

US EPA ARCHIVE DOCUMENT



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

012593

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

DATE: April 23, 1998

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

FROM: David G Anderson, Toxicologist
Reregistration Branch-2
Health Effects Division (7509C)

David G Anderson 4/22/98

and

Jess Rowland, Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

Jess Rowland 4/22/98

THRU:

Clark Swentzel, Chairman
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

M. Clark Swentzel 4/22/98

and

Mike Metzger, Co-Chairman
Hazard Identification assessment review Committee
Health Effects Division (7509C)

Michael J. Metzger 4/22/98

TO:

Alan Nielsen, Branch Senior Scientist
Reregistration Branch-2
Health Effects Division (7509C)

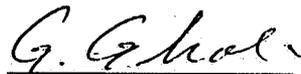
PC Code: 032501

On April 9, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee evaluated the toxicology data base of disulfuton, re-assessed the Reference Dose and select the toxicological endpoints for acute dietary as well as occupational and residential exposure risk assessments. The Committee also addressed the potential sensitivity of infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented in this report.

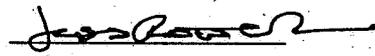
Hazard Identification Assessment Review Committee members in attendance: William Burnum, Robert Fricke, Mike Metzger, Jess Rowland, Clark Swentzel. Members in absentia Karl Baetcke, Karen Hamernik, Melba Morrow. Others in attendance were Pauline Wagner and Jonathan Becker for information on exposure.

Data Presentation:
and
Report Preparation


David G Anderson
Toxicologist


George Ghali
Toxicologist

Report Concurrence:


Jess Rowland
Executive Secretary

I. INTRODUCTION

On April 25, 1996, the Health Effect's Division RfD/Peer Review Committee evaluated the toxicology data base of Disulfoton and established the Reference Dose (RfD) of 0.0003 mg/kg/day based on a NOEL of 0.025mg/kg/day and an Uncertainty Factor of 100 for inter species extrapolation and intraspecies variation (*Memorandum: G.Ghali to G. LaRoca, April 21, 1997*).

On May 14, 1996, the Toxicology Endpoint Selection Committee selected the doses and endpoints for acute dietary and occupational as well as residential exposure risk assessments (TES Document 6/5/96).

On November 20, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) re-evaluated the toxicology data base, re-assessed the RfD and selected the toxicology endpoints for acute dietary as well as occupational and residential exposure risk assessments. In addition, the HIARC also addressed the potential enhanced susceptibility of infants and children from exposure to disulfoton as required by the Food Quality Protection Act (FQPA) of 1996.

On April 9, 1998, the HIARC reviewed the results of a two-generation reproduction study in rats (MRID# 44440801) that was recently submitted to the Agency and the impact of this study in the doses and endpoints selected for the various risk assessments. The Committee's conclusions are presented in this report.

II. HAZARD IDENTIFICATION

A. Dietary Hazard

1. Acute Reference Dose (Acute RfD)

Study Selected: Acute Neurotoxicity - Rat §81-8

MRID No. 42755801

Executive Summary: In an acute neurotoxicity screening study, disulfoton (97.8% pure) was administered in a single gavage dose to 10 male Sprague-Dawley rats at doses of 0, 0.25, 1.5, or 5.0 mg/kg and to 10 female Sprague-Dawley rats at doses of 0, 0.25, 0.75 or 1.5 mg/kg. These rats were assessed for reactions in functional observational battery (FOB) and motor activity measurements at approximately 90 minutes post-dosing and on days 7 and 14. Cholinesterase determinations (erythrocyte and plasma) were made at 24 hours post-dosing. Six rats/sex/dose were examined for neuropathological lesions.

At 0.75 mg/kg, 4/10 females had muscle fasciculations. At 1.5 mg/kg, males had muscle fasciculations, diarrhea, and sluggishness and females also had tremors, ataxia, oral staining, decreased activity/sluggishness, decreases in motor and locomotor activity (38–49% of control), and a slightly increased duration of nasal staining. One female at 1.5 mg/kg died from cholinergic intoxication on the day of dosing. At 5.0 mg/kg, males also had symptoms similar to those observed in females at 1.5 mg/kg/day, including reduced motor/locomotor activity (36–45% of control). Recovery appeared to be complete in surviving animals by Day 14. Based on the evidence of neurotoxicity (probably associated with inhibition of cholinesterase) in females at 0.75 mg/kg, the study LOEL is 0.75 mg/kg and the study NOEL is 0.25 mg/kg.

At 0.75 mg/kg in females, cholinesterase activities were inhibited by 53% (erythrocyte) and 30% (plasma) and by 75% (erythrocyte) and 52% (plasma) at 1.5 mg/kg in females. At 5.0 mg/kg in males, cholinesterase activities were inhibited by 21% (erythrocyte) and 25% (plasma). The LOEL for inhibition of cholinesterase activity is 0.75 mg/kg and the NOEL for inhibition of cholinesterase activity is 0.25 mg/kg.

Dose and Endpoints for Risk Assessment: NOEL= 0.25 mg/kg based on neurotoxicity signs, plasma and erythrocyte cholinesterase inhibition in female rats.

Comments about the study and/or Endpoint: This dose and endpoint is appropriate since the toxicological effects were observed following a single oral dose.

Uncertainty Factors (UF): 100 (10 x for inter-species extrapolation, 10 x for intra-species variability).

$$\text{Acute RfD} = \frac{0.25 \text{ mg/kg (NOEL)}}{100 \text{ (UF)}} = 0.0025 \text{ mg/kg}$$

This risk assessment is required.

