



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

MAY 12 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Chlorothalonil
[tetrachloroisophthalonitrile]

CASRN. 1897-45-6
EPA Chem. Code: 081901
Caswell No. 215B

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

TO: Cynthia Giles-Parker, PM 22
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 January 27, 1994 to discuss and evaluate the existing toxicology data in support of chlorothalonil re-registration and to re-assess the Reference Dose (RfD) for this chemical.

Material available for review included data evaluation records for chronic toxicity/carcinogenicity studies in rats (83-5 or 83-1a and -2a), carcinogenicity studies in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b) and reproductive toxicity studies in rats (83-4) with chlorothalonil, a combined subchronic and one-generation reproduction study in rats and developmental toxicity studies in rats and rabbits with chlorothalonil metabolites, and a tox. one-liner.

The Committee considered the two chronic toxicity studies in rats (83-1a, MRID No. 41250502; 00146945), when combined together, to be acceptable. The Committee recommended that additional data tables be included in the data evaluation records of these studies (HED Doc. No. 008901; 004950). There were two long-term feeding studies in dogs (83-1b, MRID No. 00114034; 00087375) available for review. When viewed together, they demonstrate a no-observable



effect level (NOEL) of 60 ppm. The Committee considered the two studies, together, to be acceptable. However, reevaluation of the more recent dog study (1970, MRID No. 00114034) was recommended because of questionable effects reported at the lowest dose tested, i. e. a NOEL was not established in the study. Kidney effects reported in this dog study should be evaluated in light of other supporting parameters.

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 41706201) to be acceptable and the data evaluation record (HED Doc. No. 010037) to be adequate. The Committee noted that pup weights were decreased only at weaning, i. e. day 21 of lactation. This decrease was only observed in one mating of one generation and was not consistent throughout both matings and both generations. This decrease in pup weight should be considered a systemic effect and not a reproductive effect. The choice of dose levels for this reproductive toxicity study was based on the results of a range finding study (MRID No. 41250504, HED Doc. No. 008901).

The data evaluation record for the developmental toxicity study in rats (MRID No. 00130733, HED Doc. No. 003797, 009445) was considered to be inadequate. The Committee recommended reevaluation of the study and updating of the data evaluation record.

Two developmental toxicity studies in rabbits were available; the first one (MRID No. 41250503, 41679301) was considered to be acceptable and the data evaluation record was considered to be adequate. The second developmental toxicity study in rabbits (MRID No. 00127855) was considered to be inadequate.

Reproductive and developmental toxicity studies with chlorothalonil metabolites [3-carbamyl-2,4,5- trichlorobenzoic acid; 2,4,5-trichloroisophthalic acid; 3-carboxy-2,5,6-trichlorobenzamide; 2,5,6-trichloro-3-carboxybenzamide] including a combined subchronic feeding and one generation reproduction study in rats (MRID No. 41564806, HED Doc. No. 008834), a developmental toxicity study in rats (MRID No. 41564808, HED Doc. 008334) and a developmental toxicity study in rabbits (MRID No. 41564810, HED Doc. No. 008334) were considered by the Committee. The three studies were considered to be acceptable and the data evaluation records were considered to be adequate.

There was no evidence, based on the available data, to suggest that chlorothalonil was associated with significant reproductive or developmental toxicity under the testing conditions.

The carcinogenicity studies in rats and mice (83-2a and -2b) were not discussed by the RfD Committee since the carcinogenicity issue had already been addressed by the Health Effects Division-Carcinogenicity Peer Review Committee (CPRC). The chemical was

increased incidence of malignant and/or combined malignant and benign tumors in both males and females of two animal species including two strains of rats and CD-1 mice (report dated July 20, 1988). The RfD Committee was informed that a potency value Q_1 was calculated for this chemical in 1983. The Committee raised a question as whether data from the more recent carcinogenicity study in rats (1989, MRID No. 41250502) has been subsequently considered in the calculation of this potency slope value.

