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

APR 21 1997

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Disulfoton (Disyston) [O-O-Diethyl S-[2-(ethylthio)ethyl]phosphorodithioate]

CASRN: 298-04-4
EPA Chem. Code: 032501
Caswell No.: 341

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

THRU: William Burnam
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Health Effects Division (7509C)

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Insecticide-Rodenticide Branch
Registration Division (7505C)

Chief, Reregistration Branch
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The Health Effects Division-RfD/Peer Review Committee met on April 25, 1996 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Disulfoton (Disyston) re-registration and to re-assess the Reference Dose (RfD) for this chemical..

Material available for review consisted of data evaluation records (DERs) for chronic toxicity/carcinogenicity studies in rats (83-5 or 83-1a and -2a), a chronic toxicity study in dogs (83-1b), a carcinogenicity study in mice (83-2b), a multi-generation reproductive toxicity study in rats (83-4), developmental toxicity studies in rats (83-1a) and rabbits (83-1b), a subchronic toxicity study in rats (82-1a), acute and subchronic neurotoxicity studies in rats (81-8 and 82-6), subchronic inhalation study in rats (82-3), 21-day dermal toxicity study in rabbits (82-2) and a battery of mutagenicity studies (84-2).

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A. Chronic and Subchronic Toxicity:

The Committee considered the chronic toxicity phase of the rat study (83-1a, 1985, MRID No. 00146873) to be acceptable, and the data evaluation record (HED Doc. No. 005029) to be adequate.

The LOEL was 1 ppm (actual concentration 0.8 ppm) or 0.04 mg/kg/day, the lowest dose tested, based on plasma, red blood cell and brain cholinesterase inhibition in both males and females.

In a special subchronic toxicity (6-month) study in rats (82-1a, 1993, MRID No. 43058401, HED Doc. No. 011249) conducted mainly to determine the NOEL for cholinesterase inhibition, the NOEL for plasma, red blood cell and brain cholinesterase inhibition was 0.5 ppm and 1 ppm (0.03 and 0.06 mg/kg/day), in females and males, respectively. The systemic NOEL was 1 ppm, the highest dose level tested.

The Committee agreed with the reviewer's evaluation and interpretation of data, as well as the classification of the chronic toxicity phase of an older feeding study in rats (83-1a, 1975, MRID No. 00069966, 00154957, HED Doc. No. 00154957), but the study was not discussed by the Committee in detail. In this study, red blood cell and brain cholinesterase inhibition was observed in both males and females at 2 ppm (0.089 and 0.1 mg/kg/day in males and females, respectively). The NOEL was 1 ppm 0.046 and 0.042 mg/kg/day in males and females, respectively).

The Committee considered the chronic toxicity study in dogs (83-1b, 1975, MRID No. 00073348) to be acceptable and the data evaluation record (HED Doc. No. 003958) to be adequate. The NOEL for plasma and red blood cell cholinesterase inhibition for both males and females was 1 ppm or 0.025 mg/kg/day, the LOEL was 2 ppm or 0.05 mg/kg/day.

There was no subchronic oral toxicity study in dogs (82-1b) available for review by the Committee.

There were two subchronic and subacute studies; a 90-day inhalation toxicity study in rats (82-3, MRID No. 41224301, HED Doc. No. 011242) and a 21-day dermal toxicity study in rabbits (82-2, MRID No. 00162338, 005556). The Committee considered both studies to be acceptable and the data evaluation records to be adequate. In the inhalation toxicity study, the NOEL/LOEL were considered to be 0.16 and 1.4 mg/kg/day, respectively, based on plasma, brain and erythrocyte cholinesterase inhibition. In the dermal toxicity study, the NOEL/LOEL were considered to be 0.4 and 1.6 mg/kg/day, respectively, based on plasma, erythrocyte and marginal brain cholinesterase inhibition.

B. Carcinogenicity:

The Committee considered the carcinogenicity phases of the combined chronic toxicity/carcinogenicity studies in rats (83-2a, MRID No. 00146873) and the carcinogenicity study in mice (83-2b, MRID No. 00129456, 00139598) to be acceptable and the data evaluation records (HED Doc. No. 005029; 003958) to be adequate as presented.

The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the carcinogenicity studies in rats and mice. The highest dose levels tested in both studies were considered to be adequate for carcinogenicity testing based on cholinesterase inhibition.

