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

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MEMORANDUM

SUBJECT: RfD/Peer Review Report of Profenofos (Curacron)™ [O-4-bromo-2-chlorophenyl O-ethyl S-propyl phosphorothioate]

CASRN: 41198-08-7
EPA Chem. Code: 111401
Caswell No.: 266AA

FROM: George Z. Ghali, Ph.D. G. Ghali 2.6.96
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam W. Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Robert Forrest, PM 14
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The Health Effects Division-RfD/Peer Review Committee met on November 09, 1995 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Profenofos reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, a chronic (6-month) toxicity study in dogs **(83-1b)**, two multi-generation reproductive toxicity studies in rats **(83-4)**, developmental toxicity studies in rats and rabbits **(83-3a and -3b)** subchronic toxicity studies in rats **(82-1a)** and dogs **(82-1b)**, a subchronic neurobehavioral toxicity study in rats **(82-7)** and a battery of mutagenicity studies **(84-2)**.

A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, MRID No. 0081685) to be acceptable and the data evaluation record for this study (HED Doc. No. 001783, 000000) to be adequate.

The no-observable effect level (NOEL) was considered to be 0.3 ppm (0.015 mg/kg/day), and the lowest-observable effect level (LOEL) was considered to be 10 ppm (0.5 mg/kg/day) based on inhibition of plasma, red blood cell and brain cholinesterase. The Committee agreed with the reviewer's evaluation and interpretation of the data and classification of the study.

The Committee examined the chronic toxicity phase of the carcinogenicity study in mice (83-2b, MRID No. 00082901) and agreed with the reviewer's evaluation and interpretation of the data (HED Doc. No. 001783, 000000).

The Committee considered the six-month feeding toxicity study in dogs (83-1b, MRID No. 00081687) to be acceptable and the data evaluation record (HED Doc. No. 001783, 007768, 000000) to be adequate. The NOEL/LOEL for both plasma and red blood cell cholinesterase in males were considered to be 0.2 ppm (0.005 mg/kg/day) and 2.0 ppm (0.05 mg/kg/day), respectively. In females the NOEL/LOEL for plasma cholinesterase were considered to be 0.2 ppm (0.005 mg/kg/day) and 2 ppm (0.05 mg/kg/day), respectively. In this study, it was noted that brain cholinesterase was inhibited at levels much higher than those causing significant inhibition of plasma and red blood cell cholinesterase. Brain cholinesterase was inhibited 5% only at 2.00 ppm dose level in males; in females, brain cholinesterase inhibition was 8%, 10%, 11%, and 5% for the 0.2, 2.0, 100.0 or 500 ppm dietary levels of profenofos, respectively.

The Committee examined several subchronic toxicity studies in rats (82-1a, MRID No. 00105255) and dogs (82-1b, MRID No. 00108016) and considered the rat study to be acceptable, while the dog study was considered to be supplementary. The findings of the two subchronic studies were supportive to the longer-term studies in these two species.

B. Carcinogenicity:

The Committee considered the carcinogenicity phase of the chronic toxicity/carcinogenicity study in rats (83-2a, MRID No. 00081685) to be acceptable and the data evaluation record (HED Doc. No. 001783, 000000) to be adequate.

The highest dose level tested in this study (100 ppm, equivalent to 5 mg/kg/day) was considered to be adequate for carcinogenicity testing in this species based on plasma and red

blood cell cholinesterase inhibition in males and females. Brain cholinesterase inhibition was significantly inhibited only in females at 105 weeks. The steep dose-response relationship characterizing the effect of this cholinesterase inhibitor posed limitation on the ability to test the chemical at higher dose levels.

The committee concluded that the treatment did not alter the spontaneous tumor profile in this strain of rats under the testing conditions.

The Committee considered the carcinogenicity study in mice (83-2b, MRID No. 00082901) to be acceptable and the data evaluation record (HED Doc. No. 001783, 000000) to be adequate.

The highest dose level tested in this study (100 ppm, equivalent to 15.0 mg/kg/day) was considered to be adequate for carcinogenicity testing in this species based on plasma and red blood cell cholinesterase inhibition in males and females. However, the same comments made above regarding the adequacy of the dose levels tested in the carcinogenicity study in rats is also applicable to the mouse study.

The committee concluded that the treatment did not alter the spontaneous tumor profile in this strain of mice under the testing conditions.

