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

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DATE: July 8,1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

BIDRIN

SUBJECT: ***DICROTOPHOS*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Ching-Hung Hsu, Pharmacologist. 7/7/98
Toxicology Branch 2
Health Effects Division (7509C)
and
Jess Rowland, Executive Secretary 7/8/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

THROUGH: K. Clark Swentzel, Chairman, 7/8/98
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Mike Metzger, Co-Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Jose J. Morales, Risk Assessor
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

PC Code: 035201

On May 7, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of **Dicrotophos**, established a Reference Dose (RfD) and selected the toxicological endpoints for acute dietary as well as occupational exposure risk assessments. The Reference Dose (RfD), established in 1986, is re-evaluated herein. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to ethyl parathion as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present were: Karl Baetcke, Robert Fricke, Karen Hamernik, Nancy MaCarroll, John Redden, Jess Roland (Executive Secretary), Steve Dapson and Kathleen Raffaele. Members in absentia: William Burnam, Mike Metzger and Clark Swentzel. Data was presented by Ching-Hung Hsu of Toxicology Branch 2.

Data Presentation:
and
Report Presentation

Ching-Hung Hsu.
Pharmacologist

Report Concurrence:

Jess Rowland
Executive Secretary

I. INTRODUCTION

Dicrotophos (chemically: 3-hydroxyl-N, N-dimethyl-cis-crotonamide, dimethyl phosphate) is a contact and systemic organophosphate insecticide, initially registered (1970) by Shell as an 82% aqueous formulation (Bidrin 8 Water Miscible Insecticide) for spray application on cotton and seed crops (such as soybean), and later (1972) as an 82% micro-injectible product (INJECT-A-CIDE B) for systemic suppression of certain insects on ornamental (non-crop) trees. Both of these end-use formulations of dicrotophos, as well as technical Bidrin (85% a.i.) are classified as restricted use pesticides, based on acute toxicity (Tox. Cat. I or II). A 48-hour re-entry interval was established through Part 170-Worker Protection Standards for Agricultural Pesticides (Federal Register, May 10, 1974). An RfD of 0.0001 mg/kg/day was established in 1986.

Following issuance of the Dicrotophos Registration Standard (1982), which imposed additional environmental fate, ecological and residue requirements, use on soybeans (and other seed crops) was voluntarily withdrawn. Subsequently (1986), all Shell registrations were transferred to Dupont and, early in 1994, finally assigned to AMVAC Chemical, the current registrant.

The core toxicity study requirements, as well as additional environmental fate/effects, residue, drift and re-entry data was imposed in a subsequent Data Call-In (issued in 1991), while further DCIs imposed human incident data requirements (1993), as well as worker exposure requirement (1995). Much of the available toxicology data does not satisfy current FIFRA Test Guideline requirements.

Currently the three registered products all contain dicrotophos as the active ingredient: the technical (85% a.i.); the water-miscible product for use on cotton (82%); and, the tree-injectible for use on ornamental trees. There are no multiple a.i. formulations containing dicrotophos, nor are there any (current) Section 24© products. The two end-use formulations remain restricted use products. The only established tolerance is for cotton seed at 0.05 ppm.

II. HAZARD IDENTIFICATION

NOTE: ***Toxicology database is not complete and appropriate studies are not available for precise hazard identification for the various exposure scenarios. However, from the limited studies that are available in the database, doses and endpoints have been selected which will provide upper bound risk for acute and dietary as well as occupational exposure risk assessments. Hazard identification will be revised when the toxicology data requirements are satisfied according to Subdivision F Guidelines.***

A. Acute Reference Dose (RfD)

Study Selected: Acute Neurotoxicity - Rat §81-8

MRID No.: 43759801

Executive Summary: In an acute neurotoxicity study (MRID 43759801) dicrotophos (87.65% ai) was administered by gavage to 10/sex/group Sprague-Dawley CD rats (20/sex/group) at dose levels of 0, 0.5, 5 or 10 mg/kg (in water, 10 ml/kg). The rats were evaluated for reactions in functional observations and motor activity measurements (3 hours, and 8 and 15 days postdosing). Two satellite groups (5/sex/group) were also included for the purpose of measuring plasma ChE and erythrocyte and brain AChE on days 1 and 8.