The treatment did not alter the spontaneous tumor profile in these strains of rat and mouse. The Committee, therefore, recommended that Disulfoton be classified as a "Group E", 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. Reproductive and Developmental Toxicity:

The Committee considered the reproductive toxicity study in rats (83-4, MRID No. 00157511) to be acceptable and the data evaluation record (HED Doc. No. 005796) to be adequate with the addition of an executive summary. Based upon significant depressions in brain cholinesterase in the mid and high dose groups from selected F1a male and female weanlings, it is recommended that a combined parental/reproductive NOEL be lowered to 0.04 mg/kg/day (0.8 ppm), the lowest dose level tested.

The Committee considered the developmental toxicity study in rats (83-3a, MRID No. 00129458) to be acceptable and the data evaluation record (HED Doc. No. 004067, 004223, 004698) to be adequate with the addition of an executive summary. The maternal NOEL/LOEL were considered to be 0.1 and 0.3 mg/kg/day, respectively, based on cholinesterase inhibition and clinical signs of toxicity. The developmental LOEL/NOEL were considered to be 0.3 and 1.0 mg/kg/day, respectively, based on incomplete ossification of the parietals and sternebrae.

The Committee considered the developmental toxicity study in rabbits (83-3b, MRID No. 00147886) to be acceptable and the data

evaluation record (HED Doc. No. 003958) to be adequate with the addition of an executive summary. The maternal toxicity NOEL/LOEL were considered to be 1 and 1.5 mg/kg/day, respectively. It should be noted that at 3 mg/kg/day, maternal neurotoxicity (muscular tremor, unsteadiness/incoordination) were noted within 4 hours of dosing and persisted for more than 24 hours. Later this dose was reduced to 2.0 and then 1.5 mg/kg/day due to excessive deaths. The developmental toxicity NOEL was considered to be 1.5 mg/kg/day, the highest dose level tested.

D. Neurotoxicity:

The Committee considered the acute neurotoxicity (81-7, MRID No. 42977401) and the subchronic neurotoxicity (82-7, MRID No. 42755801) studies in rats to be acceptable and the data evaluation records (HED Doc. No. 011456; 011457) to be adequate.

In the acute study, the NOEL/LOEL for systemic toxicity were considered to be 1 and 4 ppm (0.25 and 0.75 mg/kg/day) based on clinical signs in females consistent with cholinergic effects.

In the subchronic study, the NOEL for neurotoxicity was considered to be 0.071 and 0.27 mg/kg/day, in females and males, respectively. The NOEL for Cholinesterase inhibition was considered to be below 0.063 and 0.071 mg/kg/day, the lowest dose levels tested in males and females, respectively.

E. Mutagenicity:

The Committee considered the following mutagenicity studies to be acceptable:

1) Salmonella typhimurium/Escherichia coli reverse gene mutation spot test (Accession No. 072293, HED Doc. No. 004698): The test is considered positive in both species; there was, however no quantitative data and no S9 activation phase of testing.

2) Salmonella typhimurium/Escherichia coli reverse gene mutation plate incorporation assay (Accession No. 00028625, HED Doc. No. 003958): This study was conducted as part an Agency-sponsored mutagenicity screening battery. Disulfoton was negative in all strains up to the highest dose tested (5000 µg/plate +/-S9) in three independent trials. The study is currently listed as Unacceptable but should be upgraded to Acceptable since the reason for rejecting the study (number of replicates/dose not provided) is not sufficient justification.

3) Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay (MRID No. 40638401, Doc. No. 008394): The test is considered to be positive in an Unacceptable study at partially soluble levels (0.1-1.0 µL/mL -S9; 0.07-1.0 µL/mL +S9) and

insoluble doses (5-10 μL/mL -S9; 3-10 μL/mL +S9) but not active at soluble concentrations (≤0.06 μL/mL +/-S9). The mutagenic response appeared to be stronger without rather than with metabolic activation. A repeat test has been requested but not submitted. However, an acceptable mouse lymphoma assay was found in the open literature (see below).

4). Mouse micronucleus assay (MRID No. 43615701, HED Doc. No. 000000): The test is negative in NMRI mice at the only dose tested (8 mg/kg) which was administered once by intraperitoneal injection. Lethality and other signs of toxicity but no bone marrow cytotoxicity was seen.

