

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Disulfoton

Chemical Code # 000230, Tolerance # 00183

SB 950 # 010

June 2, 2000

I. DATA GAP STATUS

|                              |                                      |
|------------------------------|--------------------------------------|
| Combined, rat:               | No data gap, no adverse effect       |
| Chronic toxicity, dog:       | No data gap, no adverse effect       |
| Oncogenicity, mouse:         | No data gap, no adverse effect       |
| Reproduction, rat:           | No data gap, no adverse effect       |
| Teratology, rat:             | No data gap, no adverse effect       |
| Teratology, rabbit:          | No data gap, no adverse effect       |
| Gene mutation:               | No data gap, no adverse effect       |
| Chromosome effects:          | No data gap, possible adverse effect |
| DNA damage:                  | No data gap, possible adverse effect |
| Neurotoxicity <sup>1</sup> : | No data gap, no adverse effect       |

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<sup>1</sup> rat

Toxicology one-liners are attached.

All record numbers through 928429 were examined.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T000602

Prepared by H. Green, and P. Iyer, 2/12/99; Gee, 6/2/2000

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### COMBINED, RAT

\*\*133, 179, 190, 191, 193 033960, 074429, 096955, 096956, 097366 "Chronic Feeding/Oncogenicity Study of Technical Disulfoton (Di-Syston) with Rats", (R.H. Hayes, Mobay Chemical Corporation, Environmental Health Research, Corporate Toxicology Department, Stilwell, Kansas, Report # 90111, 25 June 1985). The test article was identified as disulfoton technical with 97.3% purity. 50 Fischer 344 rats per sex per group received nominal levels of 0, 1, 4, and 16 ppm in the diet for 105 weeks. Treatment-related reductions in bodyweight and feed consumption were seen in mid and high dose males and high dose females. Low dose males showed slightly lower weights but the significance was not clear. Mortality data suggested a treatment-related increase in females, beginning after 18 months. Blood chemistry and hematology varied within historical control ranges. **Oncogenicity was not indicated.** Chronic NOEL = 1 ppm (cystic degeneration of the Harderian gland at the mid and high dose levels in both sexes, clinical signs and decreased body weight at 16 ppm). Cholinesterase NOEL < 1 ppm. Originally reviewed as unacceptable and upgradeable (stability, missing data, etc.). (J. Christopher, 9/13/85). Re-reviewed with submission of additional data (record numbers 074429, 096955, 096956, 097366 in volumes 183-179, 190, 191, and 193). Acceptable. (H. Green, and P. Iyer, 1/11/99).

### CHRONIC TOXICITY, RAT

009, 087 928423, 014126, "2-Year Feeding Study in Rats", (Dr. S. Carpy and Dr. C. Klotzsche, Sandoz, Ltd., Agrochemical Research Department, Toxicological Section, Basle, Switzerland, Report # 47069, 25 September 1975). 60 SPF Sprague-Dawley rats per sex per group received technical grade disulfoton (95.7% purity) in the diet at 0, 0.5 (this was increased to 5.0 ppm in week 81), 1.0, or 2.0 ppm for 104 weeks. Plasma and erythrocyte cholinesterase reduction of 18% to 39% was noted for males and females at 5.0 ppm at week 91 and 103 compared to control values (the effect was more pronounced in females). At termination, brain cholinesterase values were reduced for males (26%) and females (36.5%) receiving 5.0 ppm compared to controls. **Adverse effects were not indicated. Unacceptable**, not upgradeable (no dosing rationale, incomplete observations, clinical chemistry, and limited histopathology). (J. Christopher, 2/20/85. Updated to electronic format, H. Green, 2/7/95).

