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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Memorandum

Subject: Trifluralin: Petition for tolerance of residues in/on crambe seed and crambe straw

To: Hoyt Jamerson/Lawrence Fried (PM-43)
OPP/Registration Division (H7505C)

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Chemical: Trifluralin
Tox Chem No.: 889
EPA Chem. Code: 036101
HED Project No.: 2-0460
EPA Reg. No.: 62719-116
Case No.: 282948

Action requested: The registrant, has requested a permanent tolerance for residues of trifluralin in/on crambe seed and crambe straw. The proposed tolerance for the residues of active ingredient in/on the raw agricultural products, crambe seed and crambe straw, is 0.05 ppm.

Data Considered:

Study	Results	
Acute studies		
Acute oral (rat)	LD_{50} > 5 g/kg	Cat. IV
Acute dermal (rabbit)	LD_{50} > 2 g/kg	Cat. III
Acute inhalation (rat)	LC_{50} > 4660 mg/m^3	Cat. III
Primary eye irritation (rabbit)	Conjunctival irritation, reversible within 4 days	Cat. III
Primary dermal irritation (rabbit)	No irritation	Cat. IV
Dermal sensitization (guinea pig)	Sensitizer	
Acute delayed neurotoxicity (hen)	NOEL > 5000 mg/kg	

Study	Results
Subchronic	
90-Day feeding (rat)	NOEL = 0.005% (50 ppm)
90-Day feeding (mouse)	NOEL < 400 ppm
30-Day dermal (rabbit)	NOEL = 200 mg/kg
Chronic	
1-Year feeding (dog)[a]	NOEL = 30 ppm (0.75 mg/kg/day)
2-Year feeding (rat)	Systemic NOEL = 200 ppm; no evidence of carcinogenic response at HDT (3200 ppm)
2-Year feeding (mouse)	Systemic NOEL = 50 ppm; no evidence of carcinogenic response at HDT (800 ppm)
Reproduction/Developmental	
Developmental toxicity (rat)	Systemic NOEL = 225 mg/kg/day Developmental NOEL = 475 mg/kg/day
Developmental toxicity (rabbit)	Systemic NOEL = 100 mg/kg/day Developmental NOEL = 225 mg/kg/day
2-Generation reproduction (rat)	Systemic NOEL = 200 ppm; Reproductive NOEL > 2000 ppm
Mutagenicity	
Gene mutation (Ames; forward mutation)	Negative
Chromosomal aberration (dominant lethal: rat and mouse; micronucleus)	Negative
Other mutagenicity tests (SCE))	Negative
Metabolism	
Metabolism (rat)	Not readily absorbed from GI tract; near complete elimination within 3 days of dosing (approx. 80% in feces)

a The study from which the RfD was derived.

Data Currently Lacking:
Due to the high likelihood of dermal exposure to humans in the process of application, **a dermal absorption study is required.** A dermal absorption study in rhesus monkeys was reviewed but judged to be unacceptable and inadequate for use in risk assessment.

Tolerance Summary:
The Science Analysis and Coordination Branch (SACB) will formulate the tolerance summary for trifluralin. Published tolerances to trifluralin are found in 40 CFR 180.207.

Acceptable Daily Intake (ADI) or Reference Dose (RfD):
The RfD for trifluralin is 0.0075 mg/kg/day, which is derived from the 1-year feeding study in dogs with a NOEL of 0.75 mg/kg/day (30 ppm), applying a safety factor of 100. The total amount of tolerances granted should not exceed 100% of the RfD.

Effect of Tolerance on RfD:
The Dietary Risk Evaluation System (DRES) of SACB will calculate the effect of granting this tolerance on the RfD.

Pending Regulatory Actions:
There are no known regulatory actions pending against this chemical.

Discussion and Recommendation:
In a 2-year feeding study (Eli Lilly, 1980), Fischer 344 rats received 813, 3250, and 6500 ppm of trifluralin. Study results indicated an increase in incidence of malignant or combined malignant-and-benign tumors of the renal pelvis and benign tumors of the urinary bladder and in thyroid tumors. Based upon these data, the Carcinogenicity Peer Review Committee concluded that the data available for trifluralin provides limited evidence for oncogenicity in male and female rats. Trifluralin is categorized as Category C carcinogen (possible human carcinogen with limited evidence of carcinogenicity in animals in the absence of human data) with a Q_1^* of 7.7×10^{-3}.

Toxicology Branch II (the Herbicide, Fungicide, and Antimicrobial Support Branch) defers to DRES and SACB for the effect of granting this tolerance on the RfD for Trifluralin and to Dietary Exposure Branch for validity of the residue chemistry data. If granting this use does not result in residue levels exceeding 100% of the RfD, the cancer risk is acceptable under the current EPA guidelines of less than 1 in 1×10^{-6}, and the proposed residue levels are supported by acceptable residue chemistry data, Toxicology Branch II does not object to granting this request.