US EPA ARCHIVE DOCUMENT

DATA EVALUATION RECORD

DISULFOTON

Study Type: Non-guideline; Time of Peak Cholinesterase Inhibition and Comparative Cholinesterase Studies in Preweaning and Young-adult Rats

Work Assignment No. 3-01-80; formerly 2-01-80 (MRIDs 46589701 through 46589704)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1801 Bell Street
Arlington, VA 22202

Prepared by
Pesticide Health Effects Group
Sciences Division
Dynamac Corporation
1910 Sedwick Road, Bldg 100, Ste B.
Durham, NC 27713

Primary Reviewer:
David McEwen, B.S. Signature: _____
Date: _____

Secondary Reviewer:
John W. Allran, M.S. Signature: _____
Date: _____

Program Manager:
Mary L. Menetrez, Ph.D. Signature: _____
Date: _____

Quality Assurance:
Steven Brecher, Ph.D., D.A.B.T. Signature: _____
Date: _____

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

EPA Reviewer: Louis Scarano **Signature:** _____
Toxicology Branch, Health Effects Division (7509C) **Date** _____
Work Assignment Manager: Ghazi Dannan, Ph.D. **Signature:** _____
Registration Action Branch 3, Health Effects Division (7509C) **Date** _____

Template version 11/01

DATA EVALUATION RECORD

STUDY TYPE: Non-guideline; Time of Peak Cholinesterase Inhibition and Comparative Cholinesterase Studies in Preweaning and Young-adult Rats.

PC CODE: 032501 **DP BARCODE:** DP319813
TXR#: N/A

TEST MATERIAL (PURITY): Disulfoton (97.5% a.i.)

SYNONYMS: *O,O*-diethyl *S*-[2-(ethylthio)ethyl] phosphorodithioate

CITATION: Langewische, F.W. (2005) Disulfoton: Study to establish the time of peak cholinesterase inhibition in young-adult Wistar rats treated by gavage with an acute dose of technical grade disulfoton. Bayer HealthCare AG, PH-R&D-PD Toxicology International, Wuppertal, Germany. Laboratory Report No.: AT02018, Study No.: T6073934, March 31, 2005. MRID 46589701. Unpublished.

Langewische, F.W. (2005) Disulfoton: Study to determine the time of peak cholinesterase inhibition in preweaning Wistar rats treated by gavage with an acute dose of technical grade disulfoton. Bayer HealthCare AG, PH-R&D-PD Toxicology International, Wuppertal, Germany. Laboratory Report No.: AT02019, Study No.: T0073938, April 14, 2005. MRID 46589702. Unpublished.

Langewische, F.W. (2005) Disulfoton: Cholinesterase inhibition in young-adult Wistar rats treated by gavage with an acute dose of technical grade disulfoton. Bayer HealthCare AG, PH-R&D-PD Toxicology International, Wuppertal, Germany. Laboratory Report No.: AT02065, Study No.: T9073937, May 30, 2005. MRID 46589703. Unpublished.

Langewische, F.W. (2005) Disulfoton: Study to determine cholinesterase inhibition in postnatal day 11 Wistar rats treated by gavage with an acute dose of technical grade disulfoton. Bayer HealthCare AG, PH-R&D-PD Toxicology International, Wuppertal, Germany. Laboratory Report No.: AT02066, Study No.: T1073939, May 30, 2005. MRID 46589704. Unpublished.