220 127757 "Technical Grade Disulfoton (DI-SYSTON®): A Special 6-Month Feeding Study to Determine a Cholinesterase No-Observed-Effect Level in the Rat" (W. R. Christenson and B.S. Wahle, Miles Inc., Stillwell, KS., Report #106336, 12/3/93). In the cholinesterase study, 35 Fischer 344 rats/sex/group were exposed to disulfoton at 0, 0.25, 0.5, or 1.0 ppm (nominal) in the diet for 6 months. Plasma (PchE), erythrocyte (RchE), and brain cholinesterase (BchE) activities were evaluated at 2, 4, and 6 months. No treatment-related clinical signs or changes in food consumption or bodyweight were observed at any dose level. Statistically significant inhibition of erythrocyte cholinesterase activity was observed in high dose (> 20%) males and in mid (< 20%) and high dose (> 20%) females. Plasma and brain cholinesterase activities were decreased in high dose females (7-14%) and unaffected in males. Decreases in blood ChE were considered undesirable, but used along with the brain cholinesterase inhibition to define the critical level. Hence, systemic NOELs were considered 0.5 ppm (0.03 mg/kg/day) for

females and 1.0 ppm (0.06 mg/kg/day) for males by the authors. No worksheet. Supplemental. (H. Green and P. Iyer, 10/23/98).

#### CHRONIC TOXICITY, DOG

087 928424, "S 276 (Disulfoton), Chronic Toxicity Study on Dogs (Two-Year Feeding Experiment)", (K. Hoffmann and C.H. Weischer, Bayer AG, Institut fur Toxikologie, Wuppertal-Elberfeld, Report # 45287, 15 September 1975). 4 Beagle dogs per sex per group received Disyston, 50% premix with 95.7% purity in the diet at 0, 0.5, 1.0, or 8.0 ppm (dogs received 2.0 ppm from treatment week 0 through 70; 5.0 ppm from week 71 through 73; and 8.0 ppm from week 74 through 104) for 104 weeks. ChE NOEL = 1 ppm. Chronic NOEL \$ 8 ppm. **Adverse effects were not indicated. Unacceptable** and not upgradeable (no dosing rationale, no dosing analyses, incomplete histopathology and serum chemistry). (J. Christopher, 2/20/85; updated to electronic format, H. Green, 3/7/95).

\*\*260 154293, "Technical Grade Disulfoton: A Chronic Toxicity Feeding Study in the Beagle Dog", (R.D. Jones and T.F. Hastings, Bayer Corporation, Stilwell, KS., Report # 107499, 5 February 1997). Four Beagle dogs/sex/group received disulfoton at nominal dietary concentrations of 0, 0.5, 4, and 12 ppm for 1 year (actual intake for males was 0, 0.015, 0.121, and 0.321 mg/kg/day and 0, 0.013, 0.094, and 0.283 mg/kg/day for females). Group mean bodyweights for males at 4 and 12 ppm were generally higher (5% to 10%) than controls throughout the treatment period and those for females at 0.5 and 4 ppm were lower (6% to 10%). Group mean erythrocyte cholinesterase activity was reduced 8% to 50% at the mid-dose and 11% to 70 % at the high dose for both sexes relative to controls. Compared to controls, group mean brain cholinesterase values were decreased 13% at 4 ppm and 32% at 12 ppm for males and 22% and 33% for females respectively. Cholinesterase NOEL = 0.5 ppm. No clinical signs, ophthalmological or histological effects were reported. Chronic NOEL = 12 ppm. **Adverse effects were not noted. Acceptable.** (H. Green and P. Iyer, 1/22/99).

#### ONCOGENICITY, RAT

No study on file. See Combined, Rat.

#### ONCOGENICITY, MOUSE

\*\*088, 090 012513, "Oncogenicity Study of Disulfoton Technical on Mice", (R. H. Hayes, Mobay Chemical Corporation, Environmental Health Research, Corporate Toxicology Department, KS., Report # 85938, 10 August 1983). 60 CD outbred albino mice per sex per group (10 per sex per group were used as replacements) received disulfoton technical (98.2% purity) at 0, 1, 4, and 16 ppm in the diet for 99 weeks. **Adverse effects were not indicated.** No oncogenic effects were reported. Cholinesterase NOEL < 16 ppm (decreased plasma (79%-82%) and brain (44%-46%) cholinesterase activity compared to control values). Low and mid-doses were not analyzed for ChE. Acceptable. (J. Christopher, 2/22/85, updated to electronic format, H. Green, 3/1/95).