5) E. coli DNA damage/repair test (Accession No. 072293, HED Doc. No. 004698): The test is negative up to the highest dose level tested (10,000 μg/plate +/-S9).

6) Saccharomyces cerevisiae D3 mitotic recombination assay (Accession No. 00028625, HED Doc. No. 003958): Disulfoton (up to 5% +/-S9) was negative in the Agency-sponsored mutagenicity screening battery. The study is currently listed as Unacceptable but should be upgraded to Acceptable. Upon further review of the data, it was decided that the reason for rejecting the study (number of replicates/dose not provided) did not interfere with the interpretation of the findings.

7) Sister chromatid exchange in CHO cells (MRID No. 40495001, HED Doc. No. 008394): The test is positive in a dose-related manner at 0.013-0.1 μL/mL without S9. Not active in the S9-activated phase of the study up to 0.20 μL/mL, a level causing cell cycle delay.

8) Sister chromatid exchange in Chinese hamster V79 cells (Accession No. 072293, HED Doc. No. 004223): The test is negative without metabolic activation up to the 80 μg/mL, the highest dose level tested. Subsequently tested by the same investigators (Chen et al, 1982; Environ. Mutagen. 4:621-624) in the presence of exogenous metabolic activation and found to be negative up to the 80 μg/mL, the highest dose level tested.

9) Unscheduled DNA Synthesis (UDS) in WI-38 human fibroblasts ((Accession No. 00028625; HED Doc. No. 003958): The test is positive in the absence of S9 activation at precipitating doses (1000-4000 μg/mL). Negative at comparable precipitating concentrations with S9 activation.

Disulfoton was also included in a second tier mutagenicity test battery sponsored or performed or at the request of EPA (EPA-600/1-84-003) in 1984. Although DERs have not been prepared for these additional assays, it was determined that these studies are acceptable for regulatory purposes.

1) Mouse lymphoma L5178Y $TK^{+/-}$ forward gene mutation assay: The test was positive in the absence of S9 activation with concentration-dependent and reproducible increases in the mutation frequency at 40-90 μg/mL; higher levels were cytotoxic. No mutagenic activity was seen in the presence of S9 activation up to a cytotoxic dose (150 μg/mL).

2) Mouse micronucleus assay: The test is negative in Swiss-Webster mice up to a lethal dose (8 mg/kg) administered once daily for 2 consecutive days by intraperitoneal injection. No bone marrow cytotoxicity was seen.

3) Sister chromatid exchange in CHO cell assay: The non-activated test was negative up to levels (≥0.02%) that caused cell cycle delay but the test material was weakly positive at a single dose (0.04%) with metabolic activation.

Disulfoton has been tested in a wide variety of in vitro genetic toxicology assays. The results are summarized in The Agency for Toxic Substances and Disease Registry (ATSDR) Toxicology Profile for Disulfoton (August 1995). Overall the data presented in the ATSDR document parallel the above findings and indicate that the test substance is not a mutagen for bacteria. It is generally active in cultured mammalian cells without S9 activation and either negative, weakly genotoxic or less genotoxic in the presence of S9 activation.

The lack of clear genotoxicity would appear to contradict the definitive evidence that the oxygen analog and metabolite of Disulfoton, Demeton is a known mutagen. However, there is evidence from animal studies that the toxicity of disulfoton is altered by pretreatment with inducers of hepatic microsomal systems. For example, Pawar and Fawade (1978)[1] found that complete protection against the toxicity of Disulfoton was achieved in mice and rats pre-treated with phenobarbital prior to Disulfoton exposure. They concluded that the reduced toxicity resulted from the induction of cytochrome P-450 enzymes by phenobarbital. It is of note that the S9 preparations used in the mutagenicity studies conducted with Disulfoton were derived from rats pre-treated with Aroclor 1254, an inducer of some of the same cytochrome P-450 enzymes that are induced by phenobarbital. By analogy to the animal data, it can be speculated that the lack of mutagenesis may have resulted from inactivation/detoxification of Disulfoton by the S9 preparation. It would, therefore, be reasonable to assume that under the appropriate test conditions, Disulfoton would be mutagenic in the in vitro test systems. While it would be of scientific interest

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[1]Pawar and Fawade (1978); Bull. Environ. Contam. Toxicol. 20:805-810.

to test this hypothesis in new studies conducted with uninduced S9, it is not necessary to draw meaningful conclusions. Based on all of these considerations, we believe that Disulfoton has genotoxic potential but it is not likely to be a major concern. It is not genotoxic in vivo or carcinogenic in rats or mice. Similarly, there is no evidence of significant developmental toxicity attributable to a mutagenic mode of action (i.e., decreased total implants, increased resorptions).