At 0.5 mg/kg, dicrotophos inhibited brain (21% in ♀ and 22% in ♂) and erythrocyte AChE (16% in ♀ and 19% in ♂) and plasma ChE (46% in ♀ and 38% in ♂) on day 1 (all depressions were statistically significant). Brain AChE and plasma ChE reached about 90% inhibition at 10 mg/kg. RBC AChE never exceeded 50% inhibition. Brain AChE remained inhibited (7%-14%) for males at all doses by day 16. **The NOEL and LOEL for ChE/AChE inhibition is < 0.5 mg/kg.**

At 5 mg/kg and above, dicrotophos produced clinical signs (principally decreased activity, upward curvature of spine, pinched in sides, flaccid appearance and decreased pupil response in most or all animals and several other signs in some animals. Overall some 25 in males and 24 in females FOB parameters were reported affected by treatment in the 5 and/or 10 mg/kg dose levels of dicrotophos. Motor activity was decreased. At 10 mg dicrotophos/kg produced deaths (7 ♀ and 1 ♂) within 3 hours after dosing. Most signs regressed after one day but some persisted for 3 or 4 days. **The LOEL for neurotoxicity is 5 mg/kg based on clinical signs. The NOEL is 0.5 mg/kg.**

This acute neurotoxicity study is classified **acceptable** and satisfies the guideline requirement for an acute neurotoxicity study (81-8)in rats. Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

Dose and Endpoint for Risk Assessment: LOEL=0.5 mg/kg based on the plasma, RBC and brain ChEI observed on Day 1; a NOEL was not established.

Comments about Study/Endpoint: This dose is appropriate since the effects were observed on Day 1 following a single dose. Also, an additional Uncertainty Factor of 10 was applied for the use of a LOEL for risk assessment. A UF of 10 (as opposed to a 3 x) is needed because of the severity of the effects seen at the lowest dose tested following a single dose.

Uncertainty Factor (UF): 1000 (10 x for inter-species extrapolation, 10 x for intra-species variability and 10 x for lack of a NOEL)

$$\textbf{Acute RfD} = \frac{0.5\ \text{mg/kg}}{1000} = \textbf{0.0005 mg/kg}$$

This Risk Assessment is required.

B. Chronic RfD

Study Selected: Chronic Toxicity - Dog §83-1b

MRID No.: 44328401

Executive Summary: A 2-year feeding study (MRID 44328401), dicrotophos (87.65% w/w, Batch No. 403001 B) in corn oil was administered to 4 beagle dogs/sex/dose by capsule at doses of 0 (corn oil only), 0.025, 0.1, or 1.0/0.5 mg/kg/day for 1 year (high-dose dogs received 1.0 mg dicrotophos/kg/day for 13 weeks, after which they were not dosed for 7 days, and were then given 0.5 mg/kg/day from week 15-52).

No animals died during the study. Treatment-related clinical signs were seen primarily at the high dose before it was lowered to 0.5 mg/kg/day, and were correlated with the inhibition of plasma and erythrocyte cholinesterase (ChE) activity. Signs included shaking and subdued behavior (2/4 or more dogs/sex during weeks 13-14 and in one female during week 24); unsteady gait (one female at week 13) and a slight increase in the incidence/frequency of fluid feces, regurgitation, and vomiting (both sexes). High-dose dogs also resisted dosing and males had reddening and peeling of the scrotal skin with sores primarily during the first 14 study weeks.

Weekly body weights of high-dose males were lower than those of controls (≤ 8.4%; $p < 0.05$) several times between weeks 5 and 14, and their week 1-14 body weight gain was 48% of controls. After the high dose was lowered, the body weights improved and their overall weight gain was greater than of the controls. Weekly body weights of mid- and high-dose females were up to 10.3% lower than controls throughout the study ($p < 0.05$ for weeks 6, 7, 9, 14, 47, and 49-53 at one or both doses), and their overall weight gain and food efficiency were 74-78% of controls. There were no toxicologically significant differences from the controls for hematology, clinical chemistry, urinalysis, or ophthalmoscopic parameters, organ weights, or gross and microscopic pathology. No neoplastic lesions attributable to test article administration were reported.

Based on the 26% lower overall (week 1-52) body weight gain (and food efficiency) in mid-dose females, 0.1 mg/kg/day is concluded to be the LOEL under the conditions of this study; the corresponding NOEL is 0.025 mg/kg/day. The reviewer disagrees with the study author that the body weight changes at the mid-dose were not toxicologically significant and that only the high dose represents a LOEL for body weight changes.

Plasma, RBC, and brain ChE activities were inhibited by dicrotophos treatment throughout most of the study in both sexes. The degree of inhibition was clearly dependent on the dose but not on the exposure duration. At the high dose, the plasma, RBC, and brain ChE values were 36-64% of controls ($p \leq 0.01$) and neurologic impairment was clinically evident. At the mid-dose, plasma ChE activity was 55-61% of controls ($p \leq 0.01$) in both sexes, RBC ChE activity was 83-91% of controls ($p \leq 0.05$ or 0.01 for males only), and brain ChE was 81-88% of controls ($p \leq 0.05$ for females only).

