(3-20-96)

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

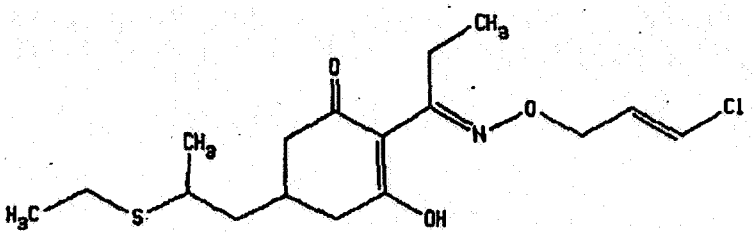
TOXICOLOGY ENDPOINT SELECTION DOCUMENT

013139

Chemical Name: Clethodim; Select®; 2-[1-[[(E-3-chloro-2-propenyl)oxy]imino]propyl]-5-[2-(ethylthio)propyl]-3-hydroxy-2-cyclohexen-1-one.

PC Code: 121011

Structure:



The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Clethodim at a meeting held on February 6, 1996. Based upon a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

TOXICOLOGIST: Alberto Protzel Date: 3/20/96

SECTION HEAD: James N. Rowe Date: 3/21/96

BRANCH CHIEF: Stephanie R. Irene Date: 3-21-96

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DERMAL ABSORPTION DATA

Study Selected: Guideline No. 85-3. Dermal penetration Study. The percutaneous absorption of ^{14}C-SELECT 2.0 EC (RE-45601) in male rats. Study No. S-2961. December 18, 1987.

MRID No.: 410302-02

% absorbed: Dermal absorption is 30% at 10 hours of exposure, following dermal application of clethodim at 0.05 mg/rat to a 10 cm^2 area.

Summary: In a dermal penetration study, 12 male Sprague-Dawley [Crl:CD (SD)Br] rats / dose group received [^{14}C]clethodim by the dermal route at levels of 0.05, 0.50, or 5.0 mg/rat onto an area of 10 cm^2 as a solution of SELECT 2EC in deionized water. Four rats/per dose level/time point were sacrificed for assessment of dermal absorption after 2, 10, and 24 hours after application. The following percent absorption values were observed:

	0.05 mg/rat			0.5 mg/rat			5.0 mg/rat		
Exposure Time (hrs)	On/In skin	Skin Wash	Absorbed	On/In skin	Skin wash	Absorbed	On/In skin	Skin wash	Absorbed
2	8.1	74.4	8.5	11.2	70,7	4.4	4.7	79.7	2.0
10	13.6	50.6	28.4[1]	14.5	59.3	14.4	8.0	69.8	6.7
24	13.4	40.5	42.8	6.6	47.0	34.1	4.2	65.2	29.7

[1] This value (rounded to 30%) was selected for risk assessment.

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - None.

MRID No.: None

Summary: None.

Endpoint and dose for use in risk assessment: Not applicable.

Comments about study and/or endpoint: A developmental toxicity study in rats (MRID No. 410301-16) established a developmental LOEL of 350 mg/kg/day based on reduction in fetal weights and increases in the incidence of skeletal anomalies. These effects were not determined to be the result of acute exposure. Maternal toxicity was limited to reduction in body weight gain and excessive salivation; NOEL = 100 mg/kg/day and the LOEL = 350

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mg/kg/day. This study was supported by a developmental study in rabbits (MRID No. 410301-15) which also established a LOEL of > 350 mg/kg/day (HDT) for developmental toxicity. Therefore, no appropriate dose or end-point was identified.

This risk assessment is not required.

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SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Study Selected - None.

MRID No.: None.

Summary: None.

Endpoint and dose for use in risk assessment: Not applicable.

Comments about study and/or endpoint: In a 21-day dermal toxicity study in Sprague-Dawley rats of both sexes (MRID No. 410301-09), the systemic NOEL was 100 mg/kg/day and the LOEL was 1000 mg/kg/day. Technical clethodim is placed in TOX. CAT. II for primary dermal irritation. However, in the rat 21-day dermal toxicity study, the LOEL for skin irritation was 10 mg/kg/day and no NOEL for dermal irritation was established. Therefore, the TESC recommended that for occupational or residential exposure concerns, the chemical should be placed in TOX. CAT. I. **No appropriate dose or end-point was identified for short-term occupational or residential exposure.**

This risk assessment is not required.

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INHALATION EXPOSURE:

Study Selected - None. **No appropriate dose or end-point was identified.**

MRID No.: None.

Summary: None.

Endpoint and dose for use in risk assessment: Not applicable.

Comments about study and/or endpoint: None.

This risk assessment is not required. Based on the LC50 of > 3.9 mg/L (Tox. Cat. III) inhalation exposure is not a concern.

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INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected: None.

MRID No.: None.

Summary: None.

Endpoint and dose for use in risk assessment: Not applicable.