The Committee recommended that this chemical be classified as a **"Group E"**, evidence of non-carcinogenicity for humans; i.e. the chemical is **not likely** to be carcinogenic to humans via relevant routes of exposure. This weight of the evidence judgment is largely based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies. It should be noted, however, that designation of an agent as being in Group E is based on the available evidence and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances.

C. <u>Reproductive and Developmental Toxicity</u>:

The Committee considered the 2-generation reproductive toxicity study in rats (83-4, 1994, MRID No. 43213308, 43213309) to be acceptable and the data evaluation record (HED Doc. No. 000000) to be adequate. However, pup weights were not included in the data evaluation record. The Committee recommended combining the developmental and systemic toxicity NOEL/LOEL.

According to the data evaluation record, the parental systemic toxicity NOEL was considered to be 100 ppm. The LOEL was considered to be 400 ppm, the highest dose level tested, based on decreased body weight and cumulative body weight gain reduction in both males and females of both F0 and F1 generations at all time

periods throughout the study, and decreased food consumption for males and females of both generations during the growth phase.

According to the data evaluation record, the NOEL for perinatal and reproductive effects was considered to be 100 ppm, and the LOEL was considered to be 400 ppm, based on decreased pup weight and cumulative body weight gain on days 14 and 21 of lactation.

The Committee considered the 3-generation reproductive toxicity study in rats (83-4, 1979, MRID No. 00082088) to be unacceptable and the data evaluation record of this study (HED Doc. No. 000822, 000821, 001629, 001573, 003001, 000000) to be adequate. However, a more recent reproductive toxicity study in rats is available and is considered adequate to satisfy the Guideline requirement for reproductive toxicity testing in rats.

The Committee considered the developmental toxicity study in rats (83-3a, 1982, MRID No. 00109313) to be unacceptable and the data evaluation record (HED Doc. No. 002247, 000000) to be inadequate. Based on the available data, the NOEL/LOEL could not be determined for parameters investigated in this study. However, the Committee noted that the lowest dose level tested in this study is higher than the lowest observable effect level for cholinesterase inhibition for rats demonstrated in other studies. The Committee also indicated that, based on the available data, it appears that the treatment was not associated with any major developmental toxicity.

The Committee considered the developmental toxicity study in rats (83-3a, 1974, MRID No. 00045031) to be acceptable and the data evaluation record (HED Doc. No. 000821, 000000) to be inadequate. However, the Committee noted that the lowest dose level tested in this study is higher than the lowest-observable effect level for cholinesterase inhibition for rats demonstrated in other studies. The Committee also indicated that it is not necessary to upgrade the data evaluation record of this study.

The Committee considered the developmental toxicity study in rabbits (83-3b, 1983, MRID No. 00128870) to be unacceptable and the data evaluation record (HED Doc. No. 003323, 004780, 000000) to be inadequate.

Overall, the Committee concluded that, with respect to the reproductive and developmental toxicity studies, the dose levels tested in these studies were equal to or much greater than the lowest-observable effect level for cholinesterase inhibition demonstrated in other studies. Therefore, repeating of studies or upgrading of the data evaluation records of these studies will not be necessary since it will not contribute additional information to the toxicological assessment of this chemical.

D. Mutagenicity:

The Committee considered the following mutagenicity studies to be acceptable:

1) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 41866901, Doc. No. 000000): the test material was negative in all strains up to 5000 μg/plate in the presence or absence of metabolic activation (+/-S9) and insoluble at ≥1250 μg/plate in the presence or absence of metabolic activation (+/-S9).

2) In vitro chromosome aberrations in Chinese hamster ovary (CHO) cells (MRID No. 41945103, HED Doc. No. 000000): The test material was negative up to cytotoxic doses (75 μg/ml -S9) or doses approaching a cytotoxic level (18.75 μg/ml +S9).

3) Mouse micronucleus assay (MRID No. 41945102, HED Doc. No. 000000): The test material was negative in Tif:MAGF mice up to a lethal dose (200 mg/kg --oral gavage) but no bone marrow cytotoxicity was demonstrated.

4) In vitro unscheduled DNA synthesis (UDS) with 1° rat hepatocytes (MRID No. 41945101, HED Doc. No. 000000): The test material was negative up to cytotoxic levels (2.91 μg/ml).

