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

JUL 7 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Fenoxycarb [Ethyl(2-{4-phenoxyphenoxy} ethyl) carbamate].

CASRN. 72490-01-8
EPA Chem. Code: 125301
Caswell No. 652C

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (H7509C)

TO: Richard Mountfort, PM 10
Fungicide-Herbicide Branch
Registration Division (7505C)

Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (7508W)

The Health Effects Division RfD/Peer Review Committee met on March 24, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Fenoxycarb re-registration and to re-assess the Reference Dose (RfD) for this chemical.

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

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 00146140, 40376901, 42343803, 42343804) and dogs (83-1b, MRID No. 42355601) to be acceptable and the data evaluation records (HED Doc. No. 008101, 010721; 010721) to be adequate. The Committee recommended to revise the no-observable effect level (NOEL) in the dog chronic study from 25 mg/kg/day, the lowest dose level tested, to 80 mg/kg/day, the middle dose level tested based on decreased body weight gain and decreased mean organ weight (brain, and liver in males). The Committee discounted the

weight changes in adrenal glands in male and female dogs since it was not accompanied by other supporting changes. The Committee noticed that the toxicology-one liner has not been revised to reflect upgrading of the rat chronic study.

The RfD/Peer Review Committee did not discuss the carcinogenicity phase of the rat study (83-2a, MRID No. 00146140, 40376901, 42343803, 42343804) and the carcinogenicity study in mice (83-2b, MRID No. 40376902, 40972701, 4234806) in detail. However, the Committee noted that the chemical was adequately tested in rats, but not in either sex of the mouse. The Committee further noted that even at these inadequate dose levels, the treatment appeared to alter the spontaneous tumor profile in male mice. The carcinogenicity issue has already been referred to the Health Effects Division Carcinogenicity Peer Review Committee (HED-CPRC) for weight of the evidence evaluation by the respective toxicology branch.

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 40376903, 42343811, 42343812) to be acceptable and the data evaluation record (HED Doc. No. 008101, 010721) to be adequate. Statistically significant body weight gain reduction in F0 was observed at all dose levels. However, the decrease at the lowest dose level was considered biologically insignificant, and therefore, was considered to be the no-observable effect level (NOEL) for maternal toxicity. The reproductive/systemic toxicity NOEL was considered to be the middle dose level. The Committee considered the developmental toxicity studies in rats (83-3a, MRID No. 00131346) and rabbits (83-3b, MRID No. 00153125) to be acceptable and the data evaluation record (HED Doc. No. 004178; 004319) to be adequate. The Committee recommended revising the NOEL for developmental toxicity in the rat study from 150 mg/kg/day to 500 mg/kg/day, the highest dose tested. The Committee determined that the incidence of resorptions observed at the highest dose level were not biologically significant and might not be treatment-related. In summary, there was no evidence, based on the available data, that Fenoxycarb was associated with significant developmental or reproductive toxicity under the testing conditions.

The Committee recommended that an RfD for this chemical be established based on a two-year feeding toxicity study in rats with a no-observable effect level (NOEL) of 8.1 mg/kg/day. Liver histopathological changes (including centrilobular hypertrophy, focal necrosis, focal fibrosis, focal cystic degeneration, basophilic foci and pigmented macrophages) and increased liver enzymes including SGOT, SGPT and alkaline phosphatase were observed at 200 ppm (24.7 and 33.1 mg/kg/day in males and females, respectively). An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.08 mg/kg/day.

It should be noted that this chemical has not been reviewed by the World Health Organization (WHO).

A. Individuals in Attendance

1. Peer Review Committee Members and Associates Present (Signature indicates concurrence with the peer review unless otherwise stated).

William Burnam

Reto Engler

Karl Baetcke

Marcia Van Gemert

Henry Spencer

William Sette

Roger Gardner

Stephen Dapson

George Ghali

Rick Whiting

2. Peer Review Members and Associates in Absentia (committee members and associates who were unable to attend the discussion; signatures (optional) indicate concurrence with the overall conclusions of the committee).

James Rowe

3. Scientific Reviewer (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Marion Copley

William Greear

4. Others:

M. Morrow, S. Williams-Fay, J. Redden, H. Pettigrew of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Marion Copley
William Greear
James Kariya
Flora Chow
RfD and Caswell Files

B. Material Reviewed

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a carcinogenicity study in mice (83-2b), a chronic toxicity study in dogs (83-1b), developmental toxicity studies in rats and rabbits (83-3a and -3b) a multi-generation reproductive toxicity study in rats (83-4), subchronic toxicity studies in rats, mouse and dogs (82-1a and -1b), and a 21-day dermal toxicity study in rats. The Committee focused the discussion on the following studies:

1. Goodyer, M. J., Hardisty, J., Stevens, T. J., Skripsky, T, and Stevens, J. (1986). Ro 13-5223/000: 104-week oral (dietary administration) carcinogenicity and toxicity in the rat with a 52-week interim kill. MRID No. 00146140, 40376901, 42343603, 42343804, HED Doc. No. 008101, 010721. Classification: Core-minimum data. This study satisfies data requirement 83-1a and -1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/oncogenicity in rats.

2. Howroyd, P. C. et al. (1987). Toxicology evaluation of Fenoxycarb (CGA-114597 Technical). MRID No. 40376902, 40972701, 4234806, 42343807, 42343808, 42343809, HED Doc. No. 008101, 010721. Classification: Core-supplementary data. Classification: Core-supplementary data. The adequacy of this study will be determined by the HED-CPRC.

3. Keller-Rupp, P. (1988). Chronic toxicity study following oral administration of Ro-5223/000 (fenoxycarb), an insect growth regulator, to dogs for period of one year. MRID No. 42355601, HED Doc. No. 010271. Classification: Core-Guideline data. This study satisfies data requirement 83-1b and -1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity in dogs.

4. Eckhardt, K. and Karrasch, S. (1983). Embryotoxicity study in rats with oral administration of Ro 13-5223/000: Segment II-teratological study with postnatal evaluations. MRID No. 00131346, HED Doc. No. 004178. Classification: Core-minimum data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity in rats.

5. Hummler, H. and McKinney, B. (1984). Embryotoxicity study in rabbits with oral administration of Ro 13-5223/000. MRID No. 00153125, HED Doc. No. 004319. Classification: Core-minimum data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity in rabbits.

6. Barker, L. and Goodyer, M. (1986). Ro 13-5223: 2-Generation oral (dietary administration) reproduction study in the rat. MRID No. 40376903, 42343811, 42343812, HED Doc. No. 008101, 010721.

Classification: Core-minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity in rats.