Comments about study and/or endpoint: None.

This risk assessment is not required (No appropriate dose or end-point was identified).

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INHALATION EXPOSURE:

Study Selected: None.

MRID No.: None.

Summary: None.

Endpoint and dose for use in risk assessment: Not applicable.

Comments about study and/or endpoint: None.

This risk assessment is not required. Based on the LC50 of > 3.9 mg/L (Tox. Cat. III) inhalation exposure is not a concern.

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CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 83-1b, chronic dog toxicity study

MRID No.: 410301-11

Summary: In a chronic oral study (MRID 410301-11), Clethodim technical (RE-45601 Technical, 83.3%; Batch No. SX-1688) was administered orally via gelatin capsules to 6 male and 6 female Beagle dogs/dose group at doses of 0, 1, 75 or 300 mg/kg/day for 52 consecutive weeks. Amounts administered were adjusted weekly based on individual body weights. Absolute and relative (to body weight or brain weight) liver weights were significantly increased in male and female dogs receiving 300 mg/kg/day. Histological changes in the liver (centrilobular to midzonal hepatocellular enlargement and increased pigment deposition) correlated with the increased liver weights at 300 mg/kg/day. Although absolute and relative liver weights were also increased in females receiving 75 mg/kg/day, there were no correlative histopathological changes in the livers at this dose. In addition, mean thyroid/parathyroid weights (absolute and relative to body weight and brain weight) were significantly increased in males administered the high dose. The toxicological significance of the increased thyroid/parathyroid weights is equivocal, since no corresponding lesions were found and a similar weight increase was not detected in females. Platelet, leukocyte, and corrected leucocyte counts were significantly increased and apparently treatment-related, in females receiving 75 mg/kg/day. In addition, glucose levels were decreased in females treated with 75 mg/kg/day. In the high-dose animals, statistically significant decreases from control values were noted for mean erythrocyte values (both sexes), hemoglobin levels (females only), hematocrit values (females only), and glucose levels (both sexes). Increases in total cholesterol levels, alanine aminotransferase activity, alkaline phosphatase activity, and triglyceride levels were seen in both sexes following oral treatment with 300 mg/kg/day.

The LOEL is 75 mg/kg/day based on increased absolute and relative liver weights in females, and alterations in hematology and clinical chemistry parameters males and females. The NOEL is 1 mg/kg/day.

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Endpoint and dose for use in risk assessment: 1 mg/kg/day (The NOEL). The LOEL (75 mg/kg/day) was based on increased absolute and relative liver weights and alterations in hematology (increases in platelets and WBC) and clinical chemistry parameters (decreased glucose).

Comments about study and/or endpoint: This dose/study was used to establish the RfD. It should be noted, however, that because of the wide difference between the low-(1 mg/kg/day) and the mid-(75 mg/kg/day) doses the LOEL established (which is the mid-dose) could be lower. Therefore, if chronic exposure is a concern, the toxicology branch should be consulted for appropriate criteria that will be used in risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE:

Study Selected - None.

MRID No.: None.

Summary: None.

Endpoint and dose for use in risk assessment: Not Applicable.

Comments about study and/or endpoint: None.

This risk assessment is not required. Based on the LC50 of > 3.9 mg/L (Tox. Cat. III) inhalation exposure is not a concern.

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CANCER CLASSIFICATION AND BASIS:

Q_1* = Not Applicable. Treatment-related increases in tumor incidence were not 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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RfD AND BASIS: 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. The LOEL is 75 mg/kg/day based on increased absolute and relative liver weights in females, and alterations in hematology and clinical chemistry parameters males and females.

NOEL for critical study: 1 mg/kg/day

Study Type - Guideline No.: 83-1b, chronic dog toxicity study

MRID: 410301-11

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of Clethodim

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral (Rat)	409745-07	LD_{50} = 1.63 g/kg (♂); 1.36 g/kg (♀)	3
81-2	Acute Dermal (Rabbit)	409745-10	LD_{50} > 5.0 g/kg (♂ & ♀)	4
81-3	Acute Inhalation (Rat)	409745-12	LC_{50} > 3.9 mg/L	3
81-4	Primary Eye Irritation (Rabbit)	409745-14	Irritation cleared within 7 days or less	3
81-5	Primary Skin Irritation (Rabbit)	409745-16	Severe erythema observed at 72 hours	2*
81-6	Dermal Sensitization Guinea pig	409745-18	Not a sensitizer	-
81-8	Acute Neurotoxicity	-	Not required	-

* In the rat 21-day dermal toxicity study (conducted at doses of 0, 10, 100, or 1000 mg/kg/day), the LOEL for skin irritation was 10 mg/kg/day and no NOEL for dermal irritation was established. Thus, the TESC recommended that for occupational or residential exposure concerns, the chemical should be placed in TOX. CAT. I.

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