

9



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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: *TETRACHLORVINPHOS* Report of the Hazard Identification Assessment Review Committee. (THIRD REPORT)

FROM: Paul Chin *Paul Chin 3/12/02*
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair *Jess Rowland*
and
Elizabeth Doyle, Co-Chair *E. a. Doyle*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Christina Swartz, Risk Assessor
Reregistration Branch I
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PC Code: 083701

On August 10, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of tetrachlorvinphos (TCVP) and selected the toxicity endpoints and doses for risk assessment (Report of the Hazard Identification Assessment Review Committee, August 15, 2000, TXR No. 014293).

On January 24, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data of TCVP because the registrant recently submitted a 21-day oral toxicity study to provide cholinesterase inhibition data for an acute neurotoxicity study. The HIARC considered the results of the 21-day oral study in rats (MRID No. 45570601) for selecting the acute RfD and short-term incidental oral toxicity endpoints and the conclusions drawn at this meeting are presented in this report.



Committee Members in Attendance

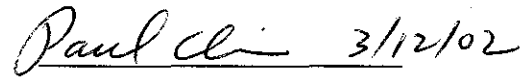
Members present were: Bill Burnam, Jess Rowland, John Liccione, Pamela Hurley, David Nixon, Elizabeth Doyle, Virginia Fornillo, Paula Deschamp, and Jonathan Chen

Member(s) in absentia: Elizabeth Mendez and Ayaad Assaad.

Data evaluation prepared by: Paul Chin, Reregistration Branch I

Also in attendance were: Whang Phang, Mike Metzger, and Susan Hanley, Reregistration Branch I, HED and John Leahy and Demson Fuller, Registration Branch I, SRRD.

Data Evaluation / Report Presentation


Paul Chin
Toxicologist

1. INTRODUCTION

The data base of this chemical was first evaluated by Toxicity Endpoint Selection Committee (TES) in 1994.

On August 1998, the FQPA Safety Factor Committee determined that the 10x FQPA safety should be removed for TCVP (FQPA Safety Factor report dated Aug. 6, 1998).

On August 10, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology database of this chemical selected toxicity endpoints and doses for risk assessment. The HIARC selected an oral NOAEL of 4.2 mg/kg/day from the 90-day feeding study in rats for the acute dietary reference dose because an acute oral toxicity study containing ChE inhibition data was not available. Also, the HIARC committee selected an oral NOAEL of 4.2 mg/kg/day from the 90-day feeding study in rats for short term incidental oral exposure assessment because the 90-day study was considered appropriate for endpoint and duration for the population (toddlers) and exposure period (1-30 days) of concern. The LOAEL was 43.2 mg/kg/day based on reduced plasma and red blood cell (RBC) ChE activity in both sexes (Report of the Hazard Identification Assessment Review Committee, August 15, 2000, TXR No. 014293).

On January 24, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data of TCVP because the registrant recently submitted a 21-day oral toxicity study to provide cholinesterase inhibition data for an acute neurotoxicity study. The HIARC considered the submitted 21-day oral study in rats (MRID No. 45570601) for selecting the acute RfD and short-term incidental oral toxicity endpoints and the conclusions drawn at this meeting are presented in this report.

2. HAZARD IDENTIFICATION

The committee evaluated the data from the 21-day oral toxicity study and decided that the data from the 21-day toxicity study actually confirmed the accuracy of the previously selected toxicity endpoints for both acute and short-term exposures. The reasons are presented in the Comments sections for relevant toxicity points.

2.1 Acute Reference Dose (RfD)

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: Tetrachlorvinphos was given to Sprague Dawley rats in the diet at doses of 0, 100, 2000, or 5000 ppm (0, 6.7, 142, and 375 mg/kg/day for males; 0, 10.0, 197, and 467 mg/kg/day for females) for 13 weeks. The NOAEL was 100 ppm for both sexes. The LOAEL was 2000 ppm based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes. At the highest dose, these effects were seen along with reduced brain cholinesterase activity in females. The two highest doses had reduced body

weights and reduced weight gains, as well as bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females and mid-dose males, and higher adjusted adrenal weights in females. In both sexes at the two highest doses there were thyroid follicular cell hypertrophy and higher adjusted liver weights (GLN 82-1; MRID 43371201).

