics in human lymphocytes Lab: ICI Central Tox. Laboratory MRID: 418371-01 Report # SV0481 Date: 3/13/91 Acceptable	Dose levels tested: 10, 50, 100 µg/ml both with and without metabolic activation. Tested up to levels of cytotoxicity. Results negative. Positive controls verified sensitivity.
84-2 (c)	Other Genotoxicity Assays: Mouse micronucleus assay Lab: ICI Central Tox. Laboratory MRID: 418133-01 Report # CTL/P/3153 Date: 01/17/90 Acceptable	Dose levels tested: 6 and 9.5 mg/kg. No increases in micronucleated PCE's. Indications that it was tested up to level of cytotoxicity.
85-1	Metabolism Lab: Stauffer Chemical MRID: 00090876 Report # Pest Bio Path1:256 Date: 1971 Acceptable	Dose levels tested: Single oral dose of 2.0, 4.0, 8.0 mg/kg to male rats were eliminated greater than 94% in urine and feces at 48 hrs. (C^{14} in the ethyl moiety).
85-1	Metabolism Lab: Stauffer Chemical MRID: 00043508, 00090824 Report # ARC-B-14 Date: 1/12/67	Results: One minor water soluble metabolite (not identified) in corn was not observed in rat urine.

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Guide-line #	Study Identification and Classification	Results
	Supplementary	
85-1	Metabolism Lab: Stauffer Chemical MRID: 00090875 Report # Not given Date: 12/13/77	Results: No significant influence on excretion of dyfonate (2.0 mg/kg, oral, periodically over 16 days) due to 3-day hepatic enzymes at 0.5 mg/kg/day. Biliary excretion shows 15% enterohepatic recirculation in noninduced rats.
	Supplementary	
85-1	Metabolism Lab: Stauffer Chemical MRID: 00090877 Report # Life Sci. 10:1311 Date: 1971	Results: Chemical oxidation with m-chloroperbenzoic acid yields o-ethyl-ethanephosphonothioc acid (ETP), o-ethylethanephosphonic acid (EOP), thiophenol and sulfur.
	Supplementary	
85-1	Metabolism Lab: Stauffer Chemical MRID: 00090879 Report # J.J. Mimm ARC-B-17 Date: 1967	Results: 60 hrs. after single oral doses of either 0.5 or 6 mg/kg to rats (male and female), radiolabel was excreted at 94.4% and 75.8% for the low and high dose respectively, mostly hair and hide.
	Supplementary	
85-1	Metabolism Lab: Stauffer Chemical MRID: 00090800 Report # Not given Date: 12/12/66	Results: Both C^{14} and S^{35} labels were 90-97% recovered at 96 hours from either oral or i.p. administration in either sex. Tissue retention was 2.3% mostly in blood, liver, kidney, and intestines.
	Supplementary	

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Guide-line #	Study Identification and Classification	Results
85-1	Metabolism Lab: Stauffer Chemical MRID: 00092025 Report # Life Sci. 10:947 Date: 1971 Supplementary	Results: In vitro microsomal metabolism yields oxon analogue, ETP, EOP & thiophenol.

Data Gaps: Subchronic and chronic dog feeding studies, reproduction study and the 6-month dog ocular study.

Actions Being Taken to Obtain Additional Information or Clarification: These studies have been requested through the FIFRA '88 process. The reproduction study will be requested in a future action.

Reference Dose (RfD):

The recommended RfD is 0.0075 mg/kg/day. This value was calculated by using the chronic toxicity study in the rat and the subchronic neurotoxicity study in the rat NOELs of 0.75 mg/kg/day and a safety factor of 100. This RfD has been verified or approved by the Health Effects Division RfD Committee. The NOEL and LOEL are based on brain cholinesterase inhibition, clinical signs of toxicity and decreased motor activity.

Pending Regulatory Actions: None

Toxicologic Issues Pertinent to This Request: Toxicologic issues pertain to either missing or inadequate studies. These are explained further in the profile summary.