In addition, two studies (Microbial gene mutation assay; HED Doc. No. 000821 and a dominant lethal assay in mice; HED Doc. No. 000821) were conducted in 1978 and 1974, respectively. Only summarized information was available for review. Since an acceptable microbial gene mutation assay exists, a reevaluation of the 1978 S. typhimurium assay was not considered necessary. Similarly, the results of the dominant lethal assay (negative) did not add substantively to the genetic toxicology database. Reevaluation of this study was also not warranted. However, the dominant lethal assay should be downgraded to unacceptable.

The O-ethyl S-propyl phosphorothioate portion of the molecule is consistent with a cholinesterase inhibitor. No data were found in the open literature on the halogenated phenol portion of the molecule. However, 2,4-dichlorophenol, which is structurally similar, has been tested in the NTP and found to be neither mutagenic nor carcinogenic.

The Committee overall concluded that the acceptable studies satisfy the pre-1991 mutagenicity initial testing battery. Based on the available toxicology data, there is no concern for mutagenicity at this time.

E. Acute and Subchronic Neurotoxicity:

The Committee considered the subchronic (90 day) neurobehavioral toxicity study in rats (82-7, MRID No. 43213303, 43213304) to be acceptable, after examination of summary data tables from the study subsequent to the meeting. These summary tables were not included in the data evaluation record (HED Doc. No. 000000) at the time of the meeting. The Committee considered the data evaluation record would be adequate provided that summary tables on motor activity (pp 194-5 of the study as well as pp 196 and 202, which would cover pre-exposure and week 13 intervals) are included. In addition, some descriptive summary of the positive results from the FOB and report of its quantitative measures, e.g. grip strength and foot splay are warranted. The Committee agreed with the reviewer's evaluation and interpretation of the data as presented in the data evaluation record of this study (HED Doc. No. 000000).

Although not available for review by the Committee, it should be noted that acute delayed neurotoxicity studies in hens (81-7) and an acute neurotoxicity study in rats (81-8) have been conducted with profenofos. In the delayed neurotoxicity study in hens with a formulation containing 38% profenofos (MRID No. 00082084), no effects were noted at dose levels up to 52 mg/kg/day of body weight, and 100% mortality occurred at the next higher dose level (104 mg/kg). Negative results were also reported in two supplementary studies on technical profenofos (MRID No. 00082083; 00082085). In the acute oral neurotoxicity study in rats (MRID No. 42939801, 42939802), the NOEL for neurotoxicity was 95 mg/kg of body weight (based on multiple effects observed at 190 mg/kg/day). The NOEL for cholinesterase inhibition in this study was $\leq$ 95 mg/kg, based on significant inhibition of both plasma and red blood cell cholinesterase at this dose, which was the lowest dose tested.

F. Reference Dose (RfD):

The Committee recommended that the RfD for this chemical remain unchanged. The RfD has been established based on the long-term (6-month) toxicity study in dogs with a NOEL of 0.2 ppm (0.005 mg/kg/day). Erythrocyte and plasma cholinesterase inhibition was observed at the next higher dose level of 2 ppm (0.05 mg/kg/day). In this dog study, brain cholinesterase was apparently inhibited only at much higher dose levels than those eliciting significant inhibition of plasma and red blood cell cholinesterase. However, this difference might be due to possible defects in the methodology used for determining effects on brain cholinesterase.

Furthermore, in a 21-day dermal toxicity study of profenofos in rabbits (MRID No. 41644501), profenofos elicited significant inhibition of cholinesterase activities in brain (70-80% of control values) and in plasma and red blood cells (51-83% of control values) at the same dose level (10 mg/kg/day). The results of this

21-day dermal toxicity study indicate that it is prudent to assume that doses of profenofos which elicit inhibition of cholinesterase activities in plasma and red blood cells might also cause inhibition of brain cholinesterase.

An Uncertainty Factor (UF) of 100 was applied to account for both the interspecies extrapolation and intraspecies variability. On this basis, the RfD was calculated to be 0.00005 mg/kg/day.

It should be noted that this chemical has been reviewed by the WHO/FAO joint meeting on pesticide residues (JMPR) in 1990 and an Acceptable Daily Intake (ADI) of 0.01 mg/kg/day has been established.

In the JMPR evaluation, the following studies were considered to be significant in the assessment of the ADI for this chemical:

1) A mouse study with a NOEL of 30 ppm, equal to 5.8 mg/kg/day in females.

2) A rat reproduction study with a NOEL of 20 ppm, equal to 1.0 mg/kg/day.

3) A rat long-term study with a NOEL of 100 ppm, equal to 5.7 mg/kg/day.

4) A dog study with a NOEL of 2.9 mg/kg/day.