Dose and Endpoint for Establishing the Acute RfD: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Uncertainty Factor (UF): 100 account for inter-species extrapolation (10 x) and intra-species variability (10 x).

$\text{Acute RfD} = \frac{6.7 \text{ (NOAEL) mg/kg}}{100 \text{ (UF)}} = 0.067 \text{ mg/kg}$

Comments about Study/Endpoint/Uncertainty Factor(s): Previously, the HIARC selected a NOAEL from a 90-day feeding study in rats because the acute neurotoxicity study did not measure ChE inhibition. A 21-day oral toxicity study in rats which was specifically conducted to supplement the acute neurotoxicity study, currently became available. This study is classified as **acceptable/nonguideline**. This study contained plasma, RBC, and brain ChE inhibition data with a single oral dose administration; the data from this study provided additional support for the appropriateness of the previous selection. The reasons are the following:

- a. As shown in Table below, there was statistically significant plasma ChE inhibition in all dose groups in males (19% at the lowest dose, 8 mg/kg). The Committee considered the effect seen at the lowest dose to be biologically relevant because there was a dose-related inhibition in all four dose groups. In addition, there seemed to be a relationship between brain and plasma ChE inhibition; as the plasma ChE inhibition approached approximately 50% (comparing the plasma ChE inhibition value to the pretest value), a statistically significant inhibition in brain ChE was observed. Therefore, a NOAEL could not be established. To use the ChEI data from this study in selecting a dose would require the use of an uncertainty factor (3X) for estimating a NOAEL since a NOAEL was not established for plasma ChEI. In contrast, the previous endpoint/dose was selected based on a true NOAEL (6.7 mg/kg) and provides support for the results of this study (extrapolated NOAEL = $8 \div 3 = 2.7$ mg/kg).
- b. The RBC ChE inhibition measurements in the 21-day toxicity study were judged to be unreliable because reproducibility of ChE activity of the rat RBC samples was poor, and the standard deviations were large for all groups. As reported by Wilson et al. (1996), reduced reproducibility and sensitivity of the ChE values of the rat RBC samples are due to a high tissue blank,

relatively low RBC activity and absorption of hemoglobin at the wavelength of the Ellman's method (Wilson et al, Journal of Toxicology and Environmental Health, 48: 187-195, 1996). Therefore, the HIARC concluded not to use RBC due to lack of confidence in the results.

- c. The toxicity endpoint previously selected from the subchronic rat study was based on the plasma and RBC ChE inhibition.

TABLE . Cholinesterase measurements after a single oral dose of tetrachlorvinphos (U/L) (Compare to pretest values)						
Tissue	0 mg/kg	8 mg/kg	12 mg/kg	20 mg/kg	50 mg/kg	
Male						
Plasma	day -7	687 ± 73.6	683 ± 75.9	688 ± 140.3	682 ± 109.6	700 ± 132.0
	day 0	606 ± 80.5 (12%)*	551** ± 77.3 (19%)	499** ± 86.6 (27%)	393** ± 78.0 (58%)	226** ± 70.4 (68%)
Brain (day 0)	52024 ± 2527.1	51126 ± 1724.6	49065 ± 2641.3 (6)	40611** ± 3439.1 (22)	24032** ± 5877.2 (54)	
Female						
Plasma	day -7	1348 ± 333.4	1267 ± 279.5	1110 ± 157.0	1425 ± 274.0	1277 ± 392.0
	day 0	1579 ± 559.0	1214 ± 280.2 (4%)	935 ± 194.0 (16%)	919** ± 147.6 (35.5%)	516** ± 120.2 (59.6%)
Brain (day 0)	55537 ± 4117.8	54952 ± 4144.0	54575 ± 5665.2	50044 ± 2587.1 (10)	42928** ± 7572.0 (23)	

Data taken from Table 9, pp. 60-62 and 66-68, MRID 45570601.

Significantly different from pretest values: *p ≤ 0.05; **p ≤ 0.01.

^a Number in parentheses is percent inhibition: I = [(control - treated)/control] × 100; calculated by reviewer.