## REPRODUCTION, RAT

\*\*269 159416, "A Two Generation Reproductive Toxicity Study with Disulfoton Technical (DISYSTON) in the Sprague-Dawley Rat", (A. Barry Astroff, Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS., Report # 95-672-FZ, 19 November 1997). 30 Sprague-Dawley rats per sex per group received disulfoton technical (98.6% purity) in the diet at 0, 0.5, 2.0, and 9.0 ppm through 2 generations with one litter per generation. Treatment began 10 weeks prior to mating. Group mean maternal F0 bodyweights were lower (7% to 10%) than controls at 9.0 ppm during lactation. Group mean F1a pup bodyweights at 9.0 ppm were significantly decreased (16%-29%) relative to controls and remained depressed through selection of F1 parents, so that F1 parental bodyweights were 16% to 18% below those of control animals on pre-mating day 0 and remained lower throughout mating for both sexes and, for dams, through gestation and lactation. Incidences of hypoactivity, tremors, gasping, and locomotor incoordination were increased for F0 dams during lactation at 9.0 ppm. F2 maternal clinical signs during lactation included increases in hypoactivity, tremors, and corneal opacity at the high dose level. Parental chronic NOEL = 2.0 ppm. Mean F1a and F2a pup weights at 9.0 ppm were 16% to 29% lower than controls. Mean F2a live litter size at birth for high dose animals was reduced (23%) compared to controls. Reproductive NOEL = 2.0 ppm. Plasma, erythrocyte, and brain cholinesterase activities were reduced greater than 20% at 9.0 ppm for all groups and also at 2 ppm in F1 females. Cholinesterase NOEL = 0.5 ppm. **No adverse reproductive effects are indicated.** Acceptable. (H. Green and P. Iyer, 10/20/98).

\*\*142 042520, "Effect of Disulfoton (@Di-Syston) on Reproduction in Rats", (E. J. Hixson and T. R. Hathaway, Mobay Chemical Corporation, Environmental Health Research, Corporate Toxicology Department, 17745 South Metcalf, Stilwell, KS., Report # 90965, 12 February 1986). 26 albino CD Sprague-Dawley rats per sex per group received technical disulfoton (97.91% purity) at 0 (corn oil), 1, 3, and 9 ppm (effective doses of 0.81, 2.4 and 7.3 ppm) in the diet through 2 generations with 2 litters per generation. F0 parents were treated 15 weeks prior to mating; F1s 13 weeks. All F0 parents were diagnosed with sialodacryoadenitis virus (swollen salivary glands were noted) during gestation of F1b litters. At 9 ppm, the number of litters, number of pups per litter, and 21-day pup weights were reduced for both litters of each generation. **A possible adverse reproductive effect was indicated:** a reduced number of offspring per litter was noted at the mid-dose level. Parental NOEL = 3 ppm (reduced bodyweights at the high dose level, tremors in some F0 females). Reproductive NOEL = 1 ppm (reduced number of pups per F2b litter at 3 and 9 ppm, reduced number sperm positive and reduced % of mated that delivered at 9 ppm). Offspring Cholinesterase NOEL = 1 ppm (24% to 32% brain cholinesterase activity reduction at 3 ppm and 50% to 59% reduction at 9 ppm compared to control values). Pup culling and mating procedure not as per guidelines. **Acceptable.** (H. Green and P. Iyer, 10/20/98).

003 026 928429, 063232, 928427, 928430, "Di-Syston, Three Generation Breeding Study on Rats", (Richard E. Taylor, Harris Laboratories Incorporated, Lincoln, NE., Report # 18154, 5 May 1966). 10 male and 20 female Holtzman rats per group received Di-Syston in the diet at 0, 2, 5, and 10 ppm through 3 generations (2 litters per generation). **Adverse effects were not indicated. Unacceptable** and not upgradeable (no dosing level rationale, no analysis of dosing diet, incomplete necropsy and histopathology, number per group). (J. Christopher, 2/21/85; updated to electronic format, H. Green, 3/10/95).