Although there were no visible neurological effects at the mid-dose, because the parameter most germane to neurotoxicity, i.e. brain ChE, was statistically significantly inhibited in females (19%, $p \leq 0.05$), and plasma ChE was substantially inhibited in both sexes, the NOEL and LOEL for ChE/AChE inhibition is <0.025 mg/kg/day. The reviewer disagrees with the study author that the high dose is the LOEL for ChE inhibition.

This study is classified as acceptable and satisfies the guideline requirement for a chronic oral toxicity study (83-1b) in the dog.

Dose and Endpoint for Establishing RfD: LOEL= 0.025 mg/kg based on the plasma ChEI observed in both sexes. This value was recommended for the endpoint because a NOEL was not established.

Uncertainty Factor(s): 1000 (10 x for inter-species extrapolation, 10 x for intra-species variability and 10 x for lacking of a NOEL)

$$\textbf{Chronic RfD} = \frac{0.025 \text{ mg/kg/day}}{1000} = \textbf{0.000025 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: An additional Uncertainty Factor of 10 was applied for the use of a LOEL for risk assessment. A UF of 10 is needed because of the severity of the effects seen at the lowest dose tested.

This risk assessment is required.

C. Occupational/Residential Exposure

There are no residential uses. Therefore, doses and toxicology endpoints were selected only for occupational exposure risk assessments.

1. Dermal Absorption

Dermal Absorption Factor: 100% Default is used due to lack of a dermal absorption study **as well as appropriate oral and dermal studies in the same species for extrapolation of a dermal absorption factor.**

2. Short-Term Dermal - (1-7 days)

Study Selected: Acute Neurotoxicity - Rat §81-8

MRID No.: 43759801

Executive Summary: See Acute Dietary

Dose and Endpoint for Risk Assessment: oral LOEL= 0.5 mg/kg based on the plasma, RBC and brain ChEI observed on Day 1. This value was recommended for the endpoint because a NOEL was not established.

Comments about Study/Endpoint: This dose/endpoint/study was selected due to the lack of a 21-day dermal toxicity study. Also, the effects observed in this study after a single dose is appropriate for risk assessment for this exposure period of concern (i.e., 1-7 days). Since an oral LOEL was selected a dermal absorption factor of 100% should be used for this risk assessment.

This Risk Assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Chronic Toxicity - Dog §83-1b

MRID No.: 44328401

Executive Summary: See Chronic Dietary

Dose/Endpoint for Risk Assessment: oral LOEL= 0.025 mg/kg based on the plasma ChEI in both sexes observed at Week 13 measurement.

Comments about Study/Endpoint: The 2-year study was used for this risk assessment since neither a 21-day dermal toxicity study nor 90-day toxicity studies (oral or dermal) were available. Also, the endpoint (plasma ChEI) was measured at 13-weeks which is appropriate for this exposure period of concern (i,e., 7-days to several months). An additional Uncertainty Factor of 10 was applied for the use of a LOEL for risk assessment. A UF of 10 (as opposed to a 3 x) is needed because of the severity of the effects seen at the lowest dose. Since an oral LOEL was selected a dermal absorption factor of 100% should be used for this risk assessment.

This Risk Assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Based on the use pattern, long-term exposure risk assessment is not required.

5. Inhalation Exposure (Any Time Period).

Study Selected: Acute Neurotoxicity §81-8

MRID No.: 43759801

Executive Summary: See Acute Dietary

Dose/Endpoint for Risk Assessment: oral LOEL=0.5 mg/kg based on the plasma, RBC and brain ChEI.

Comments about Study/Endpoint: Due to the lack of an acceptable inhalation study, an oral LOEL was selected. The following steps must be used for route to route extrapolation (i.e., oral to inhalation):

Step I. The inhalation exposure component (i.e. μG a.i./day) using 100% absorption rate (default value) and application rate should be converted to an **equivalent oral dose** (mg/kg/day).

Sept II. The dermal exposure component (mg/kg/day) using a 100% dermal absorption rate and application rate should be converted to an **equivalent oral dose**. The dose should then be combined with the oral dose in Step I.

Step III. The combined dose from Step II should then be compared to the oral LOEL of 0.5 mg/kg/day to calculate the MOE for Short-Term exposure and the oral LOEL of 0.025 mg/kg/day to calculate the MOE for Intermediate-Term exposure. Long-Term exposure risk assessments are not required based on the use pattern.

This risk assessment is required.