SPONSOR: Bayer CropScience AG, Alfred Nobel Str. 50, Monheim, Germany

EXECUTIVE SUMMARY - In two independent non-guideline time of peak-effect studies (MRIDs 46589701 [young adult] and 46589702 [preweaning]), disulfoton (97.5% a.i.; Batch #: 3-08-5013JC158) in PEG 400 was administered once via gavage (5 mL/kg) to 6 young-adult Wistar rats/sex/sacrifice time at doses of 0, 0.75 (females), or 1.5 (males) mg/kg. Plasma, erythrocyte, and brain cholinesterase activities were determined at 2, 4, 6, and 8 hours post-dosing in the treated animals and at 4 hours post-dosing in the controls. Similarly, disulfoton in PEG 400 was administered once via gavage (5 mL/kg) to 10 Wistar rat pups/sex/sacrifice time at doses of 0 or 0.5 mg/kg on post-natal day 11. Plasma, erythrocyte, and brain cholinesterase activities were determined at 4, 6, 8, and 24 hours post-dosing in the treated animals and at 6 hours post-dosing in the controls. Additionally, in two independent cholinesterase inhibition studies (MRIDs 46589703 [young adult] and 46589704 [preweaning]), disulfoton (same batch) in PEG 400 was administered once via gavage (5 mL/kg) to 6 young-adult Wistar rats/sex/dose at doses of 0, 0.25, 0.75, or 1.5 mg/kg (males) or 0, 0.25, 0.5, or 0.75 mg/kg (females). Plasma, erythrocyte, and brain cholinesterase activities were determined at 6 (males) and 8 (females) hours post-dosing (time of peak-effect) in all groups. Similarly, disulfoton in PEG 400 was administered once via gavage (5 mL/kg) to 10 Wistar rat pups/sex/sacrifice time at doses of 0, 0.125, 0.25, or 0.5 mg/kg. Plasma, erythrocyte, and brain cholinesterase activities were determined at 24 hours post-dosing (time of peak-effect) in all groups. Benchmark doses (BMD) of 10 and 20% cholinesterase inhibition were calculated for each compartment in both studies.

There were no treatment-related effects on mortality or clinical signs of toxicity in either of the time to peak effect studies. Cholinesterase activity was decreased ($p<=0.05$) in the adults in both sexes throughout all time points as follows: (i) plasma (decr 56-85%); (ii) erythrocyte (decr 25-65%); and (iii) brain (decr 15-42%). In the pups, cholinesterase activity was decreased ($p<=0.05$) in both sexes throughout all time points as follows: (i) plasma (decr 29-54%); (ii) erythrocyte (decr 23-56%); and (iii) brain (decr 12-34%). Based on the levels of cholinesterase inhibition, 6 and 8 hours post-dosing were determined to be the estimated time of peak-effect in adult males and females, respectively, and 24 hours post-dosing was determined to be the estimated time of peak-effect in pups of both sexes.

There were no treatment-related effects on mortality or clinical signs of toxicity in either of the comparative cholinesterase inhibition studies. Cholinesterase activity was dose-dependently decreased ($p<=0.05$) in the adults in both sexes as follows: (i) plasma at >=0.75 mg/kg in the males (decr 35-67%) and at all doses in the females (decr 16-84%); (ii) erythrocytes at 1.5 mg/kg in the males (decr 46%) and at >=0.5 mg/kg in the females (decr 34-70%); and (iii) brain at all doses in the males (decr 4-32%) and at >=0.5 mg/kg in the females (decr 17-43%). In the pups, cholinesterase activity was dose-dependently decreased ($p<=0.05$) in both sexes as follows: (i) plasma at >=0.25 mg/kg in the males (decr 24-56%) and at all doses in the females (decr 11-53%); (ii) erythrocytes at 0.5 mg/kg (decr 52-53%); and (iii) brain at all doses (decr 5-39%). In the adults, the following benchmark doses (mg/kg) were calculated for levels of 10 and 20% cholinesterase inhibition, respectively: (i) plasma (0.33 and 0.54, males; 0.09 and 0.18, females); (ii) erythrocytes (0.58 and 0.82, males; and 0.22 and 0.36, females); and (iii) brain (0.66 and 0.95, males; 0.38 and 0.54, females). Similarly in the pups, the following benchmark doses (mg/kg) were calculated: (i) plasma (0.11 and 0.20, males; 0.08 and 0.16, females); (ii) erythrocytes (0.14 and 0.24, males; and 0.11 and 0.20, females); and (iii) brain (0.15 and 0.27, males; 0.13 and 0.25, females).

These studies are classified as **acceptable/non-guideline**.