Combining the acceptable studies with the additional EPA-sponsored studies will satisfy the pre-1991 mutagenicity initial testing battery guidelines. No further mutagenicity testing has been identified at this time.

F. Reference Dose (RfD):

The Committee recommended that the RfD for this chemical be established based on the combined chronic and subchronic (6-month) toxicity studies in rats with an overall NOEL of 0.03 mg/kg/day. Plasma, erythrocyte and brain cholinesterase inhibition was observed at the next higher dose level of 0.07 mg/kg/day. The Committee recommended that the two-year feeding study in dogs with a NOEL of 0.025 mg/kg/day and an LOEL of 0.05 mg/kg/day be used as a co-critical study.

An uncertainty factor (UF) of 100 was applied to account for both inter-species extrapolation and intra-species variability. On this basis, the RfD was estimated to be 0.0003 mg/kg/day.

It should be noted that this chemical has been reviewed by the FAO/WHO joint committee meeting on pesticide residue (JMPR) and an acceptable daily intake (ADI) of 0.0003 mg/kg/day has been established in 1991.

G. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief TB II), Albin Kocialski (Senior Science Advisor, HED), Nancy McCarroll, Guruva Reddy, Kit Farwell, Henry Spencer, and Rick Whiting.

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

David Anderson

Karen Hamernik/
Edwin Budd

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

Karl Baetcke

CC: Stephanie Irene
Albin Kocialski
Karl Baetcke
Karen Hamernik
Edwin Budd
David Anderson
Amal Mahfouz (OW)
RfD File
Caswell File

H. Material Reviewed:

1. Hayes. R. H. (1985). Chronic feeding/oncogenicity study of technical disulfoton (DI-SYSTON) with rats. MRID No. 00146873, HED Doc. No. 005029. Classification: Core minimum data. This study satisfies data requirement 83-5 or 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

2. Christenson, W. R. and Wahle, B. S. (1993). Technical grade disulfoton (DiSyston): A special 6-month feeding study to determine a cholinesterase no-observed-effect level in the rat. MRID No. 43058401. HED Doc. No. 011249. Classification: Acceptable data. This study was not conducted to fulfill a specific data requirement under Subpart F of the Pesticide Assessment Guideline; the study was designed to clarify issues in the chronic toxicity study in rats.

3. Carpy, S. et al. (1975). Disulfoton: 2-year feeding study in rats. MRID No. 00069966, 00154957, HED Doc. No. 003958. Classification: Core-supplementary data. This study does not satisfy data requirement 83-5 or 83-1a and -2a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity/carcinogenicity testing in rats.

4. Hayes, R. H. (1983). Oncogenicity study of Disulfoton technical on mice. MRID No. 00129456, 00139598, HED Doc. No. 003958. This study satisfies data requirement 83-2b of Subpart F of the Pesticide Assessment Guideline for carcinogenicity testing in mice.

5. Hoffman, K. et al. (1975). S 276 (Disulfoton) Chronic Toxicity Study on Dogs (Two-year Feeding Experiment). MRID No. 00073348, HED Doc. No. 003958. Classification: Core minimum data. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

6. Hixon, E. J. and Hathaway, T. R. (1986). Effect of Disulfoton (Di-Syston) on Reproduction in Rats. MRID No. 00157511, HED Doc. No. 005796. Classification: Core minimum data. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

7. Lamb, D. W. and Hixon, E. J. (1983). Embryotoxic and teratogenic effects of Disulfoton. MRID No. 00129458. HED Doc. No. 004067, 004223, 004698. Classification: Core Minimum data. This study satisfies data requirement 83-3a

of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

8. Tesh, J. M. et al. (1982). Effects of Oral administration upon pregnancy in the rabbit. MRID No. 00147886. HED Doc. No. 003958. Classification: Core supplementary data. This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

9. Sheets, L. P. and Hamilton, B. F. (1993). A subchronic dietary neurotoxicity screening study with technical grade disulfoton (DI-syston) in Fischer 344 rats. MRID No. 42977401, HED Doc. No. 011456. Classification: Core guideline data. This study satisfies data requirement 82-6 of Subpart F of the Pesticide Assessment Guideline for subchronic neurotoxicity testing in rats.