2.2 Chronic Reference Dose (RfD)

Study Selected: 2 year feeding study in rats

Guideline #: 83-1, 83-2

MRID No.: 42980901

Executive Summary: A two-year study with Sprague Dawley rats used doses of 0, 100, 1000, or 2000 ppm (0, 4.23, 43.2, and 88.5 mg/kg/day for males; 0, 5.93, 62.7, and 125.3 mg/kg/day for females) tetrachlorvinphos in the feed. The NOAEL for systemic toxicity was 4.23 mg/kg/day. The LOAEL was 43.2 mg/kg/day based on histological changes in liver and adrenal glands in both sexes, reduced female weight gains, and depression of plasma cholinesterase in females. High dose females also had elevated cholesterol levels. At termination, there were more thyroid C-cell adenomas for male rats in the high dose

than in the controls, but this was not statistically significant (GLN 83-1, 83-2; MRID 42980901).

Dose and Endpoint for Establishing the Chronic RfD: NOAEL of 4.23 mg/kg/day based on histological changes in liver and adrenal glands in both sexes, reduced female weight gains, and depression of plasma cholinesterase in females observed at 43.2 mg/kg/day (LOAEL).

Uncertainty Factor(s): 100 to account for inter-species extrapolation (10X) and intra-species variability (10X).

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is appropriate for the route and duration of exposure and was previously selected by RfD committee.

$\text{Chronic RfD} = \frac{4.23 \text{ (NOAEL) mg/kg}}{100 \text{ (UF)}} = 0.0423 \text{ mg/kg}$

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1 -30 days) Incidental Oral Exposure

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: Tetrachlorvinphos was given to Sprague Dawley rats in the diet at doses of 0, 100, 2000, or 5000 ppm (0, 6.7, 142, and 375 mg/kg/day for males; 0, 10.0, 197, and 467 mg/kg/day for females) for 13 weeks. The NOAEL was 100 ppm for both sexes. The LOAEL was 2000 ppm based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes. At the highest dose, these effects were seen along with reduced brain cholinesterase activity in females. The two highest doses had reduced body weights and reduced weight gains, as well as bilateral basophilic tubules of the kidneys in males, increased fat deposition in the adrenal cortex of females, centrilobular hepatocellular hypertrophy in females and mid-dose males, and higher adjusted adrenal weights in females. In both sexes at the two highest doses there were thyroid follicular cell hypertrophy and higher adjusted liver weights (GLN 82-1; MRID 43371201).

Dose and Endpoint for Establishing the Acute RfD: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Comments about Study/Endpoint: The HIARC reaffirms the use of the 6.7 mg/kg/day selected previously for the same reasons presented under acute RfD.

2.3.2 Intermediate-Term (1-6 Months) Incidental Oral Exposure

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: See Acute RfD.

Dose and Endpoint for Risk Assessment: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This endpoint was selected from the subchronic rat study because route and duration of exposure is appropriate for intermediate term exposure scenario and population (toddlers).

2.3.3 Dermal Absorption

Dermal Absorption Factor: 9.57%

Study selected: A dermal absorption study in rats

Guideline #: 85-2

MRID No.: 42111501

Executive Summary: A study was conducted with male CD rats using doses of 0.01, 0.1, 1 or 5 mg/cm² radiolabeled tetrachlorvinphos, with some of each dose group sacrificed at 0.5, 1, 2, 4, or 10 hours. Additionally, there was a group of animals, sacrificed at 72 hours, in which the skin was washed at 10 hours. The area of the dermal application was washed to recover unabsorbed tetrachlorvinphos. Then, the skin, urine, feces, and carcass were analyzed for percent of total tetrachlorvinphos applied. For the group sacrificed at 10 hours, 84 % of the total tetrachlorvinphos applied (0.1 mg/cm²) was recovered in the wash, and 9.57 % was in the skin, urine, feces, and carcass. The percent absorption increased with duration of exposure and generally decreased with increasing dose. The actual quantity of tetrachlorvinphos absorbed increased with increasing dose (GLN 85-2; MRID 42111501).

Comments about Dermal Absorption: none

2.3.4 Short-Term Dermal (1 day - 1 month) Exposure

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: See Acute RfD.

Dose and Endpoint for Risk Assessment: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Comments about Study/Endpoint: A 21-day dermal study in rats (MRID No.: 41342001) is available and would be most appropriate for selecting short- and intermediate-term dermal toxicity endpoints. However, the HIARC, after careful review of the ChEI data, determined that this study is not adequate for regulatory purpose because of the low confidence in the study results with regard to ChE data. The deficiencies in the ChEI data of concern are as follows:

- 1) All dose groups contained only 5 animals/group. Particularly for low dose female rats, only 3 samples were available for analysis. Therefore, the statistical analysis based on such a small sample size may not be reliable.
- 2) The standard deviations were large in plasma ChE values of all groups.
- 3) Low-dose female rats had higher cholinesterase values than controls suggesting a variable dose-response.