2. Chronic RfD

Study Selected: Chronic Feeding Dog

§83-1

MRID No. 44248002

Executive Summary: In a chronic toxicity study, disulfoton (97% a.i.%) was administered orally in the diet to purebred beagle dogs (4/sex/dose) at dose levels of 0.5, 4 or 12 ppm (equivalent to 0.015, 0.121 and 0.321 mg/kg/day for males; and 0.013, 0.094 and 0.283 mg/kg/day for females) for one year. Potential ocular and neurologic effects were addressed. Plasma cholinesterase was decreased starting at day 7 in the 4.0 ppm dose

groups of the study through to termination (males 39% to 46%; females 32% to 45%). Erythrocyte cholinesterase was decreased starting at day 91 in the 4.0 ppm dose groups through to termination (males 23% to 48%; females 17% to 49%). Not all the values at 4.0 ppm were statistically significant, probably because of the wide range in values, but at least 2 animals per group showed biologically significant cholinesterase inhibition. By termination cholinergic effects of the plasma, erythrocytes, brain, and ocular tissues were observed in both sexes in the 4 and 12 ppm treatment groups. Plasma and erythrocyte cholinesterase depression are compared to pretreatment values. Brain, cornea, retina and ciliary body cholinesterase depression are compared with concurrent control values at termination only. In the 12 ppm treatment groups, depressed cholinesterase was observed in plasma (56%-63%), erythrocytes (30%-91%), and brain (32%-33%) compared to their respective controls. In the 4 ppm treatment groups in males and females, cholinesterase was depressed in plasma (38%-46%), erythrocytes (40%-38%), and brain (females only, 22%). Disulfoton inhibited cholinesterase of the cornea, retina, and ciliary body, but did not appear to alter the physiologic function of the visual system. In the 12 ppm treatment groups, depressed cholinesterase was observed in the cornea (60-67%), ciliary body (45-54%), and retina (males only; 67%). In the 4 ppm treatment groups, cholinesterase was inhibited in the cornea (50-60% lower), and retina (females only, 25%). No treatment-related ophthalmology findings or histological or electrophysiological changes in the retina were observed. No other treatment-related effects were observed. No animals died during the study. No treatment-related effects were observed in systemic toxicity including food consumption, body weights, clinical signs, hematology, clinical blood chemistry or urinalysis parameters, electrocardiogram, electroretinograms or clinical neurological findings, organ weights or gross or microscopic post-mortem changes in any treatment group. No neoplastic tissue was observed in dogs in the treatment and control groups. The LOEL is 4 ppm (0.094 mg/kg/day), based on depressed plasma, erythrocyte, and corneal cholinesterase levels in both sexes, and depressed brain and retinal cholinesterase levels in females. The NOEL is 0.5 ppm (0.013 mg/kg/day). These LOEL/NOEL for plasma cholinesterase inhibition extend from day 7 to termination and for erythrocyte cholinesterase inhibition they extend from day 91 to termination.

Dose and Endpoint for Establishing the RfD: The NOEL is 0.5 ppm (0.013 mg/kg/day) based on depressed plasma, erythrocyte and corneal cholinesterase levels in both sexes and depressed brain and retinal cholinesterase levels in females.

Uncertainty Factors (UF): 100 (10 x for inter-species extrapolation, 10 x for intra-species variability).

$$\text{Chronic RfD} = \frac{0.013 \text{ mg/kg (NOEL)}}{100 \text{ UF}} = 0.00013 \text{ mg/kg}$$

This risk assessment is required.

B. Occupational/Residential Exposure**1. Dermal Absorption;**

§ 85-2

MRID No.: 43360201

Percentage absorbed: At 1, 4 or 10 hours, the following percentages of applied dermal doses were absorbed in the rat. Application site was washed after the 10 hour exposure and the 168 hour exposure (168 hour exposure data not given). Disulfoton is volatile and 10% to 30% of the applied dose was found to be volatile over a 10 hour period. The volatility of disulfoton is probably the reason for some of the low recoveries, but since volatility would also be present under field conditions it was not considered in the percentage absorption.

Dose in ($\mu\text{g}/\text{cm}^2$ on a 15 cm^2 site) & mg/kg based on 250 g rat	Exposure hours	Percentage absorbed
Concentration administered ($0.85 \mu\text{g}/\text{cm}^2$)		
0.051 mg/kg	1	5.9
0.051 mg/kg	4	13.9
0.051 mg/kg	10	26.0
Concentration administered ($8.5 \mu\text{g}/\text{cm}^2$)		
0.51 mg/kg	1	4.6
0.51 mg/kg	4	15.9
0.51 mg/kg	10	36.2*
Concentration administered ($85 \mu\text{g}/\text{cm}^2$)		
5.1 mg/kg	1	3.6
5.1 mg/kg	4	12.5
5.1 mg/kg	10	25.3

* = % dermal absorption factor chosen by TES of 5/14/96.

Dermal Absorption Factor: 36% at approximately $8.5 \mu\text{g}/\text{cm}^2$ or 0.51 mg/kg for 10 hours should be used to convert oral studies to dermal studies where necessary.

Comments about the Study Endpoint: The TES Committee indicated that dermal absorption of 36%, obtained after 10 hours exposure at a concentration of $8.5 \mu\text{g}/\text{cm}^2$

(0.51 mg/kg), should be used for correcting oral dosing to dermal dosing. If the exposure deviates by a large amount from $8.5 \mu\text{g}/\text{cm}^2$ for 10 hours then a different percentage dermal absorption may be appropriate. The risk assessor should refer to the above table or HED Doc# 011316, MRID# 43360201, for a more complete understanding of the dermal absorption percentage and the relationship between percentage absorption and the dose applied to the skin. The HIARC concurred with the TES Committee on this approach for the use of the dermal absorption factor.

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

Study Selected: 21-day dermal study in rabbits §82-3

MRID No. 00162338

Executive Summary: In a 21-day dermal study, disulfoton, technical (97.8%) was administered dermally in a Cremophor EL emulsion to 5 New Zealand White rabbits/sex/group at 0, 0.4, 1.6 or 6.5 mg/kg/day for 15 separate exposures, 5 day/week for 6 hours/day for 21 days. No skin irritation occurred at any dose level. Females at the 6.5 mg/kg/day died (a total of 6) after 1-3 weeks of treatment and males (unknown numbers) died at 6.5 mg/kg/day after 3 days and 2 weeks of treatment. At 1.6 mg/kg/day, plasma cholinesterase was inhibited (41%) in females and (32%) in males after 1 week of treatment. At the same dose level, erythrocyte cholinesterase was inhibited (16% from pre-dosing values, but 21% from the concurrent control at 2 weeks and at termination 33% from control, but increased 3% from pre-dose values. Brain cholinesterase was marginally inhibited at 1.6 mg/kg/day in females (8%) and in males (7%) at termination (3-weeks).

The NOEL was 0.4 mg/kg/day based on plasma, erythrocyte and brain cholinesterase inhibition in females and males.

Dose and Endpoint for use in risk assessment: NOEL = 0.4 mg/kg/day was based on plasma, erythrocyte cholinesterase inhibition after 1 week of dosing.

