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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Amended Request for Tolerances for the Use of Poast® on Alfalfa Hay and Forage and Soybean Hay and Forage

EPA No. 3F-2904 Project No. 123
Record No. 149959 Caswell No. 72A
40 CFR § 180.412

TO: Robert J. Taylor, PM Team #25
Registration Division (TS-767c)

FROM: John E. Whalan, Toxicologist
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c) 12-5-85

THRU: Edwin R. Budd, Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769c) 12/6/85 12/8/85

Background:

BASF Wyandotte Corporation is requesting the issuance of tolerances for the use of the herbicide Poast® (2-[1-(ethoxyimino)butyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one) and its metabolites on alfalfa and soybean hay and forage.

The Registrant had previously requested tolerances for these crops (20 ppm for alfalfa hay and forage, and 20 ppm for soybean hay and forage). The Toxicology Branch (ref. Minnie Sochard review of PP 3F-2904, 1-3-84) had no objections to the issuance of the proposed tolerances once two requirements were met:

1. Additional testing of sethoxydim metabolites was required (per the Minnie Sochard and Edwin R. Budd review of PP 2F-2670 and EPA 7969-LI, 3-9-83).

2. Toxicology Branch deferred to Residue Chemistry Branch to determine whether the proposed tolerances are supported by residue data, and sufficient to cover the proposed use.

The registrant has since submitted an amended report supporting PP 3F-2904 (EPA Accession No. 071661, submitted May 22, 1983). The proposed tolerances requested in this amended petition are as follows:

Soybean hay	10.00 ppm
Alfalfa hay and forage	40.00 ppm
Milk	0.05 ppm

The amended petition includes an amended label, an amended toxicology section (with three reports), an amended residue chemistry section (with reports), and an amended tolerance proposal. Of specific concern to this action is the submission of a Rat Metabolism study of the parent compound (sethoxydim or NP-55) which identified a previously unknown metabolite - Nor-MSO (also called Me-MSO), and an Acute Oral Study in Rats and an Ames Assay performed using the metabolite Nor-MSO.

The Rat Metabolism study established that an unknown metabolite (first observed in goat urine) was Nor-MSO, and represented 2.1% of the parent/metabolite excreted in rat urine. The report was difficult to interpret and was lacking in detail because it was presented as a "Supplemental Report" to RD-8025/8148 (ref. Minnie Sochard review of PP 2F-2670 and EPA 7969-LI, 3-8-83).

The metabolite Nor-MSO was tested in two studies. An Acute Oral Study in Rats demonstrated that this metabolite has an LD_{50} >5000 mg/kg and caused minor toxic signs (in comparison, acute rat LD_{50} for sethoxydim is 3125 mg/kg for males and 2676 mg/kg for females). Thus, the LD_{50} for Nor-MSO is approximately the same as the other metabolites previously evaluated (ref. Minnie Sochard review of PP 2F-2670 and EPA 7969-LI, 3-8-83). An Ames Assay of this metabolite did not show any increase in revertants in the nonactivated or activated systems, even at cytotoxic doses. The Ames Assay report and review were critiqued by Irving Mauer, Geneticist, Toxicology Branch.

Poast will be applied to soybeans at the rate of 1 to 1.5 pints/acre. Multiple applications will be used as needed at a rate not to exceed 5 pints per acre per season. There will be a PHI of 90 days. Treated soybean fields may not be grazed, and treated forage or ensilage must not be fed to livestock; treated soybean hay may be fed, however.

Poast will be applied to alfalfa at the rate of 1 to 2 pints/acre. Multiple applications will be used as needed at a rate not to exceed 5 pints per acre per season. There will be a PHI of 7 days for feeding, grazing or harvesting of forage, and a PHI of 20 days for feeding or harvesting hay.

The Registrant failed to submit a complete label. Rather, a "Supplemental Labeling" was provided. The last complete label received (5-21-85) was for the use of Poast on soybeans, cotton, ornamental, nursery and other non-food crops. The label is acceptable provided it includes the "Danger" signal word.

Of the proposed tolerances, only milk is a human food item. Since the milk tolerance of 0.05 ppm is already published, there will be no change in ADI and TMRC values. The Toxicology Branch has no objection to granting these tolerances.

The adjoining pages include an 8-Point Summary and reviews of the following toxicology studies:

1. Acute Oral Toxicity Study of Me-MSO in Rats
2. Ames Assay of Me-MSO
3. Metabolism Study of NP-55 (Sethoxydim) in Rats

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Summary of Toxicity Data
and
Eight Point Free Standing Summary

1. Summary of selected toxicology data considered for these actions:

STUDY	RESULTS	TOX CATEGORY	CLASSIFICATION
Data on Technical NP-55 (sethoxydim):			
Acute Oral LD_{50}, Rat	3125 mg/kg (males) 2676 mg/kg (females)	III	Guideline
Acute Dermal LD_{50}, Rat	>5000 mg/kg (males and females)	III	Guideline
Acute Inhalation LC_{50}, Rat (4 hours)	6.03 mg/l (males) 6.28 mg/l (females)	III	Guideline
Primary Eye irritation, Rabbit	No irritation	IV	Guideline
Primary Dermal Irritation, Rabbit	No irritation	IV	Guideline
Dermal Sensitization, Guinea Pig	Negative	-	Minimum
14-Week Mouse Feeding Study	NOEL = 300 ppm	-	Minimum
14-Week Rat Feeding Study	NOEL = 300 ppm	-	Guideline
6-Month Dog Feeding Study	NOEL = 20 mg/kg/day (males and females) LEL = 177 mg/kg/day (males) 223 mg/kg/day (females) (values based on analysis of diet and food) Non-specific anemia, liver effects, and possible kidney effects.	-	Guideline

STUDY	RESULTS	TOX CATEGORY	CLASSIFICATION
2-Year Mouse Chronic Feeding/ Oncogenicity Study	NOEL = 120 ppm (18 mg/kg/day) LEL = 360 ppm (non-neoplastic liver lesions) Not oncogenic in BDF_1 mice.	- -	Guideline [Chronic feeding] Guideline [Oncogenicity]
2-Year Rat Chronic Feeding/ Oncogenicity Study	NOEL $\geq$360 ppm (18 mg/kg/day - highest dose tested)	- -	Guideline [Chronic feeding] Guideline [Oncocenicity]
Teratology Study, Rats	Teratogenicity NOEL = 250 mg/kg/day (highest dose tested) Maternal NOEL = 40 mg/kg/day Maternal LEL = 100 mg/kg/day (significantly decreased adrenal weight)	-	Guideline
Teratology Study, Rabbits	No terata at $\leq$160 mg/kg/day. Effects observed at 480 mg/kg/day (increased number of a variety of random effects including skeletal and visceral abnormalities, reduced fetal weight, and changes in male/female ratios) considered due to extreme toxicity in dams, Maternal NOEL = 160 mg/kg/day. Maternal LEL = 480 mg/kg/day (severe weight loss, 5/16 deaths, 6/16 abortions, and reduction in the number of litters and viable fetuses).	-	Minimum
Two-Generation Reproductive Study, Rats	No reproductive effects. NOEL = 360 ppm	-	Guideline

STUDY	RESULTS	TOX CATEGORY	CLASSIFICATION
Mutagenicity Studies:			
A. Rec-Assays and Forward Mutations, B. subtilis, E. coli, S. typhimurium	Negative at concentrations of chemical to 100%	-	Minimum
B. Mouse Host-Mediated Assay, S. typhimurium	Negative at up to 2500 mg/kg bw/day of chemical.	-	Minimum
Metabolism Study, Rats	Tissue accumulation of chemical negligible and excretion extremely rapid, assuming DMSO vehicle does not affect storage or excretion of the chemical.	-	Guideline
Data on Formulated Product - BAS 9052 OH (EPA #7969 - LI):			
Acute Oral LD_{50}, Rat	4918.7 mg/kg	III	Guideline
Acute Dermal LD_{50}, Rat	>4000 mg/kg	III	Guideline
Acute Inhalation LC_{50}, Rat	>7.6 mg/l	III	Guideline
Primary Eye Irritation, Rabbit Study No. 1	P.I. = 32 (24 hours); 35 (48 hours); 29 (72 hours) Scarring in 5/6 animals at 8 days, corneal opacity in one animal at 8 days.	I	Minimum
Primary Eye Irritation, Rabbit Study No. 2	P.I. indices: Washed eyes - 6.0, 6.0, 1.3, 0.7, and 0 at 24, 48, and 72 hours, and 4 and 7 days, respectively. Unwashed eyes - 32.0, 31.0, 28.0, 17.6, and 7.7 at 24, 48, and 72 hours, and 4 and 7 days, respectively.	I	Minimum

STUDY	RESULTS	TOX CATEGORY	CLASSIFICATION
Primary Dermal Irritation, Rabbit	P.I. = 4.0 (numerical score indicates moderate irritation but one animal had necrosis and 5/6 had severe scaling at 8 days, thus upgrading classification to Category I).	I	Minimum
Data on Hydroxymetabolite 5-OH-MSO2 (MU-1):			
90-Day Feeding Study, Rat	NOEL >1080 ppm (70.2 mg/kg/day for males; 74.0 mg/kg/day for females) [HDT].	-	Minimum
Teratology, Rat	Teratogenic NOEL >250 mg/kg/day [HDT] Fetotoxic NOEL >250 mg/kg/day. Maternal NOEL >250 mg/kg/day.	-	Minimum
Mutagenicity Studies:			
A. CHO-HGPRT Forward Mutation Assay in Chinese Hamster Ovary Cells	Not mutagenic with or without S-9 activation at doses of 2.0-10.0 mg/ml.	-	Acceptable
B. Chinese Hamster Bone Marrow Cytogenetic Assay	Not mutagenic at oral doses as high as 10,000 mg/kg.	-	Acceptable
Data on Hydroxymetabolite MeMSO (Nor-MSO):			
Acute Oral LD_{50}, Rat	>5000 mg/kg in males.	IV	Minimum
Mutagenicity - Ames Assay	Negative in nonactivated and activated systems.	-	Acceptable
Metabolism Study, Rat	Radiolabelled MeMSO represented 2.1% of the radioactivity in urine at an unspecified time.	-	Minimum

2. Summary of Data Considered Desirable but Lacking for This Action:

A protocol to evaluate unscheduled DNA synthesis in rat liver primary cell cultures was reviewed by the Toxicology Branch (ref. M. Sochard memorandum, 7-9-84); the final report has not yet been received.

3. Action Being taken to Obtain the Lacking Information or Other Additionally Needed Information:

John Whalan (TB) asked Vickie Walters (RD) the status of the mutagenicity study. The registrant believes that the study was performed, and will ask the performing laboratory in Germany to expedite completion of the final report.

4. A Summary of Other Permanent Tolerances Granted for This Herbicide:

Meat (including poultry) - 0.2 ppm; Milk and dairy products - 0.05 ppm; Eggs - 0.5 ppm; Cottonseed (oil) - 5.0 ppm; Soybeans (oil) - 10.0 ppm; Sugar (cane and beet) - 0.1 ppm

5. There will be no change in ADI and TMRC values as a result of this action.

6. The 2-Year rat chronic feeding/oncogenicity study with a NOEL of 360 ppm (18.0 mg/kg/day) was used to set the ADI. The safety factor employed was 100. The ADI is 0.18 mg/kg/day. The MPI is 10.8 mg/day (for a 60 kg person).

7. There are at this writing no pending regulatory actions against the registration of this pesticide.

8. Other Relevant Considerations in Setting These Tolerances:

None.

ACUTE ORAL TOXICITY STUDY OF Me-MSO IN RATS

Nisso Institute for Life Science; Report No. 0158; August 16, 1984; Accession No. 073398

PROTOCOL: Groups of 5 fasted male Slc:SD rats (162-188 g, 5 weeks old) were dosed by stomach tube with single 1000, 3000, and 5000 mg/kg doses of Me-MSO (97.2% pure) dissolved in distilled water. They were observed for toxic signs for 14 days. Body weights were measured on the day of dosing, and on days 1, 2, 3, 7, and 14. Food and water were available ad libitum. All rats were necropsied and observed for gross lesions.

RESULTS: One rat dosed at 5000 mg/kg died on day 3. No other deaths occurred. The LD_{50} is therefore >5000 mg/kg. No toxic signs were seen other than urine incontinence in one high-dose rat on day 1. Mean body weights were significantly reduced in the high-dose group from day 1 to day 14. No gross lesions were seen in any rats including the one which died on study.

This study is CORE MINIMUM - Toxicity Category IV. Only males were used in this study; a like number of females should have been used.

AMES ASSAY OF Me-MSO

Nisso Institute for Life Science; Report No. 0154; July 30, 1984; Accession No. 073398

PROTOCOL: An Ames Assay of reverse mutagenic potential was performed using Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-98, and TA-100, and the Escherichia coli WP2 uvrA strain (modified Ames method introduced by Yahagi). Cultures were dosed with Me-MSO (97.2% pure) in water, positive controls in DMSO, and a water vehicle control (100,000 ug/plate) as follows:

S. typhimurium	Me-MSO Dose (ug/plate)		Positive Control (ug/plate)[a]	
	Nonactivated	Activated	Nonactivated	Activated
TA-1535	50-100,000	10-50,000	EENG (5.0)	2AA (2.0)
TA-100	50-100,000	10-50,000	AF-2 (0.01)	B(α)P (5.0)
TA-1537	50-100,000	10-50,000	9AA (10.0)	B(α)P (5.0)
TA-1538	50-100,000	10-50,000	4NOPD (5.0)	B(α)P (5.0)
TA-98	50-100,000	10-50,000	AF-2 (0.02)	B(α)P (5.0)
E. coli				
WP2 uvrA	50-100,000	10-50,000	AF-2 (0.01)	2AA (80.0)

[a] EENG - N-ethyl-N'-nitro-N-nitrosoguanidine
AF-2 - 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide
9AA - 9-aminoacridine
4NOPD - 4-nitro-o-phenylenediamine
2AA - 2-aminoanthracene
B(α)P - benzo(α)pyrene

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Phenobarbital and 5,6-benzoflavone induced rat S-9 mixture was used in the activated systems. All assays were performed twice.

RESULTS: The doses selected were sufficient to cause complete cytoxicity at the highest doses. Typically, there was a sharp cut-off in colony survivability between the 10,000 and 50,000 ug/plate dose in both the nonactivated and activated systems. Although all of the positive control assays had >3.6 fold increases in revertant colonies compared to the vehicle (water) controls, there was no evidence of increased revertant colonies following dosing with Me-MSO in the nonactivated and activated systems.

This study is ACCEPTABLE.

METABOLISM STUDY OF NP-55 (SETHOXYDIM) IN RATS

**** SUPPLEMENTAL REPORT to RD-8025/8148 ****

Nippon Soda Co. Ltd.; Report No. 8466; August 1, 1984; Accession No. 073398

INTRODUCTION: In the previously submitted reports RD-8025 and 8148, several metabolites of NP-55 were identified in the elimination products of rats. In this Supplemental Report, yet another metabolite, "nor-MSO," was identified. Nor-MSO was first identified in goat urine as a S-methyl analogue of the main metabolite MSO.

PROTOCOL: Three male Fischer rats (9 weeks old, 228 g mean body weight) were orally dosed (presumably gavage) with ^{14}C-radiolabelled NP-55 (sethoxydim) in DMSO (22.5 mg/ml) at a dose of 18 mg/kg/day for 7 days. This dose level was based on a NOEL of 360 ppm in the diet as established in a chronic feeding study. Twenty-four hour group urine samples were obtained once daily, then frozen until analysis. The cages were washed daily with a minimal amount of 90% aqueous methanol. Urine samples collected on days 1, 3, and 7 were analyzed within 2 days for metabolite fractions. The dichloromethane (DCM) extracts were separated from the urine by the use of silica gel chromatography and a preparative TLC, and the fractions were analyzed by mass spectrometry.

RESULTS: The newly identified metabolite ^{14}C-nor-M-SO was found to represent 2.1% of the radioactivity in rat urine (the day of sample collection was not given). This metabolite was found in fractions 6 and 7 which also contained M-SO and small quantities of yet another unidentified metabolite. The other metabolites found in the rat urine included M2-SO_2, M1-SO_2, 6-OH-M2-SO_2, and Nor-M2-SO_2, with mean radioactivity percentages of 36.1%, 6.6%, 0.7%, and 2.4%, respectively (the mean values are for days 1, 3, and 7; the values were similar on all three days).

This study is CORE MINIMUM. Many of the specifics on the study design were missing from this supplemental report because they, "had been described in the previous papers RD-8025 and 8148." These deficiencies were compounded by the poor translation and lack of definitions for abbreviations, thus making study review difficult. The primary purpose of this report was to define the previously unidentified metabolite and assess its percentage in rat urine; this purpose was achieved.