D. Recommendation for Aggregate (Food, Water and Dermal) Exposure Risk Assessments

Not required since there are no residential uses.

E. Margins of Exposures for Occupational Exposure Risk Assessments

A MOE of 1000 is required for both dermal and inhalation exposure risk assessments and includes the conventional 100 and an additional 10 for the use a LOEL for all risk assessments.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Under review.

2. Carcinogenicity Study in Mice

Under review.

3. Classification of Carcinogenic Potential

The carcinogenic potential of Dicrotophos could not be made since the recently submitted carcinogenicity studies in mice and rats are still under review.

IV. MUTAGENICITY

Salmonella (Ames) study (MRID 43603301): Cultures of five Ames (TA) strains of *Salmonella typhimurium* were exposed to Dicrotophos for 48 hours, , with/without mammalian activation (S9). No increased reversions were recorded up to limit dosing, 5000μg/plate. This study is **acceptable**-guidelines (§84-2a), demonstrating **negative** for reverse mutation in Ames Testing.

Chromosome damage *in vivo* (Mouse MT, MRID 43603302): Mice were administered single doses of Dicrotophos by i.p. injection, and bone marrow sampled for the presence of micronuclei in polychromatic erythrocyte. No increased incidences of micronuclei were found at doses up to a severely toxic level (6.6 mg/kg). This study is **acceptable**-guidelines (§84-2b), demonstrating **no induction** of micronuclei (chromosome damage) in bone marrow PCEs of mice treated up to lethal doses.

Mammalian gene mutation *in vitro* (MRID 43591401): Cultures of mouse lymphoma (L5178Y) cells were exposed with/without S9-activation of Dicrotophos in two separate trials. Dose-dependent and reproducible gene mutation was recorded in both the presence and absence of S9 activation at non-toxic doses of 750 μg/ml up to the cytotoxic HDTs, 2000-3000 μg/ml.

For both mutagenesis assays the TFT colonies for the cultures treated with the three highest doses and the solvent control were sized according to diameter over a range from 0.2 to 1.1 mm. The data on colony size distributions from both the initial and confirmatory mutagenesis assays in the absence of S9 and from the initial assay in the presence of S9 showed an increase in the frequency of small colonies when the cultures treated with the highest dose were compared to the solvent control cultures. This increase is consistent with damage to multiple loci on chromosome 11 in addition the loss of the TK locus. The colony size distribution data from the confirmatory mutagenesis assay in the presence of S9 showed an increase in the frequency of medium to large colonies when the cultures treated with the highest dose were compared to the solvent control cultures.

This study is **acceptable**-guidelines (§84-2a), demonstrating **positive** dose-dependent forward gene mutation at the thymidine kinase (TK) locus of mouse lymphoma (L5178Y) cell cultures, beginning at 750 μg/ml up to cytotoxic HDTs, 2000-3000 μg/ml, both in the presence and absence of metabolic activation.

V. FQPA CONSIDERATIONS

1. Neurotoxicity:

(I) Hen: Data Gap

Single oral doses of technical dicrotophos up to an acute LD_{50} (7.4 ± 0.7 mg/kg) did not produce signs of acute delayed neurotoxicity in hens (1963, MRID 00013444). A single oral dose of 8 mg/kg technical dicrotophos (the LD_{50}) in atropine and protopam-protected hens produced no signs of acute delayed neurotoxicity (1965, MRID 00014010). Lack of suitable control groups and insufficient information on histopathology, however, invalidate this study.

(ii) Rat:

In an **acute** neurotoxicity study (MRID 43759801) dicrotophos (87.65% ai) was administered by gavage to 10/sex/group Sprague-Dawley CD rats (20/sex/group) at dose levels of 0, 0.5, 5 or 10 mg/kg (in water, 10 ml/kg). The rats were evaluated for reactions in functional observations and motor activity measurements (3 hours, and 8 and 15 days postdosing). Two satellite groups (5/sex/group) were also included for the purpose of measuring plasma ChE and erythrocyte and brain AChE on days 1 and 8.