003 033633 "Di-syston, Three Generation Poultry Breeding Studies," (R.E. Taylor, Harris

Laboratories, 5/15/66) Leghorn Chickens 4 males and 20 females per group, were fed 0, 2, 5 or 10 ppm Di-syston. Supplemental. (J. Christopher, 2/21/85).

#### TERATOLOGY, RAT

\*\*090 012511, "Embryotoxic and Teratogenic Effects of Disulfoton", (D.W. Lamb and E.J. Hixson, Mobay Chemical Corporation, Environmental Health Research, Corporate Toxicology Department, 17745 Metcalf, Stilwell, KS., Report # 84055, 13 May 1983). The test article is identified as disulfoton technical with 98.2% purity. 25 inseminated female CD rats per group received 0, 0.1, 0.3, and 1.0 mg/kg/day by gavage on gestation days 6 through 15. **Teratogenicity was not indicated below maternally toxic dosing levels.** Maternal NOEL = 0.3 mg/kg/day (82%-90% reduction in plasma and erythrocyte cholinesterase activity at the high dose compared to control values). Developmental NOEL = 0.3 mg/kg/day (increased incidence of incomplete ossification of the sternebrae in fetuses at the high dose). Acceptable. ( J. Christopher, 2/22/85, updated to electronic format, H. Green, 2/24/95).

#### TERATOLOGY, RABBIT

\*\*078, 090 012512, "S 276: Effects of Oral Administration Upon Pregnancy in the Rabbit", (J. M. Tesh and F. W. Ross, Life Science Research, England, Report # 82725, 22 December 1982). The test article was identified as S276 (disulfoton) with 97.3% purity. 14 to 22 inseminated female New Zealand white rabbits received S 276 (disulfoton, 97.3% purity) at 0, 0.3, 1.0, or 3.0 (reduced to 2.0 and 1.5 due to toxicity) mg/kg/day by gavage on gestation days 6 through 18. Excessive maternal mortality occurred at 3.0 mg/kg/day. **Teratogenicity was not indicated. Maternal NOEL = 1.0 mg/kg/day** (mortality occurred at 3.0 mg/kg/day). **Developmental NOEL = 1.0 mg/kg/day** (treatment at the highest dose level resulted in too few dams at term for meaningful evaluation). The original high dose (3.0 mg/kg/day) data were disregarded and those for the 1.0 mg/kg/day group used as the high dose results, leaving a data pool of only a low (0.3 mg/kg/day) and a high dose. Acceptable. (J. Christopher, 2/22/85, updated to electronic format, H. Green, 2/22/95).

003 928426 - Invalid IBT study (replaced).

#### GENE MUTATION

090, 088 011242, "Mutagenicity Evaluation of S276 in the *Saccharomyces Cerevisiae* Reverse Mutation Induction Assay", (D.R. Jagannath, Litton Bionetics, Inc., Kensington, MD., Report # 80347, original report date = August 1981, revised = October 1981). The test article was identified as S276. 8 dosing levels ranging from 1.5 µl/plate to 200 µl/plate were tested (60 minute exposure) in quadruplicate using *Saccharomyces cerevisiae* strains S138 and S211 in the presence and absence of activation. **Insufficient information to make an adverse effects determination. Unacceptable and upgradeable** (dosing levels not specified, dosing rationale, results notation). (J. Wong, 2/20/85; updated to electronic format by H. Green, 6/15/95).

090, 088 012497, 038803, "Disulfoton, Mutagenicity Test on Bacterial Systems", (H. Inukai and A. Iyatomi, Nitokuno, Agricultural Chemicals Institute, Laboratory of Toxicology, Report # 86190, 30 June 1976). The test article was identified as disulfoton technical with 94.1% purity. Single cultures of *Salmonella typhimurium* strains TA98, TA100,

TA1535, and TA1537 were exposed to disulfoton technical (94.1% purity) for 48 hours at 0, 0.1, 10.0, and 1000.0 µg/plate with activation and at 0 and 1000.0 µg/plate without activation. **An increased reversion rate was not indicated.** Unacceptable and not upgradeable (dosing rationale, no replicates). (J. Wong, 2/20/85; updated to electronic format by H. Green, 6/12/95).