Based on these concerns, the HIARC recommended that this study be classified as **unacceptable** and not be used for endpoint selection.

Since an oral NOAEL was selected, a dermal absorption factor of 9.57% should be used for route-to-route extrapolation.

2.3.5 Intermediate-Term Dermal (1-6 Months) Exposure

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: See Acute RfD.

Dose and Endpoint for Establishing the Acute RfD: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: This study is appropriate for the duration of exposure of concern (1 to 6 months).

2.3.6 Long-term Dermal (longer than 6 Months) Exposure

The current use pattern does not indicate a concern for Long-Term exposure or risk.

2.3.7 Short-Term Inhalation (1 day - 1 month) Exposure

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: See Acute RfD.

Dose and Endpoint for Risk Assessment: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This study is appropriate for the duration of exposure of concern (1 day to 1 month). Since an oral NOAEL was selected, an inhalation absorption factor of 100% should be used for route-to-route extrapolation.

2.3.8 Intermediate-Term Inhalation (1-6 Months) Exposure

Study Selected: Subchronic feeding in rats

Guideline #: 82-1a

MRID No.: 43371201

Executive Summary: See Acute RfD.

Dose and Endpoint for Establishing the Acute RfD: NOAEL of 6.7 mg/kg/day based on reduced plasma and red blood cell (RBC) cholinesterase activity in both sexes observed at 142 mg/kg/day (LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: This study is appropriate for the duration of exposure of concern (1 to 6 months). Since an oral NOAEL was selected, an inhalation absorption factor of 100% should be used for route-to-route extrapolation.

2.3.9 Long-term Inhalation (longer than 6 Months) Exposure

The current use pattern does not indicate a concern for Long-Term exposure or risk.

2.3.10 Margins of Exposure for Occupational/Residential Risk Assessments

A MOE of 100 is adequate for dermal and inhalation occupational and residential exposure risk assessments.

2.4 Recommendation for Aggregate Exposure Risk Assessments

For short- and intermediate-term aggregate exposure risk assessments, the oral endpoint can be aggregated with the inhalation and dermal exposure since oral equivalents were selected for the dermal and inhalation routes.

Based on proposed and current use scenarios, long-term exposure risk assessment is not needed at this time. In the future, if long-term exposure scenarios are requested, the long-term oral, dermal and inhalation endpoints can all be aggregated together.

3. CLASSIFICATION OF CARCINOGENIC POTENTIAL

The following are summaries excerpted from the Health Effects Division Carcinogenicity Peer Review Committee (CPRC) report dated March 6, 1995.

3.1 Carcinogenicity Study in Rats

Two studies were conducted with TCVP (gardona) in the rat; one by Iveresk and the other by Gulf South (NCI sponsored).

Executive Summary: In the Iveresk study, groups of 50 male and 50 female Charles River Sprague-Dawley rats received TCVP in their diet over a 2-year period at 0, 100, 1000 or 2000 ppm (equivalent to 0, 4, 43 and 89 mg/kg/day in males and 0, 6, 63 and 125 mg/kg/day in females, respectively) (MRID No. 42980901). There were increases in the incidences of thyroid C-cell adenomas and adrenal pheochromocytomas in male rats only. Neither of these increases were statistically significant by pairwise comparison to controls, but there was a statistically significant increasing trend for the adrenal tumors.

In the Gulf South study, Osborne-Mendel rats received TCVP in their diet at doses of 0, 4250, or 8500 ppm for 80 weeks, followed by 31 weeks observation. Statistically significant increase in the incidences of adrenal cortical adenomas and thyroid C-cell adenomas were found in dosed female rats. High incidences of thyroid C-cell hyperplasia in both sexes further indicated an effect on the thyroid (MRID 00117443).