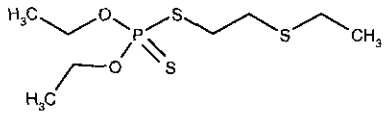
COMPLIANCE - Signed and dated Data Confidentiality, GLP Compliance, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Disulfoton

Description: Light brown liquid
Batch #: 3-08-5013JC158
Purity (w/w): 97.5% a.i.
Stability of compound: The test material was shown to be stable in the vehicle for up to 8 days at room temperature.
CAS #: 298-04-4
Structure:



2. Vehicle - PEG 400

3. Test animals

Species: Rat
Strain: Wistar Crl:GLxBrl Han: WI
Adult age/weight at study initiation: 9-10 weeks old/ 224-274 g males and 165-193 g females (for both studies)
Pup Age/weight at dosing: 11 days old/ weight not reported (both studies)
Source: Charles River Wiga (Deutschland, Sulzfeld, Germany)
Housing: Individually in Type IIIh Makrolon® cages
Diet: Mouse and Rat Maintenance Diet No. 3883.0.15 (Provimi Kliba SA, Kaiseraugst, Switzerland), *ad libitum*
Water: Tap water, *ad libitum*
Environmental conditions:
Temperature: 20±2°C
Humidity: Approximately 50%
Air changes: At least 10/hr
Photoperiod: 12 hrs dark/12 hrs light
Acclimation period: At least 7 days

B. STUDY DESIGN

1. Study purpose - The purpose of these studies was to determine the time of peak cholinesterase inhibition in young-adult and preweaning rats treated once via gavage with disulfoton, and to determine cholinesterase inhibition in young-adult and preweaning rats at the time of peak effect. These data were used to calculate the benchmark dose (BMD10 and BMD20) response for each compartment (i.e. plasma, erythrocytes, and brain), and to provide a comparison of cholinesterase activity effects in adult versus neonatal animals. These studies were designed to support a separate Development Neurotoxicity Study (OPPTS 870.6300) performed in August, 1998.

2. **In-life dates** - Start: 12/21/04 End: 12/22/04 (MRID 46589701)
Start: 01/17/05 End: 01/26/05 (MRID 46589702)
Start: 01/06/05 End: 01/07/05 (MRID 46589703)
Start: 02/01/05 End: 02/04/05 (MRID 46589704)

3. **Mating procedure for preweaning studies** - Females were paired 2:1 with males of the same strain and source overnight. Each female was examined following the mating period to identify sperm cells in a vaginal smear or the presence of a copulatory plug. If sperm or a copulatory plug were found, that day was designated gestation day (GD) 0, and each female was placed individually in a Type IIIh Makrolon® cage.

4. **Animal assignment and treatment** - For the studies using young adult rats, the animals were randomly assigned to the test groups noted in Tables 1a and 1b. It was stated that the randomization was performed taking body weight into consideration (no further details were provided). Each young adult animal received a single gavage dose at a volume of 5 mL/kg. For the studies using pups, litters were standardized to 8 pups/litter (preferably 4 pups of each sex) on post-natal day (PND) 4. If the number of males or females was less than 4, a partial adjustment was made (e.g. 3 of one sex and 5 of the other). Pups were culled randomly; pups not chosen for the study and litters that had an insufficient number of pups were killed and discarded without further examination. The pups chosen for the study were consecutively allocated (10/sex/dose group, or as nearly possible) to the groups noted in Tables 1a and 1b. Each pup received a single gavage dose at a volume of 5 mL/kg on PND 11.

Table 1a. Study design for time of peak effect studies. [a]

Group	# of Animals (M/F)	Dose (mg/kg)		Sample Time (Hrs post-dosing)
		Males	Females	
Young adult				
1 (control)	6/6	0	0	4
2	6/6	1.5	0.75	2
3	6/6	1.5	0.75	4
4	6/6	1.5	0.75	6
5	6/6	1.5	0.75	8
Preweaning				
1 (control)	9/10	0	0	6
2	11/9	0.5	0.5	4
3	10/10	0.5	0.5	6
4	10/9	0.5	0.5	8
5	10/10	0.5	0.5	24

a The data were obtained from Table 5-1 on pages 19 and 20 in MRIDs 46589701 and 46589702, respectively.

Table 1b. Study design for comparative cholinesterase inhibition studies. [a]

Group	# of Animals (M/F)	Dose (mg/kg)		Sample Time (Hrs post-dosing)
		Males	Females	
Young adult				
1 (control)	6/6	0	0	6 [M] and 8 [F]
2	6/6	0.25	0.25	6 [M] and 8 [F]
3	6/6	0.75	0.5	6 [M] and 8 [F]
4	6/6	1.5	0.75	6 [M] and 8 [F]
Preweaning				
1 (control)	10/10	0	0	24
2	10/10	0.125	0.125	24
3	10/10	0.25	0.25	24
4	9/10	0.5	0.5	24

a The data were obtained from Table 5-1 on pages 20 and 21 in MRIDs 46589703 and 46589704, respectively.

5. **Dose selection rationale** - It was stated that the dose levels used in these studies were requested by the Sponsor.

6. **Test substance preparation and analysis** - Dose formulations were prepared once prior to dosing by mixing the appropriate amounts of Disulfoton with PEG 400, and stored at room temperature until dosing the following day. The doses for each animal were determined using individual body weights. Stability data were provided from a previous study (# F7011320) in which concentrations of 0.02 and 0.40 mg/mL were evaluated for stability for up to 8 days at room temperature. These concentrations bracketed the concentrations used in the current study. Actual concentrations of the dosing formulations were determined at 1 to 3 days prior to compound administration in each study except for MRID 46589701. Homogeneity was not determined.

Results

Stability analysis (Range as % of initial): 84-99%

Concentration analysis:

MRID 46589702		MRID 46589703		MRID 46589704	
Dose (mg/kg)	% of Nominal	Dose (mg/kg)	% of Nominal	Dose (mg/kg)	% of Nominal
0.5	88	0.25	94	0.125	91
		0.5	97	0.25	89
		0.75	107	0.5	88
		1.5	80		

The analytical data indicated that the variation between nominal and actual dosage to the study animals was acceptable.

7. **Statistics** - The cholinesterase data were analyzed using an adjusted Welch test. Significance was indicated at $p \leq 0.05$ and 0.01 in the study tables.

C. METHODS

1. Observations

a. Young adults - All animals were observed once for mortality and clinical signs of toxicity.

b. Maternal animals - Dams were observed daily for mortality, moribundity, and clinical signs of toxicity. Body weight gain and food and water consumption were not evaluated.

c. Offspring - The number of live and stillborn pups was recorded for each litter, but was not reported. Pups were observed daily for mortality, moribundity, and clinical signs of toxicity from birth until sacrifice. The sex and weight (not reported) of each pup was determined as soon as possible following parturition (PND 0). Pup body weights were also recorded (not reported) on PNDs 4 and 11.

2. Body weight - All young adults and pups were weighed prior to treatment to determine individual doses.

3. Cholinesterase activity determination

a. Young adults - At each sacrifice time, blood was collected via the retroorbital venous plexus under ether anesthesia for plasma and erythrocyte cholinesterase activity determinations. Following blood collection, the animals were sacrificed by cervical dislocation under CO_2 anesthesia, and the whole brain was removed from the skull and frozen (≤-18 °C) until analysis. Cholinesterase activity determination was performed using a modification of the Ellman method. The modification consisted of using 6,6'-dithiodinicotinic acid as the coupling agent and measuring the change in absorbance at 340 nm. A gross necropsy was not performed. It was stated that brain weights were recorded after dissection (not reported).

b. Pups - At each sacrifice time, blood was collected from the pups via decapitation for plasma and erythrocyte cholinesterase activity determinations. Following blood collection, the whole brain was removed from the skull and frozen (≤-18 °C) until analysis. Cholinesterase activity determination was performed using the modification of the Ellman method described above. The dams were killed following sacrifice of the pups. A gross necropsy of the dams or pups was not performed. It was stated that brain weights of the pups were recorded after dissection (not reported).