Comments about study and/or endpoint: This endpoint and the NOEL is supported by a developmental toxicity study in the rat. In that study the maternal NOEL was 0.1 mg/kg/day based on 41% for both plasma and erythrocyte cholinesterase inhibition. When the 36% dermal absorption factor is used, the comparable dermal dose is 0.3 mg/kg/day [i.e., oral NOEL of $(0.1 \text{ mg/kg/day})/(0.36) = 0.3 \text{ mg/kg/day}$] The study represents cholinesterase inhibition after 2 weeks of dosing.

This risk assessment is required.

3. Intermediate Term O/R Exposure (1 Week to Several Months):

Study Selected - Special 6-months cholinesterase study.

MRID No.: 43058401

Executive Summary: In a 6-month study designed to establish a NOEL and LOEL for cholinesterase inhibition, technical grade disulfoton (98-99% pure) was administered in the diet to 35 male and female Fischer 344 rats for up to 6 months at levels of 0, 0.25, 0.5 or 1 ppm (approximate doses of 0, 0.02, 0.03 or 0.06 mg/kg/day for males and 0, 0.02, 0.03 or 0.07 mg/kg/day for females). At the end of 2, 4 and 6 months, 10 rats/sex/dose were taken for blood and brain cholinesterase assays. Statistically significant inhibition of cholinesterase activity was observed in erythrocytes in females at all doses (3-14% inhibition, 11-17% inhibition, and 23-29% inhibition at 0.24, 0.5, and 1.0 ppm, respectively. In addition, at 1.0 ppm, males had decreased erythrocyte cholinesterase activity (10-16% inhibition) and females had decreased plasma (8-17% inhibition) and brain (7-13% inhibition) cholinesterase activities. However, biologically significant and statistically significant inhibition of cholinesterase activity was observed only in the plasma, erythrocytes and brain of females at 1.0 ppm. No biologically significant inhibition of cholinesterase activity was observed in males. The LOEL for inhibition of cholinesterase activity was 1.0 ppm is based on a 23-29% inhibition of erythrocyte, 12-17% inhibition of plasma and 13% inhibition of brain cholinesterase in females. The NOEL is 0.5 ppm (0.03 mg/kg/day). No biological meaningful cholinesterase inhibition was observed in males at any dose level. Body weight, food consumption, and clinical signs were also monitored, but showed no treatment related effects. Based on these few parameters, no systemic effects were observed at any dose level and the NOEL for systemic toxicity was 1.0 ppm (0.06 mg/kg/day for males and 0.07 mg/kg/day for females).

Dose and Endpoint for use in risk assessment: NOEL=0.03 mg/kg/day was based on plasma, erythrocyte and brain cholinesterase inhibition in female rats.

Comments about study and/or endpoint: Since an oral NOEL was identified, a dermal absorption factor of 36% should be used for this risk assessment. This endpoint is supported by similar effects (plasma, erythrocyte and brain cholinesterase inhibition) observed in a subchronic neurotoxicity study in rats (MRID# 42977401). In addition, the new 2-generation study on reproduction (MRID# 44440801) also supports the 6-month cholinesterase study endpoints.

The Committee considered a combination of factors in the decision to use the NOEL of 0.5 ppm (0.03 mg/kg/day) from the 6-month cholinesterase study in rats for the this exposure assessment instead of the LOEL of 0.5 ppm (0.03 mg/kg/day) from new 2-generation study on reproduction. Considered were that test material consumption was measured in the 6-month cholinesterase study and the measurements were invalid in the new 2-generation study on reproduction and the 6-month study was specifically designed to determine cholinesterase inhibition. Thus, mg/kg/day were measured in the 6-months study, but mg/kg/day dose levels in the reproduction study were approximated from standard tables. In addition, adult P0 females showed marginal brain cholinesterase inhibition while the F1 adult females, dosed similarly, showed none.

This risk assessment is required.

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

Study selected: Chronic Toxicity -Dog

§83-1

MRID No. 44248002

Executive Summary: See summary under Chronic RfD.

Dose and Endpoint for Risk Assessment: NOEL=0.013 mg/kg/day based on depressed plasma, erythrocyte and corneal cholinesterase levels in both sexes and depressed brain and retinal cholinesterase levels in females.

Comments about study and/or endpoint: This dose was used to establish the chronic RfD. Since an oral NOEL was identified, a dermal absorption factor of 36% should be used for this risk assessment.

This risk assessment is required.

5. Inhalation Exposure (Any Time Period)

Study Selected: 90-Day Inhalation-Rat

§82-4

MRID No.: 41224301

Executive Summary: Disulfoton was administered by inhalation to 12 Fisher 344 rats per sex per group for air control, polyethylene glycol-400: 50% ethanol vehicle control, 0.015, 0.15 or 1.5 mg/m³ nominal dose levels for 90-days in a nose only chamber. The analytical determined mean dose levels were 0, 0, 0.018, 0.16 and 1.4 mg/m³ for male and female rats. The rats were exposed to the test material 6 hours per day, 5 days per week. The particle sizes in the inhalation chambers had a MMAD ± geometric standard deviation of 1.3 ± 1.4, 1.1 ± 1.3, 1.0 ± 1.3 and 1.1 ± 1.4 µm for the two controls, 0.015, 0.15 and 1.5 mg/m³ nominal dose levels, respectively. The range in mean daily particle sizes had a MMAD of 0.5 ± 1.0 µm to 2.6 ± 1.6 µm. At the highest dose level, plasma cholinesterase was depressed in males (19% and 14% from air controls at 38 days and term, respectively, p≤0.05) and in females (27% and 31% from air controls at 38 days and term, respectively, p≤0.05). Brain cholinesterase was depressed in males (29%) and females (28%) at termination. Erythrocyte cholinesterase was depressed in females at 38 days (11% at 38 days, p≤0.05, not considered biologically relevant) at 0.16 mg/m³ and higher in males and females at 1.4 mg/m³ at 38 days and term. Brain cholinesterase was depressed (10%, p≤0.05) at 0.16 mg/m³, but this degree of variation was not considered biologically relevant due to variation noted in this parameter. Inflammation of the male nasal turbinates occurred at 1.4 mg/m³. No other test material related effects were noted. The NOEL/LOEL is 0.16 mg/m³/1.4 mg/m³ or 0.00016/0.0014 mg/L for plasma, erythrocyte and brain cholinesterase depression.

Dose and Endpoint for use in risk assessment: NOEL=0.00016 mg/L based on plasma, erythrocyte and brain cholinesterase inhibition.

