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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/ Peer Review Report of CHLORFENPYR (PIRATE®) - Pyrrole-3-carbonitrile, 4-bromo-2-(p-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)

CASRN: 122453-73-0
EPA Chem. Code: None
Caswell No. :None

FROM: Henry W. Spencer, Ph.D. 10/21/96
Member, RfD/QA Peer Review Committee
Health Effects Division (7509C)

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

TO: Dennis Edwards, PM 19
Insecticide Branch
Registration Division (7505C)

The Health Effects Division RfD/Peer Review Committee met on July 18, 1996 to discuss and evaluate the existing toxicology data in support of the registration of the new chemical, chlorfenpyr (Pirate®). An ad hoc group of six members met a second time on October 9, 1996 to consider additional data requirements based on the conclusions of the RfD/Peer Review Committee at the July 18, 1996 meeting.

At the meeting of July 18, 1996, material available for review consisted of data evaluation records (DERs) for one chronic toxicity/carcinogenicity study in rats **(83-5 or 83-1a, 83-2a)**, one chronic toxicity/carcinogenicity study in mice **(83-5 or 83-2b)**, one chronic (one year) feeding toxicity study in dogs **(83-1b)**, one multi-generation reproductive toxicity study in rats **(83-4)**, developmental toxicity studies in rat and rabbits **(83-3a and -3b)**, subchronic toxicity studies in rats and dogs and mice **(82-1a and 82-1b)**, both acute and subchronic (one year) neurotoxicity studies in rats **(81-8 and 82-7)**, two 28 day dermal toxicity studies in rabbits **(82-2)**, and a battery of mutagenicity studies **(84-2)**.

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A. Chronic and Subchronic Toxicity:

The chronic rat toxicity study (MRID No. 43492837, 434292836) used 0, 60, 300 or 600 ppm of chlorfenpyr in the diet. The Committee considered the study to be acceptable with the NOEL established at 60 ppm (2.9 and 3.6 mg/kg/day for males and females respectively) and the LOEL set at 300 ppm (15.0 and 18.6 mg/kg/day for males and females). Although the study was considered to be acceptable, the concern over whether the study was adequately tested for carcinogenicity was left to be addressed by the Cancer Peer Review Committee. The Committee found that the draft DER was generally acceptable but the executive summary needed to be modified.

The chronic mouse study (MRID No. 43492838) used 0, 20, 120 or 240 ppm of the chlorfenpyr test material in the diet. Vacuolation of the brain and other nervous tissues occurred in both sexes of the test animals at the mid dose of 120 ppm (16.6 and 21.9 mg/kg/day in males and females respectively). The NOEL was set at 20 ppm (2.8 and 3.7 mg/kg/day in males and females) with the LOEL set at 120 ppm. The study exhibited depressed survival in females at the highest dose (240 ppm) and also showed weight losses in both males and females at 120 ppm. The study was considered to be acceptable for chronic and for oncogenicity testing and the DER adequate.

The one year feeding study of the dog (MRID No. 43492834) used 0, 60, 120 or 240 ppm of chlorfenpyr in the diet. The Committee examined the DER and generally agreed with the reviewer and considered the study acceptable. The NOEL was stated to be 120 ppm (4.0 mg/kg/day) with the LOEL of 240 ppm (8.7 mg/kg/day) based on decreased body weights and body weight gains seen in both sexes. No other treatment related effects were observed in the study.

B. Carcinogenicity:

The Committee evaluated the rat chronic/carcinogenicity study (MRID No. 43492837, 434292836) and concluded that the study should be referred to the Cancer Peer Review Committee for a final determination of carcinogenicity. The question of the adequacy of the dosages used in the study was left to the CPRC for evaluation.

The Committee also evaluated the mouse carcinogenicity study (MRID No. 43492838, 434292830) and found the study to be acceptable and the DER adequate. The incidence of hepatocellular adenomas and carcinomas when combined, was not significantly different in treated animals when compared to controls in the study. Incidence of lung tumors in the test animals also showed no significant differences compared to controls.