4. Benchmark dose response - It was stated that the BMD was calculated using the non-positive quadratic polynomial model as provided in the US EPA BMDS software (version 1.3.2) versus analytically confirmed doses. Benchmark dose responses of 10 and 20% cholinesterase inhibition were calculated for each compartment.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity** - It was stated that no clinical signs of toxicity were observed in any animal in all studies; however, individual data were not provided.

2. **Mortality** - All animals survived to scheduled sacrifice in all studies.

B. CHOLINESTERASE ACTIVITY - The cholinesterase data for all compartments and time points are summarized and presented in Tables 2a and 2b (time of peak effect studies) and 3a and 3b (comparative cholinesterase inhibition studies) below.

1. **Plasma cholinesterase** - In the time to peak effect studies, plasma cholinesterase activity was decreased ($p \leq 0.05$) throughout the study periods by 56-72% in the adult males; 35-85% in the adult females; 32-54% in the male pups; and 29-49% in the female pups. The maximum peak inhibition (decreased activity) in the plasma of the adults was at 6 hours post-dosing in both sexes, and in the pups it was 8 hours post-dosing in the males and 8-24 hours post-dosing in the females.

In the comparative cholinesterase inhibition studies, plasma cholinesterase activity was dose-dependently decreased ($p \leq 0.05$) in the adult males at ≥ 0.75 mg/kg (↓35-67%) and in the adult females at all doses (↓16-84%). Similarly in the pups, plasma cholinesterase activity was dose-dependently decreased ($p \leq 0.05$) in the males at ≥ 0.25 mg/kg (↓24-56%) and in the females at all doses (↓11-53%).

2. **Erythrocyte cholinesterase** - In the time to peak effect studies, erythrocyte cholinesterase activity was decreased ($p \leq 0.05$) throughout the study periods by 40-51% in the adult males; 25-65% in the adult females; 23-50% in the male pups; and 30-56% in the female pups. The maximum peak inhibition in the erythrocytes of the adults was at 6 hours post-dosing in the males and 8 hours post-dosing in the females, and in the pups it was 24 hours post-dosing in both sexes.

In the comparative cholinesterase inhibition studies, erythrocyte cholinesterase activity was dose-dependently decreased ($p \leq 0.05$) in the adult males at 1.5 mg/kg (↓46%) and in the adult females at ≥ 0.5 mg/kg (↓34-70%). Similarly in the pups, erythrocyte cholinesterase activity was decreased ($p \leq 0.05$) in the 0.5 mg/kg males (↓53%) and females (↓52%).

3. **Brain cholinesterase** - In the time to peak effect studies, brain cholinesterase activity was decreased ($p \leq 0.05$) throughout the study periods by 27-42% in the adult males; 15-38% in the adult females; 16-34% in the male pups; and 12-30% in the female pups. The maximum peak inhibition in the brains of the adults was at 6 hours post-dosing in the males and 8 hours post-dosing in the females, and in the pups it was 8 hours post-dosing in both sexes.

In the comparative cholinesterase inhibition studies, brain cholinesterase activity was dose-dependently decreased ($p \leq 0.05$) in the adult males at all doses (↓4-32%) and in the adult females at ≥ 0.5 mg/kg (↓17-43%). Similarly in the pups, brain cholinesterase activity was dose-dependently decreased ($p \leq 0.05$) at all doses in the males (↓8-39%) and females (↓5-36%).