At 0.5 mg/kg, dicrotophos inhibited brain (21% in ♀ and 22% in ♂) and erythrocyte AChE (16% in ♀ and 19% in ♂) and plasma ChE (46% in ♀ and 38% in ♂) on day 1 (all depressions were statistically significant). Brain AChE and plasma ChE reached about 90% inhibition at 10 mg/kg. RBC AChE never exceeded 50% inhibition. Brain AChE remained inhibited (7%-14%) for males at all doses by day 16. **The NOEL and LOEL for ChE/AChE inhibition is < 0.5 mg/kg.**

At 5 mg/kg and above, dicrotophos produced clinical signs (principally decreased activity, upward curvature of spine, pinched in sides, flaccid appearance and decreased pupil response in most or all animals and several other signs in some animals. Overall some 25 in males and 24 in females FOB parameters were reported affected by treatment in the 5 and/or 10 mg/kg dose levels of dicrotophos. Motor activity was decreased. At 10 mg dicrotophos/kg produced deaths (7 ♀ and 1 ♂) within 3 hours after dosing. Most signs regressed after one day but some persisted for 3 or 4 days. **The LOEL for neurotoxicity is 5 mg/kg based on clinical signs. The NOEL is 0.5 mg/kg.**

This acute neurotoxicity study is classified **acceptable** and satisfies the guideline requirement for an acute neurotoxicity study (81-8)in rats. Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

In a **subchronic** oral neurotoxicity feeding study (MRID 43980201), 12 Alpk:APfSD rats/sex/group were fed diets containing 0, 0.5, 5, or 25 ppm dicrotophos (87.65% w/w, Batch No. 403001B) for 13 weeks. Body weight, food consumption, and clinical signs were recorded weekly. Behavioral testing (Functional observation battery [FOB] and motor activity) was conducted one week prior to start of treatment and during weeks 5, 9, and 14 of dosing. At sacrifice, 6 rats/sex/group were perfused and neuropathological evaluation was conducted for the control and high dose groups; for the remaining 6 rats/sex/group, cholinesterase activity in plasma, red blood cells (RBC), and whole brain was determined. Two satellite groups, each with 6 Alpk:APfSD rats/sex/dose, were similarly treated and included for the purpose of measuring cholinesterase activity (ChE) at week 5 (Group A) and week 9 (Group B). The average consumption of test material in the 0, 0.5, 5, and 25 ppm dose groups for males was 0, 0.04, 0.39, and 2.03 mg/kg/day and for females was 0, 0.04, 0.45, and 2.38 mg/kg/day.

There was no treatment-related effect on mortality. Effects on body weights were minimal: weights were statistically significantly lower than controls at the high dose (≤ 10.4%, $p \leq 0.05$ or 0.01) during weeks 2-6 in males and 2-4 in females, and were correlated with decreased food consumption during weeks 1 and 2 (and decreased food efficiency in males). For females only, body weights, food consumption, and food efficiency were significantly increased at multiple time points starting at week 4. No notable changes were seen in behavior or appearance upon clinical examination.

Treatment-related effects on FOB and motor activity were seen only at 25 ppm in both sexes. Forelimb grip strength was decreased at weeks 9 and 14 in females (13-14%, $p \leq 0.05$ or 0.01) and at week 5 in males (14%, $p \leq 0.05$). Hindlimb grip strength was decreased only in females at week 9 (16%, $p \leq 0.05$). The mean overall motor activity was decreased at week 9 in males (34%, $p \leq 0.01$) and at weeks 9 and 14 in females (23 and 33%, respectively; $p \leq 0.05$; $p \leq 0.01$). The neurotoxic effects, as well as the statistically significant increase in brain weight in 25 ppm males (≤ 5.2%), had no histopathological correlates.

Brain, plasma, and erythrocyte ChE activities were inhibited by dicrotophos treatment in all groups of rats, most markedly in the brain: 11-20% at 0.5 ppm, 56-63% at 5 ppm, and 87-90% at 25 ppm ($p \leq 0.01$). RBC ChE inhibition range was 0-17%, 38-51%, and 46-60% at 0.5, 5, and 25 ppm, respectively. Plasma ChE inhibition varied among males and females: the range was 10-12%, 34-39%, 68-71% for males and 11-28%, 66-74%, and 84-88% for females at 0.5, 5, and 25 ppm, respectively.

Based on the decreased grip strength in females, decreased motor activity in both sexes, and marginal body weight decreases in both sexes of rats, 25 ppm (2.03 mg/kg/day for males, 2.38 mg/kg/day for females) is identified as the LOEL and 5 ppm (0.39 mg/kg/day for males, 0.45 mg/kg/day for females) is the NOEL for systemic toxicity/neurotoxicity. Based on the dose-related inhibition in brain, plasma, and erythrocyte ChE activity, 0.5 ppm (0.04 mg/kg/day for males and females) is the LOEL for ChE inhibition; a NOEL cannot be assigned because 0.5 ppm was the lowest dose tested.

This study is classified as acceptable, pending submission of requested information, satisfying the guideline requirement for a subchronic oral neurotoxicity feeding study (82-7) in the rat.