**139 041254** "Further mutagenicity studies in pesticides in bacterial reversion assay systems" (M. Moriya et al., in Mutation Research 116:185-216 (1983)) Disulfoton was considered positive with Salmonella strain TA1535 ± S9 activation, 0 - >10,000 µg/plate. No worksheet.

**\*\*173 068196**, "CHO/HGPRT Mutation Assay", (Li L. Yang, Microbiological Associates, Inc., MD., Report # 95698, 4 March 1988). In the first study, duplicate cultures of Chinese hamster ovary cells (CHO-K1-BH4) were exposed in the absence and presence of activation to Di-Syston technical (97.9% purity) concentrations of untreated, 0 (acetone), 0.1, 0.3, 0.5, 1.0, 3.0, 5.0, or 10.0 Fl/ml for 5 hours. In the second study, duplicate cultures were exposed at untreated, 0 (acetone), 30, 40, 50, 60, or 70 nl/ml. Test material was insoluble in medium at \$ 3 Fl/ml and partially soluble at 70 nl/ml. **In the initial study, mutant frequencies at all treatment levels were increased, compared to solvent control values. A dose-dependent response was not indicated.** The second study did not indicate mutant frequencies above those of the solvent control at soluble concentrations. A role of the precipitate cannot be excluded. **Acceptable** (H. Green, and P. Iyer, 12/24/98).

## CHROMOSOME EFFECTS

**\*\*239 136551**, "S276 Micronucleus Test on the Mouse", (Dr. B. Herbold, Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany, Report # 106863, 13 January 1995). 5 Hsd/Win: NMRI mice per sex per group received a single intraperitoneal injection of S276 (disulfoton, 98.7% purity) at 0 and 8 mg/kg with sampling 16, 24, or 48 hours afterward. A small increase in micronucleated polychromatic erythrocytes was noted at the 24 and 48 hour samplings, however in comparison with historical controls as well as concurrent positive control the increase seems to be equivocal. Possible adverse effect. **Acceptable**. (H. Green, and P. Iyer, 12/30/98).

091 012507, "Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect", (Dr. B. Herbold, Bayer AG, Institute for Toxicology, 5600 Wuppertal, Report # 82240, 23 December 1981). The test article was identified as S276 (disulfoton) with 50% purity. 5 Bor: NMRI (SPF Han) mice per sex per group received 2 doses (24 hours apart) by gavage at 0, 6, and 12 mg/kg. Bone marrow sampling was performed 6 hours after the second dose. **Missing information precluded an adverse effects determination. Unacceptable**, not upgradeable (dosing rationale, sampling schedule). (J. P. Christopher, 2/21/85; updated to electronic format by H. Green, 6/16/95).

078, 090 012510, "Dominant Lethal Test on Male Mouse to Evaluate S 276 for Mutagenic Potential", (Dr. B. Herbold, Bayer AG, Institut für Toxikologie, Report # 69362, 23 September 1980). 50 male NMRI/ORIG Kisslegg mice per group received a single oral dose of S276 (disulfoton, 94.9% purity) at 0 or 5 mg/kg. Immediately after dosing, each male was caged with one untreated virgin female. After a 4-day mating period this female was replaced with another. This continued until a series of 12 matings were completed. **An adverse effects determination could not be made due to deficiencies in the study. Unacceptable** and not upgradeable (no positive control, no dosing rationale). (J. Wong, 2/21/85; updated to electronic format by H. Green, 6/9/95).

183 - 129 026977 "Dominant lethal study on male mice to test for mutagenic effects." (B. Herbold, Bayer Report 86868, 5/29/79) Positive control data. Supplemental. No worksheet. (Gee, 6/2000)

003 033640 - Invalid IBT study (replaced).