Comments about study and/or endpoint: This NOEL will be used for inhalation exposure risk assessments for any time period (i.e., Short, Intermediate and Long-term). An inhalation toxicity study with 3 to 5 day exposure was available. In that study, the LOEL was <0.0005 mg/L (lowest dose tested); a NOEL was not established. Although this study could have been used for the Short-Term exposure risk assessment, the HIARC did not use this study because: (i) it demonstrated a LOEL rather than a NOEL; (ii) the use of a LOEL would have required an additional 3 x UF; and (iii) the value derived from the use of the LOEL and 3 UF (0.0005 ÷ 3 = 0.00017 mg/kg/day) is comparable the NOEL of 0.00016 mg/L in the 90-day study.

This risk assessment is required.

D. MARGINS OF EXPOSURE FOR OCCUPATIONAL/RESIDENTIAL EXPOSURES

A Margin of Exposure (MOE) of 100 is adequate for occupational exposure risk assessments. The MOEs for residential exposure will be determine during risk characterization by the FQPA Safety Committee..

E. RECOMMENDATION FOR AGGREGATE EXPOSURE RISK ASSESSMENT

For aggregate exposure risk assessment , the MOE's derived for oral, dermal and inhalation exposures may be combined to obtain a total MOE since a common toxicological endpoint (cholinesterase) was observed during all routes of exposure (oral, dermal and inhalation) in the toxicity studies.

For Short-Term aggregate exposure risk assessment:

$$MOE_{total} = \frac{1}{\frac{1}{MOE_{(oral)}} + \frac{1}{MOE_{(dermal)}} + \frac{1}{MOE_{(inhalation)}}$$

For Intermediate and Long-Term aggregate exposure risk assessment:

$$MOE_{total} = \frac{1}{\frac{1}{MOE_{(oral+oral\ dermal\ equivalent)}} + \frac{1}{MOE_{(inhalation)}}$$

III. CLASSIFICATION OF CANCER POTENTIAL:

The HED RfD/Peer Review classified disulfoton as a Group E Chemical-Not Classifiable to Carcinogenicity based on the lack of evidence of carcinogenicity study in mice and rats at dose levels adequate to test for carcinogenicity.

IV. FQPA CONSIDERATIONS

1. Neurotoxicity

The acute delayed neurotoxicity study (81-7) was unacceptable, but equivocal for delayed neurotoxicity. Another study has been requested for confirmation. Absolute brain weight was not affected by treatment in the guideline chronic studies in rodents. (The subchronic studies, which were graded unacceptable, were not provided for review.) In the rat study, treatment-related eye lesions were seen (optic nerve degeneration and corneal vascularization) and skeletal muscle atrophy were observed. The optic nerve degeneration was related to orbital sinus bleeding injury, so results were not considered treatment related. These neuropathological findings were not repeated in the 1997 1-year dog study, but cholinesterase levels in the cornea, retina, and ciliary body were depressed with treatment.

In an acutedelayed neurotoxicity study, disulfoton (97.8% pure) was administered by gavage at 30 mg/kg to 20 hens; 0.5 mg/kg of atropine was administered (im) 10 minutes before the disulfoton dose and 12.5 mg/kg of PAM-2 was administered (im) 30 minutes after the disulfoton dose. This dosing regimen was repeated at day 22. Five hens were used as a negative control. Five hens were administered atropine and PAM-2 (but no disulfoton) similarly to the disulfoton dosed group as an atropine and PAM-2 control and 10 hens were dosed with tri-O-cresol phosphate (500 mg/kg) as a positive control group. The 30 mg/kg dose level was shown to be lethal to hens without atropine administration. Samples of sciatic nerve, spinal cord (cervical, thoracic and lumbar) and brain (mid-brain, brain stem and cerebellum) were fixed in formalin and histological examination conducted. Pharmacologic signs were observed (loss of equilibrium, decreased activity, diarrhea and locomotor ataxia) in 14/20 hens after the first treatment, which subsided by day 5, except in one hen demonstrating ataxia and torticollis which decreased by day 15. These signs were considered by the report authors to be due to acute effects of disulfoton and not due to delayed neurotoxicity. Body weight of the disulfoton group (91% of the negative control and 94% of the atropine and PAM-2 treated control) and atropine and PAM-2 groups (97% of control) were lower than control hens at termination. Neuropathy in the form of degeneration digestion chambers (18/20 disulfoton treated hens versus 9/10 combined control hens), all grade 1 except one grade 2 pathology was seen at the thoracic level in a control hen, neuronal degeneration all grade 1 in (5/20 disulfoton hens versus 1/10 combined control hens, all grade 1) and axonal swelling all grade 1 (6/20 disulfoton hens versus 5/10 combined control hens) and demyelination all grade 1 (0/20 disulfoton treated hens versus 1/10 combined control hens). Macrophage accumulation occurred in 17/20 (85%) disulfoton treated hens versus 7/10 (70%) combined control hens. Macrophage accumulation an/or lymphocyte accumulation occurred in 4/5 of the disulfoton treated hens and in 1/10 of the combined control hens with neuronal degeneration. However, this accumulation was not always noted at the same site as the neuronal degeneration. This inflammation in old hens adds uncertainty to the effects seen in the

study. The study is suggestive but equivocal for delayed neurotoxic effects.

The study is unacceptable and not upgradable for an acute delayed neurotoxicity study in hens (81-7). Due to the equivocal but suggestive nature of the neurotoxic effects and the use of old hens, another study is required.

In an acute neurotoxicity study in Sprague-Dawley rats (10/sex/group), 97.8% disulfoton was administered by a single gavage dose of 0.25, 1.5, or 5.0 mg/kg in males and 0.25, 0.75, or 1.5 mg/kg in females. The NOEL for neurotoxicity and cholinesterase inhibition was 0.25 mg/kg, based on muscle fasciculations in 4/10 females and plasma and RBC cholinesterase inhibition at the LOELs of 0.75 mg/kg in females and 1.5 mg/kg in males. The incidence and type of clinical, behavioral, and neuromotor signs increased with dose. Females were clearly more sensitive. Neither brain weight nor neuropathology was affected by treatment (MRID 42755801).