2. Developmental Toxicity

(I) Rabbit: Data Gap (lack of the report)

Oral teratogenicity studies were performed in Dutch Belted rabbits (GS0003501, 1973). Technical dicrotophos was administered on days 6-18 of pregnancy at doses of 1.3, 4, or 8 mg/kg/day. Although, maternal toxicity including signs of cholinesterase inhibition, was observed at 8 mg/kg/day, no fetal toxicity attributable to dicrotophos was observed at this dose. **This study is considered to be a datagap since the study report is not available for evaluation and validation of the findings.**

(ii) Rat:

In a developmental toxicity study (MRID 00263684), five groups of Sprague-Dawley (Charles River Crl: CD [SD] Br) mated female rats (25/group) were administered single doses of 5 mL/kg/day test article (Bidrin technical, 89.7% a.i.) orally by gavage at levels of 0 (sterile water vehicle), 0.1, 0.5, 1.0, or 2.0 mg/kg/day from (presumed) gestation day 6 through 15 inclusive, and survivors sacrificed on gestation day 20.

Prior to conducting the main developmental toxicity study, a preliminary dose-selection investigation was performed, using 6 oral dosage levels (0, 0.5, 1.0, 5.0, 10.0 and 15.0 mg/kg/day) administered by gavage to groups of 8 mated Crl: CD[SD]Br females each from gestation days 6 through 15. Twenty-three animals died, one to seven days after beginning treatment: 7/8 of the 5.0 mg/kg/day group, and all 8 of both 10.0 and 15.0 mg/kg/day groups. Numerous clinical signs of compound (OP) toxicity were evident in these animals. The single survivor on 5.0 mg/kg/day lost weight and ate less during the study, and at scheduled necropsy (day 20) was found to have viable fetuses, apparently normal according to gross fetal examination. Animals of the second lowest dose group (1.0 mg/kg/day) manifested fasciculations (muscle twitching) 30 minutes following dosing, beginning on gestation day 14. No changes from control were noted at the LDT, 0.5 mg/kg/day group on fetal intrauterine survival, sex ratio, mean fetal weights, or gross examination. Based on these results, dose levels, as indicated above, for the definitive study were selected.

During the definitive study, animals were observed daily, and body weights and food consumption recorded periodically . Gross clinical, reproductive and fetal parameters were recorded at termination. One-half of each fetal litter was examined for soft tissue anomalies and fetal kidneys graded for renal papillar development, while the remainder of each litter was prepared for skeletal examination; fetal values were reported both individually as well as by litter. Statistical analyses were conducted on all relevant data sets.

No dams died, aborted or delivered spontaneously during the course of the study, but significant levels of fasciculation were recorded at 1.0 and 2.0 mg/kg/day (respectively, in 20 and 25 animals), as well as significant mean body weight losses and decreased food consumption (the latter recovered to control levels during the post-treatment period, days 16 through 20, Additionally at the HDT, 20/25 dams had tremors, 18/25 decreased limb tone, 15/25 gritting of the teeth, while shallow breathing was observed in 5/25, and salivation in 12. Finally, urogenital staining, soft stool and dried red ocular/nasal matter were common in HDT animals. No gross pathological changes attributable to test article were revealed; incidental findings unrelated to treatment were described in a small number of animals at all doses.

No compound-related adverse embryotoxic/fetotoxic effects in test animals compared to water controls were recorded for any fetal parameter. Gross external and/or visceral malformations were recorded in a few fetuses from different litters, equally distributed over the five dosage groups, while skeletal examinations revealed minor changes unremarkably similar in all groups (including controls).

Thus the maternal NOEL in this rat study appears to be 0.5 mg/kg/day, and the maternal LOEL for clinical toxicity 1.0 mg/kg/kg, while the developmental (fetal) NOEL is 2.0 mg/kg/day, with the LEL greater than the HDT.

This study is ACCEPTABLE to satisfy one of the two FIFRA Test Guideline studies required for developmental toxicity data (83-3).