## DNA DAMAGE

\*\*088 011240, "PoI Test on E. coli to Evaluate for Potential DNA Damage", Dr. B. Herbold, Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Report # 86222, 4 October 1983). The test article is identified as S 276 (disulfoton) with 97.3% purity. Quadruplicate cultures of *Escherichia coli* strains (K12)p3478 (repair-) and W3110 (repair+) were exposed to 0, 625, 1250, 2500, 5000, and 10000 Fg/plate for 24 hours in the presence and absence of activation. **Increased growth inhibition in the repair deficient strain was not indicated. Acceptable.** (J. Christopher, 2/21/85; updated to electronic format, H. Green, 6/13/95).

088 090 011243, "Mutagenicity Evaluation of S276 in the Mitotic Non-Disjunction in *Saccharomyces Cerevisiae* Strain D6", (David J. Brusick, Litton Bionetics, Inc., Kensington, MD., Report # 80346, September 1981; revised October 1981). *Saccharomyces cerevisiae* strain D<sub>6</sub> cells were exposed (3 hours) in the presence and absence of activation to disulfoton concentrations of 0, 20, 50, 100, 150, and 200 µl/ml. **Induction of aneuploidy was not indicated. Unacceptable** and upgradeable (test article/dosing solution characterization, number of plates per concentration not clear). (J. Wong, 2/21/85, updated to electronic format, H. Green, 6/15/95).

\*\*169 065287, "Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells", (Donald L. Putman, Microbiological Associates, Inc., MD., Report # 94979, 30 November 1987). Chinese hamster ovary cells were exposed in the absence (24-26 hour exposure) and presence (2-hour exposure) of activation, rat liver S-9, to Di-Syston (97.9% purity) at untreated, 0, 0.002, 0.004, 0.008, 0.013, 0.015, 0.025, 0.03, 0.05, 0.1, or 0.2 µl/ml. The assay was conducted three times without activation and twice with activation. **A weak dose-related increase in sister chromatid exchanges was indicated in the absence of activation.** Positive control increases were 2 to 3 times greater than these. **Acceptable.** (H. Green and P. Iyer, 11/10/98).

088, 090 012497, "Disulfoton, Mutagenicity Test on Bacterial Systems", (H. Inukai and A. Iyatomi, Nitokuno, Agricultural Chemicals Institute, Laboratory of Toxicology, Report # 86190, 30 June 1976). Single cultures of *Bacillus subtilis* strains NIG17 and NIG45 were exposed to disulfoton technical (94.1% purity) at 0, 3, 30, and 300 µg/disc overnight. **DNA damage was not indicated. Unacceptable** and not upgradeable (no activation, dosing level rationale, no replicates). (J. Wong, 2/20/85; updated to electronic format by H. Green, 6/12/95).

## NEUROTOXICITY - HEN

\*\*078, 090 012496, "Acute Delayed Neurotoxicity Study on Disulfoton", (E. J. Hixson, Mobay Chemical Corporation, Environmental Health Research Institute, Corporate Toxicology Department, Stilwell, KS., Report # 82655, 7 March 1983). 20 hens received 2 doses (each dose was followed by a 21-day observation period) of 30 mg/kg disulfoton technical by gavage with protection (0.5 mg/kg atropine and 12.5 mg/kg 2-PAM). 2 negative control groups (one with protection (0.5 mg/kg atropine and 12.5 mg/kg 2-PAM)

and one without) of 5 hens each were used. 10 birds received 500 mg/kg of tri-*o*-cresyl phosphate (TOCP) as a positive control group. **Acute delayed neurotoxicity was not indicated in hens that received test article.** Acceptable. (J. Wong, 2/21/85; updated to electronic format by H. Green, 6/1/95).

139 041253 One page summary of a hen neurotoxicity test, No 89020. 1964. Hens administered concentrations of 0.015, 0.02, 0.05, 0.1, 0.2, 0.25 and 0.5 g/kg were evaluated for neurotoxic impairment. High doses resulted in death within a short time. In subsequent studies, intraperitoneal administration of antidotes such as 0.1 g/kg PAM + 0.05 g/kg atropine sulfate prior to exposure to the test compound demonstrated no neurotoxic impairment. No worksheet.