In a 90-day subchronic neurotoxicity study, 98.7-99.0% disulfoton was administered to Fischer 344 rats (12/sex/group) at dietary levels of 1, 4, or 16 ppm (0.063, 0.270, or 1.08 mg/kg/day in males and 0.071, 0.315, or 1.31 mg/kg/day in females). The systemic NOEL was 1 ppm (0.063/0.071 mg/kg/day for M/F), based upon clinical signs consistent with cholinesterase inhibition (muscle fasciculations, urine staining, increased food consumption) in females at the LOEL of 4 ppm (0.270/0.315 mg/kg/day in M/F). At 16 ppm (1.08/1.31 mg/kg/day in M/F), treatment-related findings in both sexes also included increased reactivity, perianal staining, tremors, increased defecation, decreased forelimb grip strength, decreased motor and locomotor activity, decreased body weight gain, and corneal opacities. Cholinesterase inhibition (plasma, erythrocyte, and brain) was observed at all treatment levels (ChE NOEL \leq 1 ppm; 0.063/0.071 mg/kg/day for M/F). Clearly females were again shown to be more sensitive. It was noted that clinical signs were persistent throughout this study. There were no treatment-related effects on brain weight. At the high-dose level, neuropathological lesions (nerve fiber degeneration) were observed in the optic nerve, and nerve fiber degeneration was also observed in the thoracic spinal cord. These findings, however, were not judged to be unequivocal evidence of treatment-related neuropathology, since there was a confounding background incidence of these lesions (MRID 42977401).

2. Developmental Toxicity

In a prenatal developmental toxicity study in Sprague-Dawley rats (25/group), 98.2% disulfoton was administered on gestation days 6-15 by gavage in polyethylene glycol 400 at dose levels of 0.1, 0.3, or 1.0 mg/kg/day. Cholinesterase activity was measured in dams (5/group) on gestation day 15. The maternal NOEL was 0.1 mg/kg/day, and the maternal LOEL was 0.3 mg/kg/day, based on 41% inhibition of plasma and RBC cholinesterase. There was no other evidence of maternal toxicity at any treatment level. The developmental NOEL and LOEL were established at 0.3 and 1.0 mg/kg/day, based on incomplete ossification of the intraparietals and sternebrae (MRID 00129458).

In a prenatal developmental toxicity study conducted in New Zealand white rabbits (15-22/group), 97.3% disulfoton was administered by gavage in corn oil (5 ml/kg) at doses of 0.3, 1.0, or 3.0 (reduced to 2.0, then 1.5) mg/kg/day on gestation days 6-18. The maternal NOEL was

1.0 mg/kg/day; the maternal LOEL (1.5 mg/kg/day) was based upon clinical signs of cholinesterase depression (tremors, unsteadiness/ incoordination, and increased respiration, occurring within 4 hours of dosing). In addition, there were a large number of mortalities at the high-dose level. There was no evidence of developmental toxicity (developmental NOEL \geq 1.5 mg/kg/day). Neither maternal nor fetal cholinesterase levels were measured (MRID 00147886).

3. Reproductive Toxicity:

In a two-generation reproduction study in Sprague-Dawley rats (25/sex/group), 97.8% disulfoton was administered at dietary concentrations of 1, 3, or 9 ppm (calculated effective doses of 0.81, 2.4, or 76.3 ppm; equivalent to 0.04, 0.12, or 0.36 mg/kg/day mg/kg/day by test material consumption). The parental systemic NOEL was 3 ppm (0.12 mg/kg/day). The parental systemic LOEL was 9 ppm (0.36 mg/kg/day), based on decreased females mated and reduced body weight during gestation and lactation in P females. The offspring NOEL was 1 ppm (0.04 mg/kg/day), and the offspring LOEL was 3 ppm (0.12 mg/kg/day), based on decreased brain cholinesterase activity in F1a weanling pups and on decreased F2b pup survival. Although adult cholinesterase was not measured, the 2-year chronic study indicates that cholinesterase inhibition was most likely occurring at 3 ppm with a NOEL of 1 ppm; this was a conclusion of the 4/25/96 RfD PRC meeting (MRID 00157511).

In a another 2-generation reproduction study, disulfoton, technical, 99% a.i.] was administered to 30 Sprague Dawley rats/sex/dose in the diet at dose levels of 0, 0.5, 2.0 or 9.0 ppm (0, 0.025, 0.10 or 0.45 mg/kg/day by std. tables). Dosing was continuous for the P0 and F1 generation. Only one littering/animal/group was conducted. In this second 2-generation reproductive toxicity study with disulfoton, cholinesterase activity was measured in adults during pre-mating (at 8 weeks) and at termination and in pups at postnatal day 4 and day 21 in the 2 generations. The major effects noted were cholinesterase inhibition and dams with no milk. In P0 males, plasma cholinesterase (PCHE) was significantly depressed and dose related pre-mating at 9.0 ppm (\geq -34%) and at termination at 2.0 (\geq -11%) and 9.0 ppm (-46%). In P0 females, plasma cholinesterase (PCHE) was significantly depressed pre-mating (\geq -29%) and at termination (\geq -52%) at \geq 2.0 ppm. In P0 males and females erythrocyte cholinesterase (ECHE) was significantly depressed and dose related at \geq 2.0 ppm (\geq -38% & \geq -35% males and \geq -46% & \geq -80% females) a pre-mating and termination, respectively, but only in females at termination (\geq -14%) at \geq 0.5 ppm. In P0 males and females brain cholinesterase (BCHE) was significantly depressed and dose related at \geq 2.0 ppm in males (\geq -11%) and \geq -14% in females at \geq 0.5 ppm. PCHE and ECHE depression in F1 males and females followed a similar nominal pattern to that in P0 males and females, except that the statistical significance varied within the F1 between two dose levels; sometimes the dose level showing statistical significance was higher and sometime lower of the two. In F1 males and females, BCHE was significantly depressed and dose related at \geq 2.0 ppm in males (\geq -14%) and in females (\geq -50%). In F1 and F2 male and female pups at day 4 and/or day 21 of lactation, PCHE and ECHE were significantly depressed at 9.0 ppm. Values for PCHE and ECHE, respectively were at day 4 or day 21 in F1 male pups were (-24% & -47%) and for F1 female pups (-31% & -43%). Values for PCHE and ECHE, respectively, were at day 4 or day 21 in F2 male pups were (-46% & -53%) and for F2 female pups (-48% & -51%). In F1 and F2 male and female pups BCHE was significantly depressed at day 4 and day 21 at 9.0 ppm only (day 4 = -14% F1 males and -17% F1 females)(day 21 = -19% F1 males and -23% F1