C. Reproductive and Developmental Toxicity:

The Committee considered the 2-generation reproduction study in rats (MRID No. 43492836, 434292835) to be acceptable and the DER adequate. The study showed systemic toxicity to the parents (LOEL) at 300 ppm (22 mg/kg/day) based on parental weight gain and the NOEL was 60 ppm (5 mg/kg/day). There were no reproductive performance effects noted at any dose level (HDT = 600 ppm, 44 mg/kg/day) however a reduction in lactational weight gains was reported at 300 ppm. Therefore the NOEL for reproductive toxicity is 60 ppm (5 mg/kg/day) and the LOEL for reproductive toxicity is 300 (22 mg/kg/day).

A developmental toxicity study in rats (MRID No. 42770221 and 42884202, HED Doc. No 010949) was evaluated. The maternal toxicity NOEL is 25 mg/kg/day and the maternal LOEL is established at 75 mg/kg/day based on reduced body weight gain, feed intake and water consumption. No developmental toxicity was noted. The developmental NOEL was greater or equal to the high dose of 225 mg/kg/day. The study was considered to be acceptable and the DER adequate.

A developmental toxicity study in rabbits (MRID No. 42770222, HED Doc. No. 010651) was evaluated. The maternal toxicity LOEL was 15 mg/kg/day based upon reduced body weight gain during the treatment phase. The NOEL was 5 mg/kg/day. No developmental toxicity was reported at the HDT of 30 mg/kg/day. The Committee considered the study acceptable and the DER adequate.

The Committee recommended that a developmental neurotoxicity study be conducted based upon the effects of a spongyform myelopathy seen in the brain and spinal cord of treated rats and mice (see section F for details).

D. Acute and Subchronic Neurotoxicity:

The Committee evaluated the draft DER of the acute neurotoxicity study in rats (MRID No. 43492829) and considered the study to be acceptable, however, the Committee agreed that the study classification be lowered to unacceptable until the DER is amended to provide corrections and additional tables on the FOB. The study does not fulfill the neurotoxicity data requirement. Subsequent to the meeting, the additional required information was received allowing the study to be classified acceptable and to fulfill the neurotoxicity data requirements. The NOEL was established at 45 mg/kg and the LOEL was 90 mg/kg based on lethargy on the day of treatment.

The Committee considered a one-year Dietary Neurotoxicity study in rats (MRID No. 43492833) in which both male and female SD rats were given 0, 60, 300, or 600 ppm of chlorfenpyr in the feed.

After 13 weeks, histopathological staining in male nervous tissues revealed myelin sheath swelling in the spinal nerve roots in 5/5 rats at 600 ppm compared to 2/5 rats in controls. After 1 year, a more generalized myelinopathic process consisting of vacuolar myelinopathy, vacuolation and/or mild myelin sheath swelling was reported. Major areas of the brain were affected by the chemical at 300 and 600 ppm in the males. The NOEL was established at 60 ppm (2.6 mg/kg/day - males). The LOEL was 300 ppm (13.6 mg/kg/day - males).

E. Mutagenicity:

The Committee accepted the evaluations of Committee member, Nancy McCarroll, for the following acceptable studies (with MRID/Accession and/or Document Control Numbers):

1) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 42770223): Independently performed tests with chlorfenpyr (94.5%) were negative in all strains up to a cytotoxic dose (50 µg/plate +/-S9).

2) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 43492841): Independently performed tests with the chlorfenpyr impurity: 2-(6-chlorophenyl)-1-(ethoxymethyl)-5-(trifluoromethyl)-pyrrole-2-carbonitrile (96.3%) were negative in all strains up to insoluble concentrations (≥250 µg/plate -S9; ≥500 µg/plate +S9).

3) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 43492840): Independently performed tests with a chlorfenpyr metabolite and impurity: 4-bromo-2-(p-chlorophenyl)-5-(trifluoromethyl)-pyrrole-3-carbonitrile (100.3%) were negative up to a cytotoxic dose (5 µg/plate +/-S9) with all S. typhimurium strains and to the solubility limit (250 µg/plate +/-S9) with E. coli.

