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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Clethodim. Tolerance Petitions and Amended Registrations for sugar beet, onion (dry bulb), alfalfa, dry beans, peanuts and peanut meal
DP Barcode No. D203380, D210425, D210429
Submission No. S465634, S478870, S478872
ID No. 4F04340, 5F04440, 5H05713
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ACTION:

Review of Valent U.S.A. registration amendment petitions and of petitions to establish permanent tolerances for clethodim in sugar beet and onion (dry bulb) (4F04340), alfalfa, dry beans and peanuts (5F04440) and peanut meal (5H05713). Clethodim is currently approved for uses on cotton, soybeans and ornamental plants. Tolerances are proposed for Clethodim in or on the following agricultural food or feed commodities:

1

Food or Feed Commodity	Proposed tolerance:
Sugar beet roots	0.2 ppm
Sugar beet tops	0.5 ppm
Onions (dry bulbs)	0.5 ppm
Alfalfa forage	10 ppm
Alfalfa hay	15 ppm
Dry bean seeds	2 ppm
Dry bean forage	5 ppm
Dry bean straw/hay	7 ppm
Peanut nutmeat	3 ppm
Peanut hulls	2 ppm
Peanut hay	5 ppm
Peanut meal	10 ppm

CONCLUSION

The analysis of the contribution to dietary risk (% RfD occupied) in granting these petitions is performed by the Dietary Risk Evaluation System (DRES) in the Science Analysis Branch. Toxicology Branch II has no objections to the approval of these requests if the residue chemistry data are acceptable to Chemistry Branch (I/II) and granting these petitions will not result in the tolerances exceeding 100% of the RfD. An additional acute oral toxicity study submitted (MRID no. 43166401) was not formally reviewed since it was not required and did not change the acute oral toxicity category (III) for Clethodim.

Additionally, based on examination of data submitted by the Registrant, it is recommended that the 4-week repeated-dose dermal toxicity studies in rats for Technical Clethodim (MRID 41030109) and for SELECT 2.0 EC (MRID 41030201) be upgraded from Supplementary to Acceptable.

DETAILED CONSIDERATIONS

I. Toxicology Profile

The toxicology profile of clethodim is summarized in Tables 1 and 2 below. There are no data gaps in the toxicology database for clethodim.

II. Issues

A. Carcinogenicity:

No treatment-related increases in tumor incidence were seen in mice (0, 20, 200, 1000 or 3000 ppm for 78 weeks; MRID 410301-12; Core Guideline) or in rats (0, 5, 20, 500, or 2500 ppm for 2 years; 410301-21; Core Guideline).

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B. Reference Dose (RfD):

The Reference Dose (RfD) of clethodim is 0.01 mg/kg b.wt./day [OPP RfD] based on a no-observed-effect-level (NOEL) of 1 mg/kg b.wt./day from a 1-year study in dogs and an uncertainty factor of 100.

C. Pending Regulatory Actions: There are no pending regulatory actions with respect to the registration of this chemical.

D. Upgrading of 21-Day Dermal Toxicity Studies.

Four-week repeated-dose dermal toxicity studies in rats with technical clethodim (RE-45601, MRID 41030109) and SELECT 2.0 EC (26.3% RE-45601, MRID 41030101) were initially classified as supplementary pending submission of data on surface area exposure. The Registrant has now submitted the requested information (Valent Fax dated 9/29/95 of Valent Inter-office Memorandum G 0-144, dated 9/4/90): the clipped area was 32 cm^2. It is recommended that the above 4-week repeated-dose dermal toxicity studies in rats (MRID 41030109 and MRID 41030201) be upgraded from Supplementary to Acceptable.

Table 1. Toxicology profile for Clethodim. Guideline Numbers are as listed in CFR 158.340.

	REQUIRED	SATISFIED
§81-1 ACUTE ORAL TOXICITY - RAT	Y[1]	Y
§81-2 ACUTE DERMAL TOXICITY - RABBIT	Y	Y
§81-3 ACUTE INHALATION TOXICITY - RAT	Y	Y
§81-4 PRIMARY EYE IRRITATION - RABBIT	Y	Y
§81-5 PRIMARY DERMAL IRRITATION - RABBIT	Y	Y
§81-6 DERMAL SENSITIZATION - GUINEA PIG	Y	Y
§82-1 90-DAY FEEDING - RAT	Y	Y
§82-1 90-DAY FEEDING - DOG	Y	Y
§82-2 21-DAY DERMAL - RABBIT	Y	Y[2]
§82-4 SUBCHRONIC INHALATION	N	N/A
§82-5 21-DAY DELAYED NEUROTOXICITY	N	N/A
§83-1 CHRONIC FEEDING - RAT (COMBINED §83-2)	Y[3]	Y
§83-1 CHRONIC FEEDING - DOG	Y[4]	Y
§83-2 ONCOGENICITY STUDY - RAT	Y	Y
§83-2 ONCOGENICITY STUDY - MOUSE	Y	Y
§83-3 TERATOGENICITY - RABBIT	Y	Y
§83-3 TERATOGENICITY - RAT	Y	Y
§83-4 TWO-GENERATION REPRODUCTION - RAT	Y	Y
§84-2(a) GENE MUTATION	Y	Y
§84-2(b) STRUCTURAL CHROMOSOME ABERRATION	Y	Y
§84-4 OTHER GENOTOXIC EFFECTS	Y	Y
§85-1 GENERAL METABOLISM	Y	Y
§85-2 DERMAL PENETRATION	Y	Y
END-USE FORMULATIONS:		
§81-1 ACUTE ORAL TOXICITY - RAT	Y	Y
§81-2 ACUTE DERMAL TOXICITY - RABBIT	Y	Y
§81-3 ACUTE INHALATION TOXICITY - RAT	Y	Y
§81-4 PRIMARY EYE IRRITATION - RABBIT	Y	Y
§81-5 PRIMARY DERMAL IRRITATION - RABBIT	Y	Y
§81-6 DERMAL SENSITIZATION - GUINEA PIG	Y	Y

[1] Y = YES; N = NO; YES: indicates that the DER is Minimum, Guideline or Acceptable.
[2] Satisfied with the submission of additional information on amount of surface area receiving the test compound; a revised one-liner is attached to this action.
[3] Submitted as a combined chronic/carcinogenicity study.
[4] The Reference Dose (RfD) was established based upon the results of this study.

Table 2. Toxicity Summary of Clethodim.

Guideline	Study Type	Species	Route	Dose	Results	Tox. Cat.	MRID No.	CORE Grade
81-1	Acute Oral	Rat (S-D)	Oral	0-2.5 g/kg (Tech. 83.3% a.i.)	LD_{50} : ♂: 1.63 g/kg; ♀: 1.36 g/kg.	3	409745-07	Guideln.
	"	"	"	1.4 g/kg (Tech. 83.8%	Females only dosed. Five of 5 died.	-	410301-01	Supplem.
"	"	Mice (CR, CD-1)	"	0-3.5 g/kg (Tech. 83.3% a.i.)	LD_{50} : ♂: 2.57 g/kg; ♀: 2.43 g/kg.	3	409745-08	Minimum
81-2	Acute Dermal	Rabbit (NZW)	Dermal	2.0 & 5.0 g/kg (Tech. 83.3% a.i.)	LD_{50} : >5.0 g/kg, for ♂ & ♀.	4	409745-10	Guideln.
81-3	Acute Inhal.	Rat (S-D)	Inhal.	3.9 mg/l, MMAD = 2.8μm. (Tech. 83.3%)	LC_{50}: > 3.9 mg/L	3	409745-12	Minimum
81-4	Pri. Eye Irrit.	Rabbit (NZW)	Eye	0.1 ml. (Tech. 83.3% a.i.)	Mild ocular irritation.	3	409745-14	Guideln.
81-5	Pri. Der. Irrit.	Rabbit (NZW)	Dermal	0.5 ml. (Tech. 83.2% a.i.)	Severe erythema observed at 72 hours	2	409745-16	Minimum
81-6	Derm. Sensit.	Guinea Pig (Hartley)	Dermal	0.5 and 5.0 % induction; 0.5% challenge	Not a sensitizer	-	409745-18	Guideln.
-	Acute Intraperiton.	Rat (S-D)	Intraperit.	700-2000 mg/kg 83.2% a.i.	LD_{50} : 1041 mg/kg (♂) and 1200.8 mg/kg (♀).	-	409745-09	-

Table 2. Toxicity Summary of Clethodim.

Guideline	Study Type	Species	Route	Dose	Results	MRID No.	CORE Grade
82-1	Feeding - 13 week.	Rat (S-D)	In diet	0, 50, 500, 2500, or 5000 ppm for 13 weeks followed by 6 week recovery period. (♂: 0, 2.3, 25, 134, or 279 mg/kg/day; ♀: 0, 2.8, 30, 159, or 341 mg/kg/day. (Tech. 83.4% purity)	NOEL: 500 ppm. LEL: 2500 ppm [based on b.wt. and b.wt. gain depression; absolute and relative liver weights increased; and centrilobular hypertrophy of the liver observed in ♂ and ♀ at 2500 and 5000 ppm].	410301-07	Minimum
"	"	Dog (Beagle)	Oral (Gelatin capsules)	0, 1, 25, 75, or 125 mg/kg/day for 90 days. (Tech. 83.3% a.i.)	NOEL: 25 mg/kg/day. LEL: 75 mg/kg/day [based on increased absolute (HDT) and relative (MDT & HDT) liver weights]. Liver lesions (cytoplasmic vacuolation/vesiculation) were increased in both sexes at the HDT. Mean serum and cholesterol were increased in HDT females.	410301-05 410301-06	Minimum
82-2	Dermal - 3 wk.	Rat (S-D)	Dermal	0, 10, 100, or 1000 mg/kg/day (area of application: 32 cm^2); 21 applications; 6 hours/application. (Tech. 83.2% purity)	NOEL: 100 mg/kg/day. LEL: 1000 mg/kg/day [based on anogenital discharge and staining (♂ & ♀), depressions in food efficiency (♂), and increases in absolute and relative liver weights in females. The LEL for skin irritation was 10 mg/kg/day [based on dose-related incidence and severity of skin irritation.	410301-09	Minimum
"	Feed - 28 day	Mice (CD-1)	In feed	0, 150, 250, 625, 1500, or 4000 ppm for 4 weeks. (Tech. 83.3% purity).	NOEL: 625 ppm. LEL: 1500 ppm (based on dose-related decrease in erythrocytes, hemoglobin and hematocrit at 1500 and 4000 ppm; and increased liver weights in males at 1500 ppm). Increased hypertrophy of centrilobular hepatocytes was seen at 4000 ppm in both sexes.	410301-03	Supplem.

Table 2. Toxicity Summary of Clethodim (Continued).

Guideline	Study Type	Species	Route	Dose	Results	MRID No.	CORE Grade
83-1	Feeding-1 year	Dog (beagle)	Oral (gelatin capsules)	0, 1, 75, or 300 mg/kg/day, for 1 year. (Tech. 83.3% purity).	NOEL: 1 mg/kg/day. LOEL: 75 mg/kg/day [based on dose-related increases in absolute and relative liver weights and alterations in hematology (platelets & WBC) and clinical chemistry (glucose)]. Hepatocellular enlargement and increased pigment in the liver plus increased total cholesterol, alanine aminotransferase, and alkaline phosphatase were seen in ♂ & ♀ at the HDT.	410301-11	Minimum
83-2	Carcinogenicity Feeding-78 wks	Mice [Crl:CD-1(ICR)BR]	In diet	0, 20, 200, 1000, 2000/3000 ppm for total 78 weeks. [2000 ppm up to 15 weeks, 3000 ppm thereafter]. (Tech. 83.3% purity).	Not carcinogenic at the doses tested. Systemic NOEL: 200 ppm. Systemic LEL: 1000 ppm [Based on increases in absolute and relative liver weights in both sexes at 1000 and 3000 ppm at 52 weeks and in 3000 ppm females at 78 weeks. In addition, there was histopathology: in liver (centrilobular hypertrophy, increased pigment, and bile duct hyperplasia) and in lungs (amphophilic alveolar macrophages) in ♂ & ♀ at 1000 and 3000 ppm]. Survival incidence decreased at 3000 ppm at week 78. Decreases in hematology parameters at 3000 ppm	410301-12	Minimum
83-2 & 83-5	Combined chronic toxicity / carcinogenicity	Rat (S-D)	In diet	0, 5, 20, 500 or 2500 ppm for 2 years [0, 0.15, 0.57, 16, or 86 mg/kg/day (♂) or 0, 0.2, 0.72, 21, or 113 mg/kg/day (♀)]. (Tech. approx. 83% purity).	Not carcinogenic at the doses tested. Systemic NOEL: 500 ppm (19 mg/kg/day). Systemic LEL: 2500 ppm (100 mg/kg/day) [Based on body weight gain decrement greater than 10% at the HDT at 3 months in both sexes; increased liver wt. at the HDT at 12 months; decreased food efficiency in HDT males].	410301-21	Guideln.

Table 2. Toxicity Summary of Clethodim (Continued).

Guideline	Study Type	Species	Route	Dose	Results	MRID No.	CORE Grade
83-3	Developmental Toxicity	Rat [Crl:CD(COBS)]	Oral (Gavage)	0, 10, 100, 350, or 700 mg/kg/day on 6-15 d of gestation. (Tech. 82.6% purity).	Maternal NOEL: 100 mg/kg/day. Maternal LEL: 350 mg/kg/day (based on reduction in body weight gain and excessive salivation at 350 and 700 mg/kg/day. Developmental NOEL : 100 mg/kg/day. Developmental LEL: 350 mg/kg/day (Based on reduction in fetal weights and increases in the incidence of skeletal anomalies at 350 and 700 mg/kg/day	410301-16	Minimum
"	"	Rabbit (NZW)	Oral (Gavage)	0, 25, 100, or 300 mg/kg/day on 7-19 d of gestation. (Tech. 82.6%)	Maternal NOEL: 25 mg/kg/day. Maternal LEL: 100 mg/kg/day (Based on decreased weight gain and decreased food consumption). Developmental NOEL: 300 mg/kg/day. Developmental LEL: >300 mg/kg/day (No developmental toxicity was observed).	410301-15	Minimum
83-4	2-Generation Reproductive Toxicity	Rat Crl:COBS/CD(SD)	Oral (In diet)	0, 5, 20, 500 or 2500 ppm, for 2 consecutive generations. (Tech. 83.2% purity).	Parental NOEL: 500 ppm (approx. 51 mg/kg/day). Parental LEL: 2500 ppm (approx. 263 mg/kg/day) [Based on reductions in body weight, particularly in males and food consumption during both generations]. Reproductive NOEL: 2500 ppm. Reproductive LEL: > 2500 ppm (no effects on fertility, length of gestation,, or growth and development or survival of offspring were observed.	410301-20	Minimum
84-2	Mutagenicity Ames test	Salmonella sp.	-	0.1-10.0 mg/plate (Tech. 83% purity)	Negative for reverse mutation in salmonella exposed to cytotoxic levels	410301-22	Acceptab.
84-2	"	Salmonella sp. and E. Coli	-	3-10000 µg/plate (Tech. 83.3% purity)	Negative for reverse gene mutation in Salmonella and E. Coli up to cytotoxic doses with and without activation.	410301-23	Acceptab.
84-2	Chromosomal Aberration Rat bone marrow	Rat (S-D)	Oral (Gavage)	150-1500 mg/kg, (Tech. 83.3% purity)	Negative for inducing chromosomal aberrations	410301-25	Acceptab.

Table 2. Toxicity Summary of Clethodim (Continued).

Guideline	Study Type	Species	Route	Dose	Results	MRID No.	CORE Grade
84-2	Chromosome Aberrations (In vitro)	CHO cells	-	0.03-1.2 µl/ml. (Tech. 81.4% purity)	Positive for increased structural chromosome aberrations (without metabolic activation), negative with metabolic activation at doses near the limit of solubility and/or cytotoxicity.	410301-28	Acceptable
"	"	"	-	0.03-1.0 µl/ml. Cryolite-purified material. (Tech. 96.1% purity)	Negative for inducing chromosome aberrations in both nonactivated and activated CHO cells exposed up to levels of insolubility.	410301-29	Acceptable
"	DNA damage/repair	Hepatocytes from B6C3F1 ♂ mice	Oral (Gavage)	100-5000 mg/kg	Negative for inducing unscheduled DNA synthesis (UDS) in hepatocytes drawn from mice treated orally up to toxic levels of 5000 mg/kg.	410301-24	Acceptable
85-1	Metabolism	Rat (S-D)	Oral (Gavage)	4.5 or 450 mg/kg (single dose) [cyclohexenone-4,6-^{14}C]-clethodim, >96% radiochemical purity. Non-radiolabeled, Tech. was 99% pure.	Compound is readily absorbed orally and eliminated (87-92% recovered in urine and 9-17% in feces after 7 days); G.I. absorption estimated at 89-96% (both sexes, no dose or treatment-related differences). No evidence of bioaccumulation, the adrenals had the highest concentration at 7 days post-dosing (0.07-0.22 ppm for low dose; and 5.4-13 ppm for high dose). Extensively metabolized with <1% eliminated as unchanged parent. Main metabolite id clethodim sulfoxide (48-63% of the radiolabel at 48 hours).	410301-32	Acceptable
85-2	Dermal absorption	Rat (S-D)	Dermal	Doses of 0.05, 0.5, or 5.0 mg/rat to 10 cm^2 area. [Cyclohexenone-4,6-^{14}C]-clethodim, >98.7% radiochemical purity.	At 0.05 mg/rat: 8.5, 28.4 and 42.8% absorbed after 2, 10, and 24 hours, respectively. At 0.5 mg/rat: 4.4, 14.4 and 34.1% absorbed after 2, 10, and 24 hours, respectively. At 5.0 mg/rat: 2.0, 6.7 and 29.7% absorbed after 2, 10, and 24 hours, respectively.	410302-02	Acceptable