females)(day 4 = -11% F2 males and -13% F2 females)(day 21 = -35% F2 males and -37% F2 females). Muscle fasciculation (1 P0 female), tremors (15 P0 females, 10 F1 females) and dams (7 F1 dams) with no milk were noted at 9.0 ppm. No treatment related organ weight changes or histopathology were noted in P0 or F1 males or females at any dose level. Clinical observations indicate that dams were not caring for their pups. Observed affects in pups in the 9.0 ppm group included 12 F1 (2 dams) pups cold to the touch and 3 F1 (2 dams) not being cared for and 63 F2 pups (7 dams) with no milk in their stomachs and 93 F2 weak pups (10 dams) from the affected dams. In addition, 1 P0 dam was salivating and gasping and did care for the litter and the litter died at 2.0 ppm. This effect at 2.0 ppm was considered test material related by the summary author of the 6(a)(2) submission (See summary 6(a)(2) report, MRID# 44440801; memorandum from David Anderson to PM 53, dated March 24, 1998, D242573), but ignored in the final report summary. Findings at necropsy were noted in F2 pups at 9.0 ppm that were expected in view of the maternal toxicity at this dose level. The report reasonably considered the pup deaths due to failure of maternal care, because of the weak and cold to the touch pups and failure of the pups to show milk in their stomachs. On careful examination of the report, this reviewer agrees with this conclusion. Thus, under these conditions, the effects in pups were caused by maternal toxicity and not the direct toxicity of disulfoton on pups. Body weight change was lower than control values during gestation in P0 (-9%) and F1 (-15%) females. Body weights were significantly reduced at termination from control values in P0 (-6%) and F1 females (-13%) and in F1 males (-8%). No other significant body weights or changes were noted. The P0 parental LOELs were 0.5 ppm (0.025 mg/kg/day) based on brain cholinesterase activity depression in P0 females with tremors and muscle fasciculation at 9 ppm in females during gestation and lactation from both generations and with body weight decrements at 9.0 ppm, especially at termination. A NOEL of 0.5 ppm (0.025 mg/kg/day) was seen in F1 parents. F1 and F2 pup (4 day and 21 day old) cholinesterase activity, including brain cholinesterase activity was depressed only at 9.0 ppm (0.45 mg/kg/day) with 2.0 ppm (0.10 mg/kg/day) being the NOEL. The F1 pup NOEL/LOEL were 2.0/9.0 ppm (0.10/0.45 mg/kg/day) based on treatment related pup deaths and pup weight decrements at 9.0 ppm, probably from inadequate maternal care (MRID# 44440801).

4. Additional Information from the Literature

This summary is provided to develop a comprehensive picture of disulfoton toxicity. The data have not been reviewed in depth, and no statement is made regarding the accuracy or quality of the data or reports.

In a 1988 study by McDonald et al., disulfoton was administered by daily i.p. injection at 2 mg/kg/day to male Long-Evans rats for 14 days. In treated rats, muscarinic receptor binding was decreased and spacial memory was decreased in a T-maze alternation task.

5. Determination of Susceptibility

There is no indication of increased susceptibility of fetuses, infants or children over adults to disulfoton from developmental toxicity studies in rats and rabbits or from two 2-generation studies on reproduction. In these studies, toxicity to the fetus or pups occurred only at higher dose levels than to the adults (dams or parents).

6. Recommendation for Developmental Neurotoxicity Study

The HIARC determined that a **developmental neurotoxicity study was not required** based on the following weight-of-the-evidence considerations.

(i) Evidence that support requiring a developmental neurotoxicity study:

- At the high-dose level, neuropathological lesions (nerve fiber degeneration) were observed in the optic nerve, and nerve fiber degeneration was also observed in the thoracic spinal cord of the mammalian subchronic study. These findings, however, were not judged to be unequivocal evidence of treatment-related neuropathology, since there was a confounding background incidence of these lesions.
- There was equivocal evidence of delayed neurotoxicity in the acute delayed neurotoxicity study in the hen.
- In a 1988 study by McDonald et al., disulfoton was administered by daily i.p. injection at 2 mg/kg/day to male Long-Evans rats for 14 days. In treated rats, muscarinic receptor binding was decreased and spacial memory was decreased in a T-maze alternation task. Since these effects occurred only with 75% brain cholinesterase inhibition, they were of questionable relevance to lower dose levels.

(ii) Evidence that do not support a need for a Developmental Neurotoxicity Study:

- Developmental toxicity studies showed no increased susceptibility in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.
- The two-generation reproduction toxicity studies in rats showed no increased susceptibility in pups when compared to adults. In addition, the pup deaths at the highest dose level in the second study on reproduction were due to a failure of maternal care and not due to direct toxicity from disulfoton.
- There was no evidence of abnormalities in the development of fetal nervous system in the pre/post natal studies.
- All the animal evidence suggesting neurotoxicity from disulfoton exposure is equivocal at best and it occurs at the highest dose levels only, i.e., because effects were seen in control and statistical significance was not achieved.

7. Determination of the FQPA Safety Factor:

The HIARC, based on the hazard assessment, recommends to FQPA Safety Committee, that the additional 10 x factor should be removed because:

- (a) Developmental toxicity studies showed no increased susceptibility in fetuses as compared to maternal animals following *in utero* exposures in rats and rabbits.
- (b) Two, 2-generation reproduction toxicity study in rats showed no increased susceptibility in pups when compared to adults.
- (c) There was no evidence of abnormalities in the development of fetal nervous system in the pre/post natal studies. No brain weight decreases were seen in any study. The evidence that brain histopathology was equivocally affected in the subchronic neurotoxicity (perfused or unperfused) at the highest dose tested only.
- (d) The Committee determined that the unacceptable acute delayed neurotoxicity study in hens was not a data gap and would require another study only for confirmation, since there was only equivocal evidence of delayed neurotoxicity. Therefore, there is insufficient evidence to require a developmental neurotoxicity study.

The final recommendation on the FQPA Safety Factor, however, will be made during characterization by the FQPA Safety Committee.

V. DATA GAPS

There are no data gaps. Another acute delayed neurotoxicity study in hens (81-7) and a NTE study are required only for confirmation.

VI. HAZARD CHARACTERIZATION

All required guideline studies have been adequately conducted and reviewed, except that a submitted acute delayed neurotoxicity study in the hen was considered to be unacceptable and not upgradeable.