4) Salmonella typhimurium/Escherichia coli reverse gene mutation assay (MRID No. 43492842): Independently performed tests with a chlorfenpyr metabolite: 3-bromo-5-(p-chlorophenyl)-4-cyano-pyrrole-2-carboxylic acid (89%) were negative up to doses (≥1000 µg/plate -S9; 2500 µg/plate +S9) that were cytotoxic to all S. typhimurium strains. Compound precipitation was seen at the highest concentration tested (5000 µg/plate +/-S9) with E. coli.

5) Chinese hamster ovary (CHO) cell HGPRT gene mutation assay (MRID Nos. 42770224/43187601): Independently performed tests were negative up to a cytotoxic and precipitating concentration (500 µg/mL) in the presence of S9 activation or the solubility limit (250 µg/mL) without S9 activation.

6) In vitro CHO cell chromosome aberration assay (MRID No.

434928443): The test was negative up to 100 μg/mL -S9 or 25 μg/mL +S9; higher doses with or without S9 activation were cytotoxic.

7) In vitro Chinese hamster lung (CHL) fibroblasts chromosome aberration assay (MRID No. 43492839): The test was negative up to a precipitating level without S9 activation (225 μg/mL) or a concentration range of 3.5-14.1 μg/mL +S9. Higher S9-activated doses (≥28 μg/mL) were cytotoxic.

8) In vivo micronucleus assay (MRID Nos. 42770225/43187602): The test was negative in CD-1 mice administered single oral gavage doses of 7.5-30 mg/kg (males) or 5-20 mg/kg (females). Clinical toxicity (deaths in males and diarrhea in females) was seen at the HDT. There was, however, no evidence of cytotoxicity for the target organ.

9) In vitro unscheduled DNA synthesis in primary rat hepatocytes (MRID No. 42770226): The test is negative up to an actual concentration of 0.12 μg/mL; the HDT (≈0.27 μg/mL) was excessively cytotoxic.

Other Information (e.g. GeneTox printout, published studies): No additional genetic toxicology studies with chlorfenpyr were found in the open literature.

Conclusions: The available studies clearly indicate that chlorfenpyr is neither mutagenic in bacterial or mammalian cells nor clastogenic in cultured mammalian cells in vitro or in male and female mice in vivo. There was also no evidence of genotoxicity in primary rat hepatocytes.

The acceptable studies satisfy both the Pre-1991 and the New mutagenicity initial testing battery guidelines. No additional testing is necessary at this time.

F. Results of Second Meeting, October 9, 1996: concerning CNS lesions and further testing recommended by the RfD/Peer Review Committee on July 18, 1996.

The Ad Hoc Committee of six RfDC members discussed the developmental neurotoxicity study requirements as recommended by the RfD/Peer Review Committee and considered the requirements as stated in the 83-6 guidelines would be inadequate in this case.

The Ad Hoc Committee considered the following modifications necessary: a 90 day treatment period for **males and females** prior to the routine developmental phase as in 83-6. The dams would deliver their pups and come off treated feed at day 10 post-delivery. Normal testing as required in 83-6 would then commence. Further, the Ad Hoc Committee of October 9, 1996 and the Toxicology Branch consider the necessity of characterizing the nature of the

vacuoles reported in the previous studies and any found in the presently proposed study. The treated males would be used to assist in this characterization. This information may well play a great role in assessing the potential risk of this chemical. It is strongly recommended that the Registrant contact the Toxicology Branch prior to initiating the study in order to discuss dose selection and study protocol.

G. Final RfD and UF/MF values:

The RfD/Peer Review Committee of July 18, 1996 considered the NOEL in the 1-year neurotoxicity study of 2.6 mg/kg/day to be the NOEL for the chemical at that time. The second meeting group also considered the 2.6 mg/kg/day the appropriate end-point for establishing the RfD until the additional data is submitted and reviewed. Because of the type of lesions, the lack of understanding of the cause, and possible further unknown toxicity with regard to the developing young, an additional 10-fold modifying factor (MF) is considered appropriate for this chemical.