## NEUROTOXICITY - RAT

\*\*212 121521, "An Acute Oral Neurotoxicity Screening Study with Technical Grade Disulfoton (DI-SYSTON®) in Rats", (L. P. Sheets, Miles Inc., Agriculture Division, Toxicology, 17745 South Metcalf, Stilwell, KS., Report # 103992, 24 February 1993). 10 Sprague-Dawley (Sas:CD(SD)BR) rats per sex per group received a single dose of technical grade Di-Syston (97.8% purity) by gavage followed by sacrifice 15 days later. Males received 0, 0.25, 1.5, and 5.0 mg/kg. Females were treated with 0, 0.25, 0.75, and 2.5 mg/kg (reduced to 1.5 mg/kg due to toxicity). In the functional observational battery, treatment related observations which included muscle fasciculations, tremors, and ataxia were seen on day 0 only. Motor and locomotor activity were generally reduced for high dose males and females on day 0 compared to controls and unaffected on days 7 and 14. **Neurotoxicity NOEL, males = 1.5 mg/kg and females = 0.25 mg/kg (based on cholinesterase inhibition, FOB responses and motor activity observed only on day 0). Neuropathology revealed no structural lesions at the microscopic level.** Acceptable. (H. Green, and P. Iyer, 2/5/99).

\*\*215 126559, "A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Disulfoton (DI-SYSTON®) in Fischer 344 Rats", (L.P. Sheets, Miles, Inc., Agriculture Division, Toxicology, Stilwell, KS., Report # 106332, 23 September 1993). 12 Fischer 344 CDF(F-344)/BR rats per sex per group received technical grade disulfoton (98.7% purity) in the diet for 13 weeks at 0, 1, 4, or 16 ppm (nominal). These correspond to analytically-confirmed dietary levels of 0.9, 3.8 and 14.5 ppm [M: 0.063, 0.27 and 1.08 mg ai/kg b. wt.; F: 0.071, 0.315 and 1.31 mg/kg]. In the open field portion of the functional observational battery (FOB), treatment-related observations in high dose animals included muscle fasciculations, tremors, reduced movement, and increased defecation at week 4. Muscle fasciculations and increased defecation remained evident at weeks 8 and 13. Forelimb grip strength and motor and locomotor activity were reduced in high dose animals for weeks 4, 8, and 13. Necropsy and histopathology were reported as unremarkable. Clinical signs and neurobehavioral effects were noted at 14.5 ppm in males and in females at  $\geq 3.8$  ppm. There was no evidence of cumulative toxicity after 4-8 weeks. Cholinesterase NOEL for males = 0.9 ppm (plasma, RBC, and/or brain ChE inhibition ranged from 20% at 3.8 ppm to 101% at 14.5 ppm compared to controls). Cholinesterase NOEL for females < 0.9 ppm (plasma, RBC, and/or brain ChE inhibition; RBC ChE inhibition ranged from 27% at the low dose to 100% at the high treatment level compared to controls). Acceptable. (H. Green, and P. Iyer, 10/20/98).  
NOTE: A WORKSHEET HAS BEEN PROVIDED FOR A REPORT CONTAINING METHOD VALIDATION INFORMATION, BELOW. THIS REPORT WAS SUBMITTED IN SUPPORT OF ANOTHER MILES PRODUCT, SULPROFOS. THE ONE-LINER FOLLOWS.

for the acute and subchronic neurotoxicity screening battery", Miles Inc., Agricultural Division, Toxicology, Stilwell, Kansas, 3/31/93. Miles Report No. 103979. Motor activity evaluations were done for triadimefon and chlorpromazine, FOB data were obtained for acrylamide and carbaryl, and microscopy was done for acrylamide and trimethyltin studies on rats. The studies presented validate the investigators' capability to produce valid rat acute to subchronic duration neurotoxicity studies. Typical tables are included in the review as reference positive and negative control data. Data apply toward method validation for rat neurotoxicity studies of at least azinphos-methyl, sulprofos, disulfoton, and methamidophos. Aldous, 6/29/95.