3. Reproductive Toxicity:

In a multigeneration reproduction study (MRID # 44296101), Dicrotophos (87.65% a.i.; Batch No. 403001 B) was administered to groups of 26 male and 26 female Alpk:AP$_f$SD rats (from the Rodent Breeding Unit, Alderley Park) in the diet at concentrations of 0, 0.5, 5.0, or 10/15/25 ppm for two generations. Two litters were produced in the first generation and one litter was produced in the second generation. Premating doses for the adult F_0 males were 0.5, 0.49, and 2.53 mg/kg/day and for the F_0 females were 0.5, 0.53, and 2.79 mg/kg/day, respectively. Premating doses for the adult F_1 males were 0.5, 0.56, and 1.15 mg/kg/day and for the F_1 females were 0.6, 0.59, and 1.25 mg/kg/day, respectively. **Due to a high mortality in the F_{1a} pups in the 25 ppm group, the dietary concentration of Dicrotophos was lowered to 10 ppm for four dams from lactation day 8 through termination of the litter.** During mating, gestation, and lactation of the F_{1b} litters, high-dose animals were given diets containing 15 ppm. The control, low-, and mid-dose F_1 pups were weaned onto the same diets as their parents. The F_1 pups in the high dose group were weaned onto diets containing 10 ppm Dicrotophos. Animals were given test or control diet for 10 weeks then mated within the same dose group. All animals were exposed to test material either in the diet or during lactation until sacrifice.

Clinical signs of toxicity were observed during premating weeks 2-5 as involuntary shaking of the limbs in 5/26 F_0 males ($p<0.05$) and 11/26 F_0 females ($p<0.01$) given 25 ppm. No dose- or

treatment-related clinical signs of toxicity were observed in the parental F_0 or F_1 animals given diets containing less than 25 ppm. No dose- or treatment-related gross abnormalities were observed in the F_0 or F_1 adults at necropsy; histopathological evaluations were not performed.

Mid and high-dose F_0 males had significantly lower mean body weights as compared to controls ($p<0.05$ or 0.01). Food consumption was significantly ($p<0.01$) reduced in the high-dose F_0 males as compared with controls during premating. Food utilization was significantly ($p<0.05$ or 0.01) lower in the mid- and high-dose F_0 males as compared with the controls.

Mid and high-dose F_0 females had significantly lower mean body weights than the controls during premating ($p<0.05$ or 0.01). Food consumption by the high-dose F_0 females was significantly ($p<0.01$) less at the beginning of premating, but was significantly ($p<0.05$ or 0.01) greater than the controls during latter premating. High-dose F_0 females also had significantly ($p<0.01$) lower food utilization at the beginning of premating and then significantly ($p<0.05$) higher food utilization during latter premating weeks as compared with the controls.

Mean body weights of the mid- and high-dose F_1 males were significantly ($p<0.01$) lower than the controls during week 1 of the premating period. Food consumption by the F_1 males was similar between the treated and control groups throughout the premating period. Food utilization was significantly ($p<0.05$) reduced in the mid- and high-dose groups during early premating.

Mean body weights of all treated F_1 female groups were significantly ($p<0.05$ or 0.01) lower than the controls during week 1 of the premating period. No statistically significant differences in body weights occurred during the remainder of the premating period. In the high-dose F_1 females, food consumption was significantly ($p<0.05$ or 0.01) greater than the controls during most of the premating period and food utilization was significantly ($p<0.05$) greater during weeks 8-10.

The Systemic Toxicity NOEL is 0.5 ppm (0.025 mg/kg/day) and the Systemic Toxicity LOEL is 5.0 ppm (0.25 mg/kg/day) based on lower body weights in the F_0 and F_1 males and females and reduced food utilization in F_0 males and females and F_1 males.

High-dose F_0 females had significantly ($p<0.05$ or 0.01) lower body weights than the controls during gestation of litter A. No differences in body weights occurred between treated and control groups during gestation of litter B. During lactation of litter A, maternal body weights of the mid- and high-dose animals were significantly ($p<0.05$ or 0.01) lower than the controls. During lactation of litter B, maternal body weights of the mid- and high-dose animals were significantly ($p<0.05$ or 0.01) lower than the controls. Food consumption by the treated F_0 groups was greater than the controls during gestation of both the A and B litters with occasional statistical significance in the mid- and high-dose groups. In contrast, food consumption by the high-dose F_0 females was significantly ($p<0.05$ or 0.01) less than the controls throughout lactation of both litters (68-80%).

No treatment-related differences in body weights were observed in the F_1 females during gestation. However, all treated F_1 groups had significantly ($p<0.05$ or 0.01) lower maternal body weights as compared with the controls during lactation. Food consumption was significantly ($p<0.01$) greater than the controls by the high-dose F_1 females throughout gestation and once by the mid-dose F_1 females. In contrast, food consumption during lactation was occasionally significantly ($p<0.05$ or 0.01) less than the controls in all treated dams.

For the control, low-, mid-, and high-dose F_0 adults in production of litter A, the proportion of successful matings was 70%, 67.9%, 85.7%, and 33.3% ($p<0.01$), respectively; the per cent of live born pups was 97%, 99.2%, 98%, and 90.4% ($p<0.05$), respectively; and whole litter losses were 4/21, 0/19, 5/24, and 8/12 ($p<0.05$), respectively. Whole litter losses during production of litter B were 4/22, 2/18, 6/23, and 10/19 ($p<0.05$), respectively. Whole litter losses by the F_1 generation were 0/20, 1/23, 2/21, and 6/23 ($p<0.05$), for the control, low-, mid-, and high-dose groups, respectively.