Cholinesterase inhibition (plasma, erythrocyte and/or brain) is seen at the lowest dose levels tested in rats, mice, rabbits and dogs. All the endpoints are based on good dose related responses in cholinesterase inhibition. Many of the studies show clinical signs at higher dose levels. Females appear to be more sensitive to cholinesterase inhibition in most studies.

Acute and subchronic neurotoxicity in rats, probably due to the cholinesterase inhibition seen, occurred at higher dose levels than the cholinesterase inhibition. An acute delayed neurotoxicity study in the hen was considered unacceptable and not upgradeable and although another study was requested, it would be considered to be confirmatory only. The criteria for requiring a developmental neurotoxicity study was insufficient, thus the study was considered to be unnecessary. The data base relevant to infants and children was adequate to assess any

susceptibility that could have occurred.

Adequate developmental toxicity and reproductive toxicity studies show adult toxicity occurs at lower dose levels than toxicity to the fetus or offspring. Dose related responses in adequate developmental toxicity studies in rats and rabbits show that effects at the lowest dose levels are cholinesterase inhibition. Maternal cholinesterase was inhibited in rats at the two highest dose levels while developmental toxicity in the form of incomplete ossification of the intraparietals and sternbrae occurred at the highest dose level only. In rabbits, treatment related maternal mortality and signs of cholinesterase inhibition, such as tremors, unsteadiness/incoordination and increased respiration within 4 hour after dosing occurred at the highest dose level tested only in the developmental toxicity study in rabbits while no toxic effects were seen in fetuses at the highest dose level tested.

Two 2-generation reproduction studies were conducted on disulfoton. In the first study no cholinesterase was studied in parents, which showed treatment related body weight decrement in females during gestation and lactation and decreased mating success in females at the highest dose level tested. The first generation weanling pups, brain cholinesterase was decreased at the highest dose level tested and decreased survival occurred in the second generation pups. Although, adult cholinesterase inhibition was not measured in adults, the 2-year chronic study indicates cholinesterase inhibition was likely at the mid dose tested in the current study; this was the conclusion of the 4/25/96 RfD/Peer Committee meeting. In the second reproduction study, cholinesterase was measured in adults and offspring, which showed brain cholinesterase inhibition in first generation adult females at the lowest dose tested, but not in second generation females. At the highest dose level tested tremors and muscle fasciculation and body weight decrement occurred in females. First and second generation pups showed significant plasma, erythrocyte and brain cholinesterase inhibition in 4 day and 21 day old male and female pups at the highest dose level tested. Pups weights and survival was also decreased probably due to failure of adequate maternal care and/or adequate milk supply. These decreased pup weights and survival at the highest dose level tested were considered to be due to direct toxicity of disulfoton on the dams and not to the pups.

Acute cholinesterase inhibition was seen at the mid dose level where clinical signs such as muscle fasciculation were seen in a mammalian acute neurotoxicity study. Because of high background lesions, only equivocal neuropathological lesions (nerve fiber degeneration in the optic nerve and thoracic spinal cord) were seen in the subchronic neurotoxicity study at the highest dose level tested (not statistically significant), but cholinesterase inhibition (plasma, erythrocyte and brain) was seen at all dose levels. There is a high degree of confidence in the developmental toxicity studies and studies on reproduction and the dose response curve. The confidence in the neurotoxicity studies in rats is a little less because of the equivocal effects at the highest dose tested, but the dose response relationship was adequate for the cholinesterase inhibition. The disulfoton sulfoxide, disulfoton sulfone, disulfoton O-analog, disulfoton O-analog sulfoxide and disulfoton O-analog sulfone are toxic metabolites (total of 5), which occur during the studies in rats and therefore these metabolites are included in the toxicity of disulfoton.

There is no required guideline study data gaps. There is no developmental neurotoxicity study, but the HAZID did not believe that one was necessary. There is an unacceptable acute delayed neurotoxicity study in hens that shows equivocal delayed neuropathy. This was considered to be not a data gap and although, other study was requested, the results will be considered to be confirmatory only.

This literature summary is provided to develop a comprehensive picture of disulfoton toxicity. The data have not been reviewed in depth, and no statement is made regarding the accuracy or quality of the data or reports.

In a 1988 study by McDonald et al., disulfoton was administered by daily i.p. injection at 2 mg/kg/day to male Long-Evans rats for 14 days. In treated rats, muscarinic receptor binding was decreased and spacial memory was decreased in a T-maze alternation task. These effects occurred in the presence of -75% BCHE inhibition, therefore the effects may not be relevant at the NOEL for BCHE.

There is no evidence to support increased susceptibility of infants or children. The only possible evidence that offspring may be susceptible to neurotoxic effects is the non-statistically significant equivocal evidence at the highest dose level in the subchronic neurotoxicity study in rats (also not statistically significant).

There is no indication of increased susceptibility of fetuses, infants or children over adults to disulfoton from developmental toxicity studies in rats and rabbits or from two 2-generation studies on reproduction. In these studies, toxicity to the fetus or pups occurred only at higher dose levels than to the adults (dams or parents). Thus, there is no evidence of increased susceptibility to the fetus or to offspring.

Some organophosphates cause effects in pups at lower dose levels than adults, but the percentage is not large. Therefore, the structural relationship of being an organophosphate is insufficient to show increased susceptibility of offspring.

Adverse effects associated with various endpoints noted are plasma, erythrocyte and/or brain cholinesterase inhibition. At higher dose levels than the LOELs for these endpoints are effects possibly related to decreased muscle strength, possible nerve transmission rate, breathing difficulties and death.

These organophosphates have a common mode of action in that they decrease erythrocyte and/or brain cholinesterase in animals and humans. Plasma cholinesterase inhibition is a surrogate for possible muscle and brain cholinesterase inhibition. Neuropathy may result from higher exposures to these inhibitors. The rabbit 21-day dermal study did not show as consistent cholinesterase inhibition with time as other studies showed. The results were somewhat dependent on whether concurrent controls were used or the values for the individual animals at the beginning of the study were used for comparison.

Cholinesterase inhibition occurred at the LOEL in rats, mice, rabbits and dogs. Therefore the effects are very uniform across species. The female of the species appears to be more sensitive than the male and the cholinesterase inhibition occurs at slightly different dose levels across the species. The cholinesterase inhibition appears to be slightly greater in the female than the male

in most studies. There is insufficient studies with common dosage regimens to determine the most sensitive species except that the rat is more sensitive than the mouse in oncogenicity studies.