Table 2a. Mean (±SD) cholinesterase activity in young-adult rats treated once via gavage with Disulfoton. [a]

Dose (mg/kg)	0	1.5	1.5	1.5	1.5
Time Post-dosing (Hrs)	4	2	4	6	8
Males					
Plasma (kU/L)	0.36±0.10	0.27±0.07 (25)	0.16±0.05** (56)	0.10±0.04** (72)	0.16±0.09** (56)
Erythrocyte (kU/L)	1.19±0.10	1.04±0.15 (13)	0.67±0.14** (44)	0.58±0.14** (51)	0.71±0.27* (40)
Brain (U/g)	11.03±0.78	10.16±0.62 (8)	8.06±0.98** (27)	6.40±0.68** (42)	7.68±1.84** (30)
Females					
Plasma (kU/L)	1.67±0.40	1.09±0.14* (35)	0.54±0.27** (68)	0.25±0.07** (85)	0.27±0.04** (84)
Erythrocyte (kU/L)	1.69±0.23	1.26±0.05** (25)	1.16±0.33** (31)	0.69±0.07** (59)	0.59±0.13** (65)
Brain (U/g)	11.24±0.47	11.21±0.23	9.50±0.97* (15)	7.17±0.60** (36)	6.97±1.37** (38)

a Data were obtained from Table 6-2 on page 26 and pages 31 and 32 of MRID 46589701; n=6. Percent inhibition (decreased activity) is included in parentheses.

* Significantly different from controls at $p \leq 0.05$

** Significantly different from controls at $p \leq 0.01$

Table 2b. Mean (±SD) cholinesterase activity in rat pups treated once via gavage with Disulfoton on PND 11. [a]

Dose (mg/kg)	0	0.5	0.5	0.5	0.5
Time Post-dosing (Hrs)	6	4	6	8	24
Males					
Plasma (kU/L)	0.72±0.06	0.49±0.11** (32)	0.39±0.08** (46)	0.33±0.10** (54)	0.37±0.10** (49)
Erythrocyte (kU/L)	2.20±0.48	1.70±0.37* (23)	1.70±0.37* (23)	1.34±0.43** (39)	1.10±0.57** (50)
Brain (U/g)	5.51±0.24	4.63±0.75** (16)	4.20±0.64** (24)	3.63±0.60** (34)	4.10±0.78** (26)
Females					
Plasma (kU/L)	0.72±0.09	0.51±0.07** (29)	0.45±0.11** (38)	0.37±0.10** (49)	0.37±0.12** (49)
Erythrocyte (kU/L)	2.20±0.41	1.88±0.23 (15)	1.53±0.23** (30)	1.27±0.50** (42)	0.97±0.47** (56)
Brain (U/g)	5.61±0.54	4.95±0.56* (12)	4.44±0.69** (21)	3.94±0.84** (30)	4.13±0.73** (26)

a Data were obtained from Table 6-2 on page 28 and pages 33 and 34 of MRID 46589702; n=9-11. Percent inhibition (decreased activity) is included in parentheses.
* Significantly different from controls at $p \leq 0.05$
** Significantly different from controls at $p \leq 0.01$

Table 3a. Mean (±SD) cholinesterase activity at the estimated time of peak effect in young-adult rats treated once via gavage with Disulfoton. [a]

Males				
Compartment	**Dose (mg/kg)**			
	0	**0.25**	**0.75**	**1.5**
Plasma (kU/L)	0.43±0.08	0.39±0.04 (9)	0.28±0.05** (35)	0.14±0.04** (67)
Erythrocyte (kU/L)	1.69±0.21	1.53±0.10 (9)	1.40±0.20 (17)	0.92±0.14** (46)
Brain (U/g)	11.54±0.30	11.08±0.32* (4)	9.92±0.29** (14)	7.81±0.93** (32)
Females				
Compartment	**Dose (mg/kg)**			
	0	**0.25**	**0.5**	**0.75**
Plasma (kU/L)	1.56±0.17	1.31±0.20* (16)	0.57±0.12** (63)	0.25±0.10** (84)
Erythrocyte (kU/L)	1.51±0.24	1.41±0.21 (7)	1.00±0.13** (34)	0.45±0.10** (70)
Brain (U/g)	10.74±0.42	10.71±0.50	8.87±0.71** (17)	6.10±0.64** (43)

a Data were obtained from Table 6-2 on page 26 and pages 32 and 33 of MRID 46589703; n=6. The estimated time of peak effect was 6 (males) and 8 (females) hours post-dosing. Percent inhibition (decreased activity) is included in parentheses.
* Significantly different from controls at $p \leq 0.05$
** Significantly different from controls at $p \leq 0.01$

