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WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

TXR#: 0054033
Date: 07/10/06

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM:

Subject: PC 103801: DER for a Comparative Cholinesterase study in Young Adults and 11-Day Old Pups (MRID# 466153011).

DP Barcode: D304359
Decision#: 345193
PC Code: 103801

CAS# 23135-22-0

From: David G Anderson, PhD
RRB-2, HED (7509P)
David G Anderson 7/10/06

To: Michael Goodis/Rosanna Louie, PM 53
Reregistration Branch 2
SRRD (7508P)

Thru: Alan Nielsen, BSS
RRB-2, HED (7509P)
Alan Nielsen 7/13/06

The registrant submitted a comparative cholinesterase study in young adults and 11-day old pups. The data is this study showed cholinesterase inhibition at lower dose levels than a previous acute neurotoxicity study [MRID# 44254401, 44420301 and 44740701] in the same strain of rat. This difference may be due to random variation in cholinesterase determinations or other unknown reasons.

CONCLUSIONS for MRID# 46615301

For young adult males/females the LOAEL = 0.15 mg/kg [LDT] based increased erythrocyte cholinesterase inhibition [25% in males and 22% in females] and brain cholinesterase inhibition [10% in males]. A NOAEL of 0.15 mg/kg was seen in females only for brain cholinesterase inhibition [3%].

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For males/female 11 day old pups the LOAEL = 0.075 mg/kg based on erythrocyte cholinesterase inhibition [18% in males and 16% in females] and brain cholinesterase inhibition [11% in males and 7% in females]. No NOAEL was seen.

The study is **ACCEPTABLE/NON-GUIDELINE** for acute cholinesterase data in 11-Day old pups and young adults. A bench mark dose calculation for the data in MRID# 46615301 will be conducted by the Agency.

COMPLIANCE: A statement of no-confidentiality of data and compliance with GLPs was signed. Although benchmark dose calculations are best way to analyze these data, for preliminary evaluation, a statistical analysis of the data should have been submitted.

2

EPA Reviewer: David G Anderson, Ph.D. **Signature:** David G Anderson
Reregistration Branch 2, Health Effects Division (7509C) **Date** 7/10/06
EPA Secondary Reviewer: Elissa Reaves Ph.D. **Signature:** Elissa Reaves
Reregistration Branch 2, Health Effects Division (7509C) **Date** 7/10/06

TXR#: 0054033

DATA EVALUATION RECORD

STUDY TYPE: Cholinesterase Inhibition in Young Adults and 11 Day Old Pups - Rat [NG Study Supplement to OPPTS 870.6300 (§83-6)] OECD 426]

PC CODE: ~~103250~~ 103801 **DP BARCODE:** D304359

DECISION: 345193

TEST MATERIAL (PURITY): Technical Grade Oxamyl (98.0%)

SYNONYMS: Oxamyl, technical (DPX-D1410), Ethanimidothioic acid, 2-(dimethylamino)-N-[[(methylamino)carbonyl]oxy]-2-oxo-, methyl ester

CITATION: Malley, L. (2005) Oxamyl (DPX-D1410) Technical (98% w/w): Relative Sensitivity of Preweanling Rat Pups and Adult Rats to Inhibition and Recovery of Cholinesterase Activity. Project Number: DUPONT/16755, 969, 970. Unpublished study prepared by DuPont Crop Protection. 70 p. Category: Complete primary report -- experimental research Receipt Date: 04-Aug-2005. MRID# 46615301.

SPONSOR: DuPont Crop Protection

EXECUTIVE SUMMARY: The relative sensitivities to cholinesterase inhibition at peak inhibition by oxamyl were measured in young-adult and neonatal rats (MRID 46615301). In these studies on young-adult and neonatal Charles River strain Crl:CD(SD)IGS BR rats, oxamyl was administered (98.0% a.i., batch # DPX-D1410-196) in a single gavage dose in 2 mL water/kg to 42 day old young adult rats or 11-day-old neonatal rats in 3 subsets of experiments. Subset 1: Peak cholinesterase inhibition was determined in 11-day old pups [5/sex/group] dosed at 0.1 mg/kg, approximately 30, 60, 120, 180, 240 or 360 minutes after administration. Subset 2: Erythrocyte [ECHE] and brain cholinesterase [BCHE] was determined on 11-day old pups [10/sex/group] at peak cholinesterase inhibition of 30 minutes after administration of doses at 0, 0.075, 0.10, 0.125, or 0.15 mg/kg. Subset 3: Erythrocyte [ECHE] and brain [BCHE] was determined in young adults (10/sex/group) at peak inhibition of 30 minutes and after recovery at 240 minutes after administration of doses at 0, 0.15, 0.20, or 0.25 mg/kg. No statistical analyses of this data was presented.

These data should be evaluated by Benchmark dose calculations, since no NOAELs were seen except for BCHE in adult females. Cholinesterase appeared to be decreased at all dose levels in the two compartments tested [erythrocytes and brain] in 11-Day old male and female pups and young males and female adult rats.

The 11-Day old pups showed increased cholinesterase inhibition at 0.075, 0.10, 0.125 or 0.15 mg/kg in erythrocytes [18%-16%, 17%-20%, 15%-15%, 38%-36%, respectively in males and females] and brain [11%-7%, 12%-10%, 12%-9%, 23%-23%, respectively in males and females] at all dose levels tested At dose levels below 0.15 mg/kg, the increase appeared to be

significant, but these was no dose response relationship. This may be due to the narrow separation of the dose levels and variation among the individuals tested.

The young adults showed dose related increased cholinesterase inhibition at 0.15, 0.20 or 0.25 mg/kg in erythrocyte [25%-22%, 30%-37%, and 46%-53%, respectively in males and females] and brain [10%-3%, 13%-15%, 22%-19%, respectively in males and females] significant at all dose levels tested, except BCHE in females at 0.15 mg/kg (LDT).

The cholinesterase inhibition appeared to be greater in 11-Day old pups than in young adult rats. Extrapolation of the steep dose vs. inhibition line to zero inhibition in a semi-log plot of inhibition vs. dose was seen roughly around 0.04 mg/kg for 11-day old male and female pups and roughly around 0.10 mg/kg for young adult males and females. The difference seen between males and females in young adults or 11-Day old pups appeared to be due to variation rather than a difference in cholinesterase levels. A benchmark dose calculation may raise or lower these zero inhibition endpoints.

For young adult males/females the LOAEL = 0.15 mg/kg [LDT] based increased erythrocyte cholinesterase inhibition [25% in males and 22% in females] and brain cholinesterase inhibition [10% in males]. A NOAEL of 0.15 mg/kg was seen in females only for brain cholinesterase inhibition [3%].

For males/female 11 day old pups the LOAEL = 0.075 mg/kg based on erythrocyte cholinesterase inhibition [18% in males and 16% in females] and brain cholinesterase inhibition [11% in males and 7% in females]. No NOAEL was seen.

The study is **ACCEPTABLE/NON-GUIDELINE** for acute cholinesterase data in 11-Day old pups and young adults. A bench mark dose calculation for the data in MRID# 46615301 will be conducted by the Agency.

COMPLIANCE: A statement of no-confidentiality of data and compliance with GLPs was signed. Although benchmark dose calculations are best way to analyze these data, for preliminary evaluation, a statistical analysis of the data should have been submitted.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material:	Technical grade Oxamyl
Description:	Off-white solid
Lot/Batch #:	DPX-D1410-196
Purity:	98.0 % a.i.
Compound Stability:	Stable during test
CAS # of TGAI:	23135-22-0

4

2. **Vehicle control:** Nano-water (pure water) at 2 ml/kg.

3. **Test animals (P):**	For suppling neonatal pups for dosing and time to peak activity.	
Species:	Rat	
Strain:	Charles River Crl:CD(SