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

JUN 23 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of Trifluralin [trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine]
CASRN. 1582-09-8
EPA Chem. Code: 036101
Caswell No. 889

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Rich J. Whitey
6/22/94
for

The Health Effects Division RfD/Peer Review Committee met on June 02, 1994 to discuss and evaluate the toxicology data submitted in support of Trifluralin re-registration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review included data evaluation records (DER's) for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), two chronic toxicity studies in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), two multi-generation reproductive toxicity studies in rats (83-4), subchronic toxicity studies in rats (82-1a) and dogs (83-1B), and subchronic toxicity studies in rats mice and dogs (82-1a and -1b).

The Committee considered the chronic toxicity studies in rats (83-1a, MRID No. 00153496, 00162456, 00162457, 00162458) and dogs (83-1b, MRID No. 42447001; 00151908) to be acceptable and the data evaluation records (HED Doc. 006355; 010237; 005898) to be adequate.

The carcinogenicity issue has already been discussed by the HED-Carcinogenicity Peer Review Committee (CPRC). The chemical has been classified as a "Group C", possible human carcinogen, based on increased incidences of combined malignant and benign tumors of the renal pelvis and benign tumors of the urinary bladder. Quantitation of human risk using a low dose model (Q_1) extrapolation was recommended (report dated April 4, 1986).



The Committee considered the reproductive toxicity studies in rats (83-4, MRID No. 00162543; 00151903) and the data evaluation records (HED Doc. No. 005553; 005898) to be adequate. The Committee noted that the body weight decreases observed at the high dose levels were generally accompanied by decreases in food consumption, and absence of clinical signs suggesting that palatability may be a factor in the animal response. The Committee further noticed that, although only relative kidney weights are increased in the first study, there are some indications from other studies, e.g. chronic study in rats, that the kidney is a target organ for this chemical. Pup weights were significantly decreased during the latter portions of lactation, and this effect should be classified as reproductive/systemic effect, for which a NOEL was considered to be 200 ppm. The Committee recommended that the two reproductive toxicity studies should be viewed together. There was no evidence, based on the available data, to suggest that the treatment was associated with significant reproductive toxicity under the testing conditions.

The Committee considered the developmental toxicity study in rats (MRID No. 00152419) to be acceptable and the data evaluation record (HED Doc. No. 005899) to be adequate. The Committee recommended upgrading this study to Core-minimum data. The Committee considered the data evaluation record (HED Doc. No. 004419) for the other developmental toxicity study in rats (83-1a, MRID No. 00151899) to be inadequate. The developmental toxicity studies in rabbits (83-3b, MRID No. 00151900; 0015241) and the data evaluation records (HED Doc. No. 005898; 004419) were considered to be adequate. The Committee recommended that the two studies be viewed together. The NOEL and LOEL were discussed in the second developmental toxicity study in rabbits (MRID No. 0015241) and were considered to be 100 and 225 mg/kg/day, respectively, for maternal toxicity (manifested as reduced food consumption and increased abortion), and 225 and 500 mg/kg/day for developmental toxicity (manifested as increased resorptions, reduced litter size and decreased fetal weights). Overall, there was no evidence, based on the available data, to suggest that the treatment was associated with significant developmental toxicity under the testing conditions.

The RfD for this chemical was first assessed by the Agency RfD Work Group on May 30, 1986 and then reassessed by the HED-RfD Committee on January 16, 1987 and once again on March 30, 1989 and then submitted to the Agency RfD Work Group for verification on February 18, 1987 and once again on April 20, 1989. At that time, the RfD was based on a one-year feeding study in dogs (1984, MRID No. 00151908) with a NOEL of 0.75 mg/kg/day. Increased liver weight and methemoglobin was observed at the next higher dose of 3.75 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.0075 mg/kg/day.

Subsequently, a new one-year feeding study in dogs (1992, MRID No. 42447001) was submitted to the Agency's Office of Pesticide Programs indicating a slightly higher NOEL (2.4 mg/kg/day). The Committee determined that the RfD for this chemical should be established based on a the new long-term feeding study in dogs with a NOEL of 2.4 mg/kg/day. Decreased body weight of females, increased absolute and relative liver weights in males and females, increased methemoglobin in males and females and cholesterol and triglycerides levels in males were observed at the next higher dose level of 40 mg/kg/day. An uncertainty factor of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.024 mg/kg/day.

It should be noted that this chemical has not been reviewed by the joint meeting of WHO/FAO on pesticide residues (JMPR).

B. Material Reviewed

Material available for review included data evaluation records (DER's) for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), two chronic toxicity studies in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b), two multi-generation reproductive toxicity studies in rats (83-4), subchronic toxicity studies in rats (82-1a) and dogs (83-1B), and subchronic toxicity studies in rats mice and dogs (82-1a and -1b).

1. Donaubauer; Schutz; Weigand (1985). Trifluralin (code: HOE 38474 OH AT208) chronic feeding carcinogenicity study in rats (28-month feeding study). MRID No. 00153496, 00162456, 00162457, 00162458, HED Doc. No. 006355. Classification: Guideline data. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
2. Adams, E. R. et al. (1992). A chronic toxicity study of trifluralin (compound 036352) administered orally to beagle dogs for one year. MRID No. 42447001, HED Doc. No. 010237. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
3. Bathe, R. (1984). Twelve-month oral toxicity (feeding) study with trifluralin, substance technical grade, (code Hoe 38474 OH AT210) in beagle dogs. MRID No. 00151908, HED Doc. No. 005898. Classification: Guideline data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
4. Markham, J. K. (1986). A one-year two generation reproduction study in CD rats maintained on diets containing trifluralin. MRID No. 00162543, HED Doc. No. 005553. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
5. Becker, H., et al (1984). Multiple generation study with trifluralin substance technical grade (code: HOE 38474 OH AT210) in the rat. MRID No.-00151903, HED Doc. No. 005898. Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.
6. Baeder; Mayer (1983). HOE 38474-active ingredient, testing for embryotoxicity in Wistar rats following oral administration. MRID No. 00151899, 00159620, HED Doc. No. 005898. Classification: Core-supplementary data as upgraded by the RfD Peer Review Committee. This study satisfies data requirement 83-3a of Subpart

F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

7. Markham, J. K. and Byrd R. D. (1984). A teratology study of trifluralin (EL-152, compound 36352) administered orally to Charles River CD rats. MRID No. 00152419, HED Doc. No. 004419. Classification: Core-supplementary data as downgraded by the RfD Peer Review Committee. This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

8 Becker, H. (1984). Embryotoxicity study with trifluralin-substance technical grade (code: HOE 038474 OH ZD99 0002) in the rabbit (oral administration). MRID No. 00151900, HED Doc. No. 005898. Classification: Core-supplementary data. The study should be considered adequate when viewed together with another study cited below (MRID No. 0015241).

9. Markham, J. K. and Byrd R. D. (1984). A teratology study (II) of trifluralin (EL-152, compound 36352) administered orally to Dutch Belted rabbits. MRID No. 00152419, HED Doc. No. 004419. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.