The RfD is therefore: 2.6 mg/kg/day with a 1000-fold UF/MF. Thus, the RfD is **0.003 mg/kg/day.**

H. Individuals in Attendance:

Peer Review Committee members and associates present in the meeting of July 18, 1996 were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), Henry Spencer, Rick Whiting, Karl Baetcke, (Chief, TBI), Jim Rowe. Nancy E. McCarroll, Albin Kocialski, Debbie McCall, Kit Farwell, Esther Rinde, G. Reddy, Marion Copley, Mike Ioannou (Chief TB2).

Peer Review Committee members and associates present in the meeting of October 9, 1996 were William Burnam (Chief, SAB; Chairman, RfD/QA Peer Review Committee), Henry Spencer, William Sette, Robert Fricke, G. Reddy, Marion Copley.

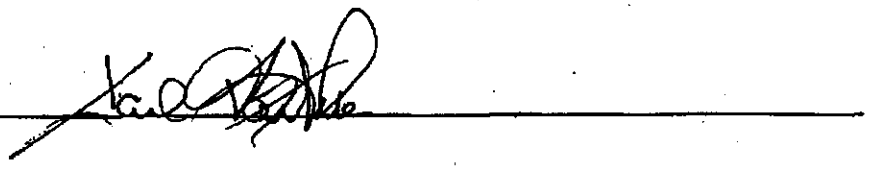
Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signatures(s) indicate technical accuracy of panel report).

Guruva Reddy M.C. For G.R.

Marion Copley Marion Copley

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

stated)

Karl Baetcke 

CC: Margaret Stasikowski
Stephanie Irene
Marion Copley
Guruva Reddy
Karl Baetcke
Albin Kocialski
Debbie McCall
Beth Doyle
RfD File
Caswell File

I. Material Reviewed:

1. Trutter, J.A. (1994). A chronic dietary toxicity and oncogenicity study AC 303,630 in rats. MRID No. 43492837. Classification: Acceptable. This study satisfies the data requirements of 83-2 and 83-1 of Subpart F of the Pesticide Assessment Guideline for toxicity and carcinogenicity testing in rats.

2. Bernier, L. (1994). A chronic dietary toxicity and oncogenicity study with AC 303630 in Mice. MRID No. 43492838. Classification: Acceptable for oncogenicity, and unacceptable for chronic toxicity testing. This study satisfies the data requirement of 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

3. Kelly, C. (1993). One year dietary study with AC 303,630 in purebred beagle dogs. MRID No. 43492834. Classification: Acceptable. This study satisfies the data requirements of 83-1b of Subpart F of the Pesticide Assessment Guideline for toxicity testing in the dog.

4. Schroeder, R. E. (1994). A two-generation (one-litter) reproduction study with AC 303,630 in rats. MRID No. 43492836. Classification: Acceptable. This study satisfies the data requirements of 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in the rat.

5. Martin, Terry (1993). An oral developmental toxicity (embryo-fetal toxicity/teratogenicity) definitive study with AC 303630 in rats. MRID No. 428842-02/427702-21, HED Doc. No.010949. Classification: Acceptable, guideline. This study satisfies the data requirements of 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in the rat.

6. Hoberman, Alan M. (1993). An oral developmental toxicity (embryo-fetal toxicity teratogenicity) definitive study with AC 303,630 in rabbits. MRID No. 427702-22, HED Doc. No. 010651. Classification: Acceptable. This study satisfies the data requirements of 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in the rabbit.

7. Fischer, Joel E. (1993). AC 303,630: 13-week and 28-day dietary toxicity studies in the albino rat. MRID No. 427702-19, HED Doc. No. 010949. Classification: Acceptable, guideline. This study satisfies the data requirements of 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in the rat.

8. Fischer, J. E. (1994). AC 303630: 13-week and 28-day dietary toxicity studies in the albino mouse. MRID No. 43492830. Classification: Acceptable. This study satisfies the data

requirements of 82-1a of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in rodents.

9. Kelly, Catherine M. (1993). 90-Day dietary toxicity study with AC 303630 in beagle dogs. MRID No. 427702-20, HED Doc. No. 010651. Classification: Acceptable. This study satisfies the data requirements of 82-1b of Subpart F of the Pesticide Assessment Guideline for subchronic toxicity testing in dogs.