Adequacy of the Dose Levels Tested: The CPRC concluded that the highest dietary exposure level (2000 ppm) in the Inveresk chronic rat study was adequate for assessment of the carcinogenic potential of TCVP. This was based on depressions of mean plasma cholinesterase activity at several blood sampling times in both sexes (also observed in 1000 ppm females) and the findings from the preliminary 13-week subchronic study which utilized dietary exposure levels of 0, 100, 2000 and 5000 ppm. At 13 weeks in the subchronic study, the mean body weight gains in 5000 ppm males and females were respectively 80 and 88% of their control values, and males and females at 2000 and 5000 ppm had significantly reduced mean red blood cell and plasma cholinesterase activities.

Discussion of tumor data: In the Inveresk study, there were increases in the incidences of thyroid C-cell adenomas and adrenal pheochromocytomas in male rats only. Neither of these increases were statistically significant by pairwise comparison to controls, but there was a statistically significant increasing trend for the adrenal tumors. The increased incidences of C-cell adenomas and adrenal pheochromocytomas were consistent with what was observed in the 1978 (Gulf South) NCI-sponsored study.

3.2 Carcinogenicity Study in Mice

Two studies were conducted with TCVP in the mouse; one by Hazleton and the other by Gulf South.

Executive Summary: In the 1980 Hazleton study, B6C3F1 mice were fed diets containing 0, 17.5, 64, 320, 1600, 8000, or 16000 ppm tetrachlorvinphos for two years in a carcinogenicity study. For systemic toxicity, the NOAEL was 1600 ppm (240 mg/kg/day) and the LOAEL was 8000 ppm (1200 mg/kg/day), based on decreased weight gain. Administration of TCVP in the diet to B6C3F1 mice resulted in statistically significant increases in hepatocellular adenomas, carcinomas and combined adenomas/carcinomas (with carcinomas predominant) in females, and in combined hepatocellular adenomas/carcinomas in males. In male mice there were also statistically significant increases in renal adenomas, carcinomas and combined adenomas/carcinomas. The statistically significant increases in tumors noted above, all occurred only at doses of TCVP of 8000 ppm or greater, except for the combined hepatocellular adenomas/carcinomas in female mice, which also occurred at 1600 ppm. (GLN 83-2; MRID 00126039).

In the Gulf South study, B6C3F1 mice were fed diets containing 0, 8000, or 16000 ppm TCVP for 80 weeks, followed by 12 weeks observation. Increased incidences of hepatocellular carcinomas and granulomatous lesions of the liver were found in the dosed mice (GLN 83-2; MRID 00117443).

Adequacy of the Dose Levels Tested: The 1988 Peer Review Committee evaluated these two mouse studies and other relevant studies in determining the adequacy of the doses. The Committee concluded that:

1. The carcinoma incidence constituted over 60% of the tumor response at 8000 and 16,000 ppm. In addition, there were statistically significant increases in tumors of the liver (combined adenomas/carcinomas) and kidney (adenomas, carcinomas and combined adenomas/carcinomas) in males at 16,000 ppm, but not at lower doses.
2. The 8000 ppm dose was adequate or slightly excessive (body weight gain depression >15%), and that the top dose of 16,000 ppm was excessive (severe liver necrosis); however **the 1600 ppm dose was adequate** to access the carcinogenic potential of TCVP.

The present CPRC agreed with the previous 1988 Peer Review evaluation and conclusion, that there was a statistically significant increase in hepatocellular adenomas/carcinomas in female mice, even at a dose that was not excessively toxic (1600 ppm).

Discussion of Tumor Data: Carcinogenic potential was evidenced by an statistically significant increases in combined hepatocellular adenoma/carcinomas (primarily carcinomas) in the female B6C3F1 mouse.

3.3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

TCVP was previously evaluated by the Toxicology Branch Peer Review Committee (TBRC) as a Group C with a Q_1^* (Memo, dated April 14, 1988). At that time, the TBRC found that there were deficiencies in the rat study, and recommended that another rat study be performed by the Registrant. In response to this recommendation, a new rat study was submitted, and this second peer review was convened to evaluate the new rat study, and re-evaluate the weight-of-the-evidence for TCVP.

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on, Dec. 12, 1994 to discuss and re-evaluate the toxicology database of TCVP, with particular reference to its carcinogenic potential. The CPRC concluded that the classification of TCVP should remain as Group C with a Q_1^* of 1.83×10^{-3} , based on statistically significant increases in combined adenomas/carcinomas (predominantly carcinomas) in the female B6C3F1 mouse, suggestive evidence of thyroid C-cell adenomas and adrenal pheochromocytomas in the rat, mutagenicity concerns, and SAR support [Carcinogenicity Peer Review of Gardona (2nd) dated March 6, 1995].