The RfD for this chemical was assessed by the RfD Committee on March 14, 1986 and verified by the Agency RfD Work Group on April 8, 1986 on the basis of a chronic feeding study in dogs with a NOEL of 1.5 mg/kg/day. Renal tubular vacuolization was observed at the next higher dose level of 3 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.015 mg/kg/day. In the meeting of January 27, 1994, the RfD Committee recommended that the RfD remain unchanged until the reevaluation of the chronic feeding study in dogs is completed.

It should be noted that this chemical has been reviewed and an Acceptable Daily Intake (ADI) of 0.03 mg/kg/day was established by the World Health Organization (WHO) in 1990. The ADI was established by the FAO/WHO joint meeting on pesticide residues (JMPR) based on a dog study with a NOEL of 120 ppm (3mg/kg/day) with a Safety Factor of 100.

A. Individuals in Attendance

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

William Burnam

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

Stephen Dapson

James Rowe

George Ghali

Wm L Burnam

Karl P. Baetcke

Henry Spencer

William Sette

Roger Gardner

Stephen C. Dapson

James N. Rowe

G. Ghali

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

Reto Engler

Marcia Van Gemert

Reto Engler

Marcia Van Gemert

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

Alan Levy

Jess Rowland

Alan C. Levy

Jess Rowland

3. Others:

S. Reilly and B. Backus of HED as an observer.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Jess Rowland
Alan Levy
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), carcinogenicity studies in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b) and reproductive toxicity studies in rats (83-4), and a tox. one-liner.

1. Wilson, N. H. et al. (1989). A tumorigenicity study of technical chlorothalonil in rats. MRID No. 41250502, HED Doc No. 008901. Classification: Core-supplementary data. This study, when viewed together with the other rat study (1985, MRID No. 00146945), satisfies data requirement 83-1a of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
2. Busey, W. D. (1985). Tumorigenicity study in rats. MRID No. 00146945, HED Doc. No. 004950. Classification: Guideline. This study, when viewed together with another rat study (1989, MRID No. 41250502), satisfies data requirement 83-1a of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.
3. Diamond Shamrock Chemical Company (1970). Two year feeding study in dogs. MRID No. 00114034, HED Doc No. 003975. Classification: Guideline. This study, when viewed together with another dog study cited below (1966, MRID No. 00087375), was considered to be acceptable. Reevaluation was recommended.
4. Diamond Alkali Company (1966). Two-year feeding study in dogs. MRID No. 00087375, HED Doc. No. 003975. Classification: Core supplementary. This study, when viewed together with another dog study cited above (MRID No. 00114034), satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.
5. Lucas, F. and Benz, G. (1990). A two-generation reproduction study in the rat. MRID No. 41706201, HED Doc. No. 010037. 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. Mizens, M. et al. (1983). A teratology study in rats with technical chlorothalonil. MRID No. 00129623, 00130733, HED Doc. No. 003797, 009445. Reevaluation was recommended. The study as presented does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.
7. Wilson, N. H. and Killeen, J. C. (1988). A teratology study in rabbits with technical chlorothalonil. MRID No. 41250503, 41679301, HED Doc. No. 008901, 009445. Classification: Guideline. This study satisfies data requirement 83-3b of Subpart F of the

Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

8. Diamond Shamrock Agricultural Chemicals (1975). Developmental toxicity study of chlorothalonil in rabbits. MRID No. 00127855, HED Doc. No. 007775, 007790. Classification: Core-supplementary data. This study does not satisfy data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

9. Serrone, D. M. and Killeen, J. C. (1988). Combined 90-day feeding study and one-generation reproduction study in rats with 3-carboxy-2,5,6-trichlorobenzamide. MRID No. 41564806, HED Doc. No. 008834. Classification: Guideline for subchronic testing, and supplementary for reproductive toxicity testing.

10. Chun, J. S. et al. (1989). A teratology study in rats with 3-carbamyl-2,4,5-trichlorobenzoic acid. MRID No. 41564808, HED Doc. No. 008334. Classification: Guideline data. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity study in rats.

11. Serrone, D. M. and Killeen, J. C. (1989). A teratology study in rabbits with 3-carbamyl-2,4,5-trichlorobenzoic acid. MRID No. 41564810, HED Doc. No. 008334. Classification: Guideline data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity study in rabbits.