It appears that the JMPR used the rat reproductive toxicity study with a NOEL of 1.0 mg/kg/day as the critical study and a Safety Factor of 100 was applied to generate the ADI for this chemical.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/QA Peer Review Committee), George Ghali (Manager, RfD/QA Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Stephen Dapson, Roger Gardner, Nancy McCarrol, Esther Rinde, William Sette, Henry Spencer and Rick Whiting. In attendance also were Kit Farwell, Barbara Madden and Paula Deschamp of HED as observers.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report)

Ray Locke Raymond K. Locke

Joycelyn Stewart Joycelyn E. Stewart

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

Karl Baetcke

CC: Stephanie Irene
Debra Edwards
Marion Copley
Karl Baetcke
Joycelyn Stewart
Ray Locke
Albin Kocialski
Karen Whitby
Paula Deschamp
Beth Doyle
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Burdock, G. A. (1981). Two-year chronic oral toxicity study in albino rats with CGA-15324 technical (Curacron). MRID No. 00081685, HED Doc. No. 001783, 000000. Classification: Acceptable. This study satisfies data requirement 83-5 (83-1a and 83-2a) of Subpart F of the Pesticide Assessment Guideline for chronic toxicity and carcinogenicity testing in rats.

2. Pence, L. A. et al. (1981). Twenty-four month carcinogenicity in mice. MRID No. 00082901, HED Doc. No. 001783, 000000. Classification: Acceptable. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Gfeller, W. et al. (1981). Six-month toxicity study with dogs, using CGA-15324 technical (curacron). MRID No. 00081687, HED Doc. No. 001783, 007768, 000000. Classification: Acceptable. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Minor, J. L. and Richter, A. G. (1994). A two-generation reproduction study in rats with CGA-15324 technical. MRID No. 43213308, 43213309, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

5. Ciba-Geigy, Ltd. (1979). Three-generation reproduction study with CGA-15324 technical in albino rats. MRID No. 00082088, 000822, 001629, 001573, 003001, 000821, 000000. Classification: Unacceptable as downgraded by the RfD Committee. This study does not satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats. However, the Committee determined that a new study will not be required.

6. Harris, S. et al. (1982). A teratology study of CGA-15324 technical in albino rats. MRID No. 00109313, HED Doc. No. 002247, 000000. Classification: Unacceptable as downgraded by the RfD Committee. This study does not satisfy data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats. However, the Committee determined that a new study will not be required at this time.

7. Fritz, H. (1974). Reproductive study--technical CGA-15324: rat: segment II (test for teratogenic or embryotoxic effects). MRID No. 00045031, HED Doc. No. 000821, 000000. Classification: Acceptable. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment

Guideline for developmental toxicity testing in rats. The Committee determined that updating of the data evaluation record will not be required at this time.

8. Holson, J. et al. (1983). Teratology study Seg. II) in albino rabbits with CGA-15324 technical. MRID No. 00128870, HED Doc. No. 003323, 004780, 000000. Classification: supplementary. This study does not satisfy data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits. However, the Committee determined that a new study will not be required at this time.

9. Reyna, M. et al. (1975). 90-Day subacute oral toxicity study with CGA-15324 technical in albino rats. MRID No. 00105255, HED Doc. No. 000000. Classification: supplementary. This study does not satisfy data requirement 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rats.

10. Nelson, R. (1975). 90-Day subacute oral toxicity study with CGA-15324 technical in beagle dogs. MRID No. 00108016, HED Doc. No. 000821, 000823, 002536, 000000. Classification: Acceptable. This study satisfies data requirement 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.

11. Pettersen, J. C. and Morissey, R. L. (1994). 90-Day subchronic neurobehavioral toxicity study with CGA-15324 technical in rats. MRID No. 43213303, 43213304, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 82-7 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.

12. Hertner, T. (1991). CGA-15342 technical: micronucleus test, mouse. MRID No. 41945102, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

13. Strasser, F. F. (1990). CGA-15342 technical: chromosome studies on chinese hamster ovary cell line 61 in vitro. MRID No. 41945103, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

14. Geleick, D. (original report 1982, supplementary report 1991). CGA-15342 technical: supplement to autoradiography DNA repair test on rat hepatocytes. MRID No. 41945101, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

15. Ogorek, B. (1991). CGA-15324 technical: Salmonella and Escherichia/liver-microsome test - gene mutation test. MRID No. 41866901, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.