



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

JUL 7 1994

FILE COPY

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Tetrachlorovinphos (Gardona)
[2-chloro-1(2,4,5-trichlorophenyl)-vinyl dimethyl
phosphate].

CASRN. 961-11-5
EPA Chem. Code: 083701
Caswell No. 217A

FROM: George Z. Ghali, Ph.D.
Manager, RfD/Quality Assurance Peer Review
Health Effects Division (7509C)

Rich J. Whaley
7/7/94
for

TO: George LaRocca, PM 13
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 May 5, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Tetrachlorovinphos re-registration and to re-assess the Reference Dose (RfD) for this chemical.

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

The Committee considered the chronic toxicity study in rats (83-1a, MRID No. 42980901) and dogs (83-1b, MRID No. 42679401, 00165248) to be acceptable and the data evaluation records (HED Doc. 010884; 010678) to be adequate. The older chronic toxicity study in rats (MRID No. 00077802, 00112525) was not discussed in the current meeting.

The reproductive toxicity study in rats (83-4, MRID No. 00077802) and the developmental toxicity studies in rats (83-1a,



Recycled/Recyclable
Printed with Soy/Canola Ink on paper that
contains at least 50% recycled fiber

MRID No. 42520101; 40152701) and rabbits (83-3b, MRID No. 00127831) were considered to be acceptable and the data evaluation records (HED Doc. No. 009792; 010761; 008124; 007181) were considered to be adequate. The Committee considered effects observed at the highest dose tested in the more recent reproductive toxicity study (MRID No. 42054301) to be marginal. This recent study should supersede the older reproductive toxicity study (MRID No. 00077802). The Committee considered the maternal and developmental toxicity NOEL to be 375 mg/kg/day, the lowest dose tested. There was no evidence, based on the available data, that tetrachlorovinphos was associated with significant reproductive or developmental toxicity under the testing conditions.

The carcinogenicity issue had already been discussed by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC) in their meeting of December 2, 1988. At that time, the chemical was classified by the CPRC as a "Group C", possible human carcinogen based on increased incidences of liver tumor. Assessment of human risk by extrapolation of a low dose model (Q1*) was also recommended. It should be noted that the evidence on carcinogenicity in the rat study was considered equivocal. A new rat study was conducted to alleviate concerns expressed by the CPRC Committee regarding possible carcinogenic response in the old rat study. In this study incidences of C-cell adenomas of the thyroid showed a significant dose-related trend in females ($P=0.013$), and there was high incidence of thyroid C-cell hyperplasia in both males and females. Cortical adenomas of the adrenal also showed a significant dose-related trend in females ($P=.017$).

In the meeting of May 5, 1994, the RfD/Peer Review Committee determined that the new rat study provided suggestive evidence of possible carcinogenic response that might impact the current classification of this chemical. In this study, incidence of C-cell adenomas of thyroid in males were increased. There was apparently no histological examination of thyroids from animals in the low- and mid-dose levels. Males of the high dose group had higher incidence of pheochromocytoma of the adrenal glands as compared to their controls. This study was, tentatively, classified as Core-supplementary data. Because of the suggestive nature of these findings, the Committee recommended referral of the carcinogenicity issue to the CPRC for reconsideration of the weight of the evidence in light of the findings of the new rat study.

The RfD for this chemical was first determined by the Health Effects Division - RfD Committee on August 4, 1986 and verified by the Agency RfD Work Group on September 2, 1986. At that time, the RfD was based on a chronic feeding study in dogs with a NOEL of 3.13 mg/kg/day. Decreased plasma cholinesterase activity and body weight gain were observed at 50 mg/kg/day and higher dose levels. An uncertainty factor (UF) of 100 to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.03 mg/kg/day.

In the meeting of May 5, 1994, a new chronic toxicity study in dogs was available demonstrating a NOEL of 6.25 mg/kg/day, i.e. higher than the NOEL in the older dog study, but slightly lower than the NOEL established in the new rat study. The Committee recommended that the RfD for this chemical be based on the new chronic feeding study in rats with a NOEL of 4.23 mg/kg/day. In this study, liver histological changes and adrenal changes were observed in both males and females at 1000 ppm (43.2 and 62.7 mg/kg/day in males and females, respectively) and higher dose levels. Body weight and plasma cholinesterase depression were observed in females of the 1000 mg/kg/day and higher dose levels. An uncertainty factor (UF) of 100 to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.04 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

W. Burnam

Reto Engler

Reto Engler

Henry Spencer

Henry Spencer

William Sette

William Sette

Roger Gardner

Roger Gardner

James Rowe

James N. Rowe

George Ghali

Richard J. Whiting for

Rick Whiting

Rick J. Whiting

2. Peer Review Committee Members and Associates in absentia
(Signature indicates concurrence with the peer review unless otherwise stated).

Karl Baetcke

Karl A. Baetcke

Marcia Van Gemert

Marcia VanGemert

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

Byron Backus

Byron T. Backus 5-19-94

Clark Swentzel

C. Clark Swentzel 5/17/94

3. Others:

E. Bud, Jane Smith and S. Dapson of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia VanGemert
Clark Swentzel
Byron Backus
James Kariya
Flora Chow
RfD File
Caswell File

B. Material Reviewed

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

1. Mulhern, M., et al. (1993). Tetrachlorovinphos: 104 week dietary combined chronic toxicity/carcinogenicity study in rats. MRID No. 42980901, HED Doc. No. 010884. Classification: Core-minimum data for chronic toxicity, and tentatively, Core supplementary data for carcinogenicity. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats. The carcinogenicity phase will be judged by the CPRC.
2. Tompkins, C. E. (1991). One-year oral (capsule) toxicity study in dogs with Rabon. MRID No. 42679401, HED Doc. No. 010678. Classification: Core-minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in a non-rodent species.
3. Barton, S. J. (1991). Tetrachlorovinphos: two-generation reproduction study in rats. MRID No. 42054301, HED Doc. No. 009792. 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.
4. Ford, W. H., et al. (1987). A teratology study in rats with technical Rabon. MRID No. 40152701, HED Doc. No. 008124. Classification: Core-supplementary data. This study, when viewed together with another study cited below (MRID No. 42520101), satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
5. Hoberman, A. M. (1992). A teratology study in rats with T-142-4. MRID No. 42520101, HED Doc. No. 010761. Classification: Core-supplementary data. This study, when viewed together with another study cited above (MRID No. 40152701), satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
6. Laveglia, J., et al. (1982). A teratology study in rabbits with DS-36779. MRID No. 00127831, HED Doc. No. 007181. 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.