During lactation, no dose- or treatment-related clinical signs of toxicity or differences in pup body weights were observed in the offspring of either generation. For both litters produced by the F_0 animals, there was a significant ($p<0.05$ or 0.01) decrease in the number of F_1 pups/litter in the high-dose group after day 1 of lactation. Pup deaths in the high-dose group resulted in significantly lower lactation indices of 56.6% ($p<0.01$) vs 88.0% for the controls for litter A and 75.4% ($p<0.05$) vs 92.7% for the controls for litter B. The number of F_2 pups/litter was significantly ($p<0.01$) decreased due to treatment in the mid- and high-dose groups as compared to controls after lactation day 1. Lactation indices for the control, low-, mid-, and high-dose F_2 litters were 96.8%, 94.1%, 83.8% ($p<0.05$), and 75.6% ($p<0.01$), respectively.

The Reproductive Toxicity NOEL is 0.5 ppm (0.025 mg/kg/day) and the Reproductive Toxicity LOEL is 5.0 ppm (0.25 mg/kg/day) based on a reduced number of F_2 pups/litter during lactation.

This study is classified as Acceptable-Guideline and satisfies the guideline requirement for a reproduction study (§83-4) in rats.

4. Additional information from the literature: None

5. Determination of Susceptibility:

The HIARC concluded that a determination of enhanced susceptibility to infants and children from exposure to Dicrotophos can not be made at this time due to the lack of a prenatal developmental toxicity study in rabbits (critical datagap).

6. Recommendation for a Developmental Neurotoxicity Study

The HIARC could not make a recommendation for this study due to the lack of two critical studies (Rabbit Developmental Toxicity and Acute Delayed Neurotoxicity) that are necessary in making this recommendation.

7. Recommendation of the FQPA Safety Factor:

The HIARC recommends to the FQPA Safety Factor Committee that the additional 10 x factor (as required by FQPA) should be retained because the toxicology data base is not complete. Data gaps exists for 1) Acute Delayed neurotoxicity and 2) Prenatal developmental toxicity study in Rabbits.

VI. HAZARD CHARACTERIZATION

Due to the unacceptable and unreviewed studies, the complete hazard characterization could not be performed.

VII. DATA GAPS

Acute Delayed Neurotoxicity - Hen
Developmental Toxicity -Rabbit
Acute Inhalation
21-Day Dermal - Rabbit
90-Day Rat
2-Year Chronic toxicity/Carcinogenicity - Rat (under review)
2-Year Carcinogenicity - Mouse (under review)

VIII. ACUTE TOXICITY

Acute Toxicity of Dicrotophos

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	/43893901	LD_{50} = 11/8 mg/kg	I
81-2	Acute Dermal	00261098	LD_{50} 876/476 = mg/kg	II
81-4	Primary Eye Irritation	00261098	Lesions reversed by 14 days	II
81-5	Primary Skin Irritation	00261098	No irritation	IV
81-6	Dermal Sensitization	00261098	Strong sensitizer	-

IX 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	LOEL= 0.5 UF = 1000	Inhibition of the plasma, RBC and brain cholinesterase activity on day 1.	Acute Neurotoxicity -Rat
	Acute RfD = 0.0005 mg/kg		
Chronic Dietary	LOEL= 0.025	Inhibition of plasma cholinesterase activity in both sexes.	Chronic Toxicity - Dog
	UF = 1000	**Chronic RfD** = 0.000025 mg/kg/day	
Short-Term* (Dermal)	LOEL= 0.5 mg/kg	Inhibition of the plasma, RBC and brain cholinesterase activity on day 1..	Acute Neurotoxicity -Rat
Intermediate-Term* (Dermal)	LOEL= 0.025 mg/kg	Inhibition of plasma cholinesterase activity in both sexes was observed at Week 13 measurement.	Chronic Toxicity - Dog
Long-Term (Dermal)	Based on the use pattern, long-term exposure risk assessment is not required.		
Inhalation* (Any Time Period)	LOEL= 0.5 mg/kg	Inhibition of plasma, RBC and brain cholinesterase activity in both sexes.	Acute Neurotoxicity -Rat

* Since an oral LOEL was selected a 100% dermal and inhalation absorption rules should be used for risk assessments. Also a MOE of 1000 is required for occupational exposure.