10. Sheets, L. P. (1993). An acute oral neurotoxicity screening study with technical grade disulfoton (Di-syston) in rats. MRID No. 42755801. HED Doc. No. 011457. Classification: Core minimum data. This study satisfies data requirement 81-7 of Subpart F of the Pesticide Assessment Guideline for acute neurotoxicity testing in rats.

11. Shiotsuka, R. N. (1989). Subchronic Inhalation Toxicology Study of Technical Grade Disulfoton (Di-Syston™) in Rats. MRID No. 41224301. HED Doc. No. 011242. Classification: Core guideline data. This study satisfies data requirement 82-3 of Subpart F of the Pesticide Assessment Guideline for subchronic inhalation toxicity testing in rats.

12. Flucke, W. (1986). Study of subacute Dermal Toxicity to Rabbits. MRID No. 00162338. HED Doc. No. 005556. Classification: Core minimum data. This study satisfies data requirement 82-2 of Subpart F of the Pesticide Assessment Guideline for subacute dermal toxicity testing in rabbits.

13. Herbold, B. and Lorke, D. (1980). Disulfoton: Thiodemeton--(R)=disyston Active Ingredient: Dominant Lethal Test on Male Mouse to Evaluate S 276 for Mutagenic Potential. MRID No. 00086073, 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. Arnold, D. (1971). Report to Chemagro Corporation: Mutagenic Study with Di-syston in Albino Mice: IBT No. E8920; 30304. MRID No. 00091120, HED Doc. No. 000000 Classification: This study satisfies data requirement 84-2

of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

15. Herbold, B. and Lorke, D. (1981). S 276 Disulfoton Thio-Demeton Disyston--Active Ingredient: Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect. MRID No. 00130617, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

16. Herbold, B. and Lorke, D. (1980). Dominant Lethal Test on Male Mouse to Evaluate S 276 for Mutagenic Potential: MRID No. 00139599, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

17. Brusick, D. (1981). Mutagenicity Evaluation of S276 in the Mitotic Non-disjunction in Saccharomyces Cerevisiae Strain D6: MRID No. 00139600, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

18. Jagannath, D. (1981). Mutagenicity Evaluation of S276 in the Saccharomyces Cerevisiae--Reverse Mutation Induction Assay: MRID No. 00139601, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

19. Chen, H. et al. (1981). Induction of sister-chromatid exchanges and cell cycle delay in cultured mammalian cells treated with eight organophosphorus pesticides. MRID No. 00139603, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

20. Mobay Chemical Corp. (1975). Toxicity: Organophosphorus Compounds): MRID No. 00139604, HED No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

21. Poole, D. et al. (1977). In vitro mutagenic acitivity of fourteen pesticides. MRID No. 00139607, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

22. Quinto, I. et al. (1981). Screening of 24 pesticides by Salmonella/microsome assay: Mutagenicity of benazolin,

metoxuron and paraoxon. MRID No. 00139608, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

23. Ricco, E. et al. (1981). Comparative studies between the S. cerevisiae D3 and D7 assays of eleven pesticides. MRID No. 00139609, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

24. Simmons, V. et al. (1979). In vitro mutagenicity and genotoxicity assays of 38 pesticides. MRID No. 00139610, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

25. Simmons, V. (1979). In vitro microbiological mutagenicity and unscheduled DNA synthesis studies of eighteen pesticides. MRID No. 00139611, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

26. Inukai, H. and Iyatomi, A. (1976). Disulfoton--Mutagenicity Test on Bacterial Systems. MRID No. 00139612. HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

27. Herbold, B. (1983). S 276 Disulfoton: Pol Test on E. coli to Evaluate for Potential DNA Damage: MRID No. 00146894, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

28. Putnam, D. (1987). Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells: MRID No. 40495001, HED Doc No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

29. Yang, L. (1988). CHO/HGPRT Mutation Assay: Di-syston Technical. MRID No. 40638401, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.

30. Herbold, B. (1995). S 276: Micronucleus Test on the Mouse: MRID No. 43615701, HED Doc. No. 000000. Classification: Acceptable. This study satisfies data

requirement 84-2 of Subpart F of the Pesticide Assessment Guideline for mutagenicity testing.