The HIARC, in accordance with the Draft 1999 Guidelines for Carcinogen Risk Assessment, classified TCVP as a "Likely to be carcinogenic to humans". The HIARC re-affirmed the low dose extrapolation (Q_1^*) method for quantification of human cancer risk.

4 MUTAGENICITY

4.1 Gene Mutation

An Ames test in Salmonella typhimurium found no mutagenic effect in strains TA98, TA100, TA1535, TA1537, and TA1538, at dose levels of 66.7, 100, 333, 667, 1000, or 3300 ug/plate with activation, or at dose levels of 10, 33.3, 66.7, 100, 333, or 667 ug/plate without activation (MRID 41222508).

4.2 Chromosomal Aberration

A test for chromosomal aberration was conducted in Chinese hamster ovary cells. It was concluded that tetrachlorvinphos was positive for inducing chromosomal aberrations at 59.9, 79.8, and 99.8 ug/mL (but not at 29.9 or 44.9 ug/mL) in the absence of metabolic activation, but that tetrachlorvinphos was negative for inducing chromosomal aberrations at 12.5, 25, 37.6, or 75.1 ug/mL in the presence of rat S9/metabolic activation. (MRID 41312901).

4.3 Unscheduled DNA Synthesis

Cultures of rat hepatocytes were dosed with 5, 7.5, 10, 15, 20, 23, 25, 27, 30, 35, or 40 ug/mL of tetrachlorvinphos. Concentrations of 35 and 40 ug/mL were lethal. Only the cultures exposed to 10, 15, 20, 23, 25, 27, or 30 ug/mL were analyzed for evidence of unscheduled DNA synthesis (UDS). The results were negative. (MRID 42156401).

5 FQPA CONSIDERATIONS

On May 12, 13, 14, 1998 the HIARC evaluate the toxicology data base of tetrachlorvinphos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to tetrachlorvinphos as required by the Food Quality Protection Act (FQPA) of 1996 (HIARC Report dated July 7, 1998).

On June 15, 16, 1998, the FQPA Committee evaluated both the hazard and exposure data for OP's including TCVP. The Committee recommended that the 10 x FQPA safety factor be removed based on the following factors:

- (a) In prenatal developmental toxicity studies following *in utero* exposure in rats and rabbits, there was no evidence of developmental effects being produced in fetuses at lower doses as compared to maternal animals nor was there evidence of an increase in severity of effects at or below maternally toxic doses.
- (b) In the pre/post natal two-generation reproduction study in rats, there was no evidence of enhanced susceptibility in pups when compared to adults (i.e., effects noted in offspring occurred at maternally toxic doses or higher).
- (c) There was no evidence of abnormalities in the development of the fetal nervous system in the pre/post natal studies.
- (d) There is no concern for positive neurological effects from the available neurotoxicity studies or for histopathology in the central nervous system from the other toxicological studies (e.g., subchronic rat, chronic dog, chronic mouse and rat).
- (e) The toxicology data base is complete and there are no data gaps according to the Subdivision F Guideline requirements.
- (f) Adequate actual data, surrogate data, and/or modeling outputs are available to satisfactorily assess dietary and residential exposure and to provide a screening level drinking water exposure assessment.

5.7 Recommendation for a Developmental Neurotoxicity Study

The Agency has issued a Data-Call-In notice (DCI) for a developmental neurotoxicity study and acute and subchronic neurotoxicity studies for all OPs; including TCVP. However, no additional evidence beyond its activity as a cholinesterase inhibiting compound suggested the need for this study.

6 HAZARD CHARACTERIZATION

Tetrachlorvinphos has relatively low acute toxicity in rats via oral (Toxicity Category III) and inhalation (Toxicity Category IV) routes, and low acute toxicity via the dermal route in rabbits (Toxicity Category III); based on studies conducted in guinea pigs, it is considered to be a dermal sensitizer. In subchronic and chronic toxicity studies in rats and dogs, red blood cell (RBC) and plasma cholinesterase inhibition (ChEI) were observed at doses ranging from 43.2 to 1000 mg/kg/day. Systemic effects observed in these studies included reduced body weights and body weight gains, liver effects including increased liver weights, thyroid effects which consisted of follicular cell hypertrophy and increased thyroid weights, and increased kidney weights. Clinical signs of neurotoxicity were not observed in the subchronic and chronic studies.