The dose level causing plasma cholinesterase inhibition was 1/3 that causing death in the rabbit dams in the developmental toxicity study. The LOEL causing brain cholinesterase inhibition in parents was 1/45 of the dose level resulting in offspring mortality in the second 2-generation reproduction study. In the acute neurotoxicity rat study reduced motor function occurred at the LOEL for PCHE, ECHE and BCHE inhibition. In the 90-day neurotoxicity study PCHE, ECHE and BCHE inhibition occurred at about 1/4 (0.063/0.27) the dose level resulting clinical signs.

VII ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of disulfoton, technical

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
81-1	Acute Oral	Acc# 072293	LD ₅₀ = M: 6.2 mg/kg; F:1.9 mg/kg	I
81-2	Acute Dermal	Acc# 07793	LD ₅₀ = M: 15.9 mg/kg; F: 3.6 mg/kg	I
81-3	Acute Inhalation	Acc# 258569	LC ₅₀ = M: 0.06 mg/L; F: 0.89 mg/L	I
81-4	Primary Eye Irritation	None	Data requirement waived.	N/A
81-5	Primary Skin Irritation	None	Data requirement waived.	N/A
81-6	Dermal Sensitization	None	Data requirement waived.	N/A
81-8	Acute Neurotoxicity	42755801	Reversible neurotoxic signs consistent with the cholinesterase inhibition 1.5 mg/kg in females and 5.0 mg/kg in males	N/A

VIII. SUMMARY OF TOXICOLOGY ENDPOINTS

The doses and toxicological endpoints selected for various exposure scenarios are summarized in the table below.

Exposure scenario	Dose (mg/kg/day)	Endpoint	Study
Acute Dietary	NOEL=0.25	Cholinesterase/clinical signs	Acute neurotox/rat
Acute dietary RfD = 0.00033 mg/kg/day			
Chronic dietary	NOEL=0.013	Cholinesterase inhibitor	Chronic/Dog
Chronic dietary RfD = 0.000044 mg/kg/day			
Short-term (Dermal)	Dermal NOEL=0.4	Cholinesterase	21-day dermal/rabbit
Correction for dermal absorption unnecessary			
Intermediate-term (Dermal)	Oral NOEL=0.03	Cholinesterase inhibition	6-months chronic/rat
Correction for oral to dermal exposure necessary (36% dermal absorption factor)			
Long-term life time (Dermal)	Oral NOEL=0.013	Cholinesterase inhibitor	Chronic/dog
Correction for oral to dermal exposure necessary (36% dermal absorption factor)			
Inhalation (Any time period) (inhalation)	NOEL=0.00016 mg/L	Cholinesterase inhibition	90-day inhalation/rat

Presentation/Hazard ID Memo, 4/21/98 for Disulfoton/DESULFOTON VOL 6 RED/A-HAZID/FINALHAZARDID.wp4/DANDERSON/4/21/98(Edited 4/21/98).

Table of values (triplicate analyses on 5 rats/sex) for plasma and erythrocyte cholinesterase inhibition in males and female Wistar rats after 4 hour inhalation exposures (nose only)/day for up to 5 days. The values in the table present % increases in cholinesterase inhibition compared with pre-dose values (Pre) or control (C) or control (C) as calculated by $\{1 - [(cholinesterase\ activity)/(pre-dose\ cholinesterase\ activity)]\} \times 100$. The acute inhalation NOEL/LOEL for males and females are 0.0005/0.0018 mg/L based on increased plasma cholinesterase inhibition and NOEL/LOEL of 0.0018/0.0098 mg/L for males and females based on increased erythrocyte cholinesterase inhibition after 1 exposure.

After 3 to 5 exposures, males showed NOEL/LOEL of 0.0005/0.0018 mg/L based on increased plasma and erythrocyte cholinesterase inhibition. Females showed NOEL/LOEL of <0.0005/0.0005 mg/L based on increased plasma cholinesterase inhibition after 3 to 5 exposures and the NOEL/LOEL are 0.0005/0.0018 mg/L based on increased erythrocyte cholinesterase after 3 to 5 exposures. Death occurs in females rats after 3 exposures at 0.0098 mg/L. Bolded values appear to be dose related.

Exposure conc. mg/L	After exposure 1				After exposure 3				After exposure 5				72 hr after exposure 5			
	Plasma		Erythrocyte		Plasma		Erythrocyte		Plasma		Erythrocyte		Plasma		Erythrocyte	
	Pre	C	Pre	C	Pre	C	Pre	C	Pre	C	Pre	C	Pre	C	Pre	C
0	-5	0	3	0	-2	0	0	0	4	0	-4	0	2	0	-4	0
0.0005	0	5	4	0	9	11	6	6	14	11	2	4	14	13	-3	1
0.0018	18	17	1	-2	43	40	19	18	53	49	16	19	14	13	12	15
0.0098	71	75	19	15	79	81	33	32	81	81	29	31	25	29	28	28

Males (sample size = 5)																
Exposure conc. mg/L	After exposure 1		After exposure 3		After exposure 5		72 hr after exposure 5									
	Pre	C	Pre	C	Pre	C	Pre	C								
	0	13	0	3	0	18	0	4	0							
0.0005	22	4	1	0	47	31	6	7								
0.0018	48	40	0	1	81	77	18	17								
0.0098	92	91	24	23	94	92	27	25								

Females (sample size = 5 except as otherwise specified)																
Exposure conc. mg/L	After exposure 1		After exposure 3		After exposure 5		72 hr after exposure 5									
	Pre	C	Pre	C	Pre	C	Pre	C								
	0	13	0	3	0	18	0	4	0							
0.0005	22	4	1	0	47	31	6	7								
0.0018	48	40	0	1	81	77	18	17								
0.0098	92	91	24	23	94	92	27	25								

* = Mean of 3/5 rats; 2 died. ^b = Mean of 2/5 rats; 3 died. ° = 1/5 rats; 4 died. Values for females at 0.0098 mg/L may not be meaningful at the day 5 exposure and after. Data were calculated from the data presented in the Table on page 14 of MRID# 00147754 Thyssen-J (1978)(S276)(Di-syston@A.I.) Acute Inhalation Toxicity Studies. Report# 7827, Bayer AG# or Mobay# 66647. September 27, 1978.

012593