Table 3b. Mean (±SD) cholinesterase activity at 24 hours post-dosing in rat pups treated once via gavage with Disulfoton on PND 11. [a]

Compartment	Dose (mg/kg)			
	0	0.125	0.25	0.5
Males				
Plasma (kU/L)	0.71±0.08	0.66±0.08 (7)	0.54±0.08**(24)	0.31±0.13**(56)
Erythrocyte (kU/L)	2.01±0.56	1.62±0.49 (19)	1.72±0.27 (14)	0.95±0.44**(53)
Brain (U/g)	6.49±0.42	5.90±0.37** (8)	5.38±0.54**(16)	3.88±0.86**(39)
Females				
Plasma (kU/L)	0.73±0.06	0.65±0.06** (11)	0.49±0.08** (33)	0.34±0.13** (53)
Erythrocyte (kU/L)	2.18±0.58	1.90±0.48 (13)	1.70±0.14 (22)	1.05±0.51** (52)
Brain (U/g)	6.47±0.39	6.13±0.28* (5)	5.23±0.51** (19)	4.12±0.73** (36)

a Data were obtained from Table 6-2 on page 27, and pages 32 and 33 of MRID 46589704; n=9-10. Percent inhibition (decreased activity) is included in parentheses.
* Significantly different from controls at $p \leq 0.05$
** Significantly different from controls at $p \leq 0.01$

C. **BENCHMARK DOSE RESPONSE** - In the adults, the following benchmark doses (mg/kg) were calculated for levels of 10 and 20% cholinesterase inhibition, respectively: (i) plasma (0.33 and 0.54, males; 0.09 and 0.18, females); (ii) erythrocytes (0.58 and 0.82, males; and 0.22 and 0.36, females); and (iii) brain (0.66 and 0.95, males; 0.38 and 0.54, females; Table 4a). Similarly in the pups, the following benchmark doses (mg/kg) were calculated: (i) plasma (0.11 and 0.20, males; 0.08 and 0.16, females); (ii) erythrocytes (0.14 and 0.24, males; and 0.11 and 0.20, females); and (iii) brain (0.15 and 0.27, males; 0.13 and 0.25, females; Table 4b).

Table 4a. Benchmark dose estimates (mg/kg) for cholinesterase inhibition in young-adult rats treated once via gavage with Disulfoton. [a]

Compartment	Males		Females	
	BMD10	BMD20	BMD10	BMD20
Plasma	0.33	0.54	0.09	0.18
Erythrocytes	0.58	0.82	0.22	0.36
Brain	0.66	0.95	0.38	0.54

a Data were obtained from Table 7-1 on page 29 of MRID 46589703. It was stated that the BMD was calculated using the non-positive quadratic polynomial model as provided in the US EPA BMDS software (version 1.3.2) versus analytically confirmed doses.
BMD10 = 10% inhibition
BMD20 = 20% inhibition

Table 4b. Benchmark dose estimates (mg/kg) for cholinesterase inhibition in rat pups treated once via gavage with Disulfoton on PND 11. [a]

Compartment	Males		Females	
	BMD10	BMD20	BMD10	BMD20
Plasma	0.11	0.20	0.08	0.16
Erythrocytes	0.14	0.24	0.11	0.20
Brain	0.15	0.27	0.13	0.25

a Data were obtained from Table 7-1 on page 29 of MRID 46589704. It was stated that the BMD was calculated using the non-positive quadratic polynomial model as provided in the US EPA BMDS software (version 1.3.2) versus analytically confirmed doses.

BMD10 = 10% inhibition
BMD20 = 20% inhibition

13544

R155699

Chemical:

PC Code:

HED File Code: 258 Contractor DER TOX Caution: This Document (review) was completed by a contractor and has not undergone secondary review. This document may not reflect Agency policies.

Memo Date:

File ID: 00000000

Accession #: 000-00-0123

HED Records Reference Center
12/19/2007