Developmental and reproductive toxicity studies conducted in rats and rabbits indicate no increased sensitivity of developing young relative to maternal animals due to either pre- or post-natal exposure to tetrachlorvinphos. In acute and subchronic neurotoxicity studies in rats, transient clinical signs characteristic of cholinesterase inhibition were observed, but ChEI was not measured; LOAELs and NOAELs in these studies were either similar to or higher than those in the chronic and subchronic toxicity studies.

In an acute delayed neurotoxicity study in hens, no signs of delayed neurotoxicity or neuropathology were observed; however, inhibition of neurotoxic esterase (NTE) was not assessed.

Tetrachlorvinphos is considered to be a possible human (Group C) carcinogen based on statistically significant increases in combined hepatocellular adenoma/carcinomas in mice, and suggestive evidence of thyroid c-cell adenomas and adrenal pheochromocytomas in rats. A cancer potency factor (Q_1^*) of 1.83×10^{-3} (mg/kg/day)⁻¹ was estimated using the time-to-tumor model.

7 DATA GAPS

After evaluating the toxicology database of TCVP, the HIARC recommended the following studies be conducted:

1. Twenty eight (28)-day inhalation study in rats (abbreviated 90-day protocol). The registrant is recommended to follow all the procedures stipulated in the Subdivision F Guidelines for the 90-day inhalation toxicity study (870.3465)

except that the exposure duration can be reduced to 28 days. The HIARC requests this study due to the potential occupational exposure via this route and there are no studies available at the present time. This study must include ChEI evaluation at the appropriate time intervals.

2. Twenty one (21)-day dermal toxicity study in rats. The HIARC requests this study due to the potential occupational exposure via this route and there are no acceptable studies available at the present time. This study must include ChEI evaluation at the appropriate time intervals.
3. Acute and subchronic neurotoxicity, and developmental neurotoxicity studies are a data gap as the Agency issued a DCI notice for these studies (Federal Register Notice dated September 10, 1999).

8 ACUTE TOXICITY**Acute Toxicity of Tetrachlorvinphos Technical**

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute Oral - Rat	41222504	LD ₅₀ = 1480 mg/kg (M) 465-965 mg/kg (F)	III
870.1200	Acute Dermal - Rabbit	41222505	LD ₅₀ > 2000 mg/kg	III
870.1300	Acute Inhalation - Rat	00138933	LC50 > 3.61mg/L	IV
870.2400	Acute Eye Irritation - Rabbit	41222506	moderate	III
870.2500	Acute Dermal Irritation - Rabbit	41222507	slight	IV
870.2600	Skin Sensitization - Guinea Pig	41377902 42981001	sensitizer	
870.6100	Acute Delayed Neurotoxicity	41905901	No clinical signs of neurotoxicity observed (NTE not measured)	

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 6.7 mg/kg/day UF = 100	Plasma/RBC ChE Inhibition at 13 weeks	Subchronic Rat
		Acute RfD = 0.067 mg/kg/day	
Chronic Dietary	NOAEL = 4.23 mg/kg/day UF = 100	Histological liver and adrenal changes; reduced weight gain/plasma ChE Inhibition in females.	Chronic Rat
		Chronic RfD = 0.0423 mg/kg/day	
Incidental Oral, Short-Term	Oral NOAEL= 6.7 mg/kg/day	Plasma/RBC ChE Inhibition at 13 weeks	Subchronic Rat
Incidental Oral, Intermediate-Term	Oral NOAEL= 6.7 mg/kg/day	Plasma/RBC ChE Inhibition at 13 weeks	Subchronic Rat
Short-Term Dermal ^a and Inhalation ^b	Oral NOAEL= 6.7 mg/kg/day	Plasma/RBC ChE Inhibition at 13 weeks	Subchronic Rat
Intermediate-Term Dermal ^a and Inhalation ^b	Oral NOAEL= 6.7 mg/kg/day	Plasma/RBC ChE Inhibition at 13 weeks	Subchronic Rat
Long-Term Dermal and Inhalation	None	Not required under the registered use patterns.	None

a = Since an oral NOAEL was selected, a dermal absorption factor of 9.57% should be used in route-to-route extrapolation.

b = Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) should be used in route-to-route extrapolation.



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