The following record numbers denote mutagenicity journal articles:

|                |                 |       |
|----------------|-----------------|-------|
| Volume 183-090 | Record Number : | 12498 |
|                |                 | 12499 |
|                |                 | 12500 |
|                |                 | 12501 |
|                |                 | 12502 |
|                |                 | 12503 |
|                |                 | 12504 |
|                |                 | 12505 |
|                |                 | 12506 |

#### SUPPLEMENTAL

139 41247 Acute toxicity studies following oral administration of E 23 323 resulting in LD50 values of 0.0036 g/kg in male rats; 0.0017 g/kg in female rats; guinea pigs LD 50 >0.0036 g/kg; rabbits- LD50 between 0.0025 and 0.0036 g/kg; cats- LD50 between 0.001 and 0.0025 g/kg. Intraperitoneal route in rats demonstrated an LD 50 of 0.005 g/kg. Dermal toxicity in male rats yielded an LD50 of 0.195 ml/kg or 0.075 ml/kg (collar method).

139 41248 Liver function test on rabbits after administration of 0.0025 g/kg showed no impairment in SGPT (serum glutamic pyruvic transaminase) or SDH (sorbitol dehydrogenase) levels.

139 41249 Effect of PAM, Atropine and BH 6 on the E23 323 intoxication of male rats. Administration of antidotes injected intraperitoneally shortly after the oral administration of the test compound resulted in the following LD 50 values. Without antidote LD50 = 0.0036 g/kg; With atropine LD50 = 0.0075 g/kg; With PAM LD 50 = 0.0136 g/kg; With BH 6 LD 50 = 0.0235 g/kg; with Atropine + PAM, LD50 = 0.0215 g/kg, with Atropine + BH6, LD 50 = 0.050 g/kg. A ten fold increase in the LD 50 was noted with the administration of suitable antidotes.

139 41252 Repeated oral administration showed that the compound E23 323 has no cumulative properties. Typical cholinesterase inhibition symptoms were noted and an acquired tolerance appears to occur. Inhalation tests showed that a 1-hour exposure has an LC 50 of 0.140 mg/liter.

087 014133 "Disulfoton, 90 day feeding study in rats" (C. Klotzche, Mobay, Report 88585, 10/26/72) SPF rats, 25/sex/group, were given 0, 0.2, 1 or 5 ppm in the diet. ChE NOEL = 1 ppm; systemic NOEL \$ 5 ppm. Supplemental.

087 014132 "Thio-demeton oral toxicity to mice dietary administration for 3 months" (K.F. Rivett et al., Huntingdon Research Centre, 11/27/72, report 88586) CF-LP mice,

12/sex/group, were fed disulfoton at 0, 0.2, 1 or 5 ppm for 13 weeks. RBC ChE NOEL = 1 ppm. Brain ChE was not affected. Systemic NOEL = 5 ppm. Supplemental.

008 928410 "the effects of diets containing Di-Syston in rats." (J. Doull and G. Vaughn, University of Chicago, 1/3/58). Di-Syston (25% wettable powder was added to the diet of 0, 1, 2, 5 or 10 ppm a.i. for 16 weeks with 3/sex/group used for cholinesterase measurements (brain, serum and submaxillary gland) at 8 and 16 weeks. Systemic NOEL \$ 10 ppm. ChE NOEL = 1 ppm (RBC, brain). Females were more affected than males. No worksheet. Supplementary (Gee, 3/26/99).

008 928351 "Toxicity and mechanism of action of Di-Syston" (T.J. Bombinski and K.P. DuBois, in : A.M.A. Archives of Ind. Health 17:192-199 (1958)). Di-Syston was given to rats, mice or guinea pigs by oral or intra-peritoneal route as a single or repeated dose ranging from 0.25 - 1.5 mg/kg Bwt. Cholinesterase activity of brain, serum of rats was determined (presented in graphic form). No worksheet. Supplementary (Gee, 3/26/99).