10. Ponnock, K. (1994). An acute neurotoxicity study with AC 303,630 in rats. MRID No. 43492829. Classification: Unacceptable, but is upgradeable. This study does not satisfy data requirements of 81-8 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in the rat.

11. Foss, J. A. (1994). A one-year dietary neurotoxicity study with AC 303,630 in rats. MRID No. 43492833. Classification: Unacceptable, but upgradeable. This study does not satisfy data requirements of 82-7SS of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in the rat.

12. Blaszcak, D. L. (1994). A 28-day dermal toxicity study with AC 303,630 3SC in rabbits. MRID No. 43492832. Classification: Acceptable. This study satisfies the data requirements of 82-2 of Subpart F of the Pesticide Assessment Guideline for a repeated dose dermal toxicity study in rabbits.

13. Blaszcak, D.L. (1993).. A 28-day dermal toxicity study with AC 303, 630 in rabbits. MRID No. 43492831. Classification: Acceptable. This study satisfies the data requirements of 82-2 of Subpart F of the Pesticide Assessment Guideline for a repeated dose dermal toxicity study in rabbits.

14. Mulligan, E. (1993). Evaluation of CL 303,630 in a Bacterial/Microsome Mutagenicity Assay. MRID No. 42770223. Classification: Acceptable. This study satisfies the data requirement of 84-2a for genetic effects of Subpart F of the Pesticide Guideline for mutagenicity testing in bacteriae.

15. Mulligan, E. (1994). Microbial Mutagenicity Plate Incorporation Assay of CL 312,094. (impurity) MRID No. 43492841. Classification: Acceptable. This study satisfies the data requirement of 84-2 for in vitro mutagenicity bacterial reverse gene mutation of Subpart F of the Pesticide Guideline.

16. Mulligan, E. (1994). Microbial Mutagenicity Plate Incorporation Assay of CL 303,268> (metabolite and impurity) MRID No. 43492840. Classification: Acceptable. This study satisfies the data requirement of 84-2 for in vitro mutagenicity bacterial reverse gene mutation of Subpart F of the Pesticide Guideline.

17. Mulligan, E. (1994). Microbial Mutagenicity Plate

Incorporation Assay of CL 322,250. (metabolite) MRID No.43492842. Classification : Acceptable This study satisfies the data requirements of 84-2 for in vitro mutagenicity bacterial reverse gene mutation of Subpart F of the Pesticide Guideline.

18. Sharma, R. K. (1993). Evaluation of CL 303,630. MRID No. 43187601,42770224. Classification: upgraded to Acceptable. This study satisfies the data requirement for a gene mutation study of 84-2 of Subpart F of the Pesticide Guideline.

19. Sharma, R. K. (1994). Evaluation of CL 303,630 in the in vitro chromosome aberration assay n Chinese Hamster ovary (CHO) cells. MRID No. 43492843. Classification: Acceptable. This study satisfies the data requirement of 84-2 of Subpart F of the Pesticide Guideline for in vitro cytogenetic mutagenicity.

20. Adams, K. (1994). AC 303,630 (MK-242) Analysis of metaphase chromosomes obtained from CHL cells cultured in vitro. MRID No. 43492839. Classification: Acceptable. This study satisfies the data requirement for in vitro cytogenetic mutagenicity studies in (84-2) of Subpart F of the Pesticide Guideline.

21. Sharma, R. K. (1994), (1993). Evaluation of CL 303,630 in the In Vivo Micronucleus Assay in Mouse Bone Marrow Cells. MRID No. 42770225, 43187602. Classification: upgraded to Acceptable. This study satisfies the data requirement of 84-2 for a structural chromosomal aberration assay of Subpart F of the Pesticide Guideline.

22. San, R. H. C. (1993). Unscheduled DNA Synthesis in Rat Primary Hepatocytes with AC 303, 630. MRID No. 42770226. Classification: Acceptable. This study satisfies the requirements of 84-4 for other mutagenic effects of Subpart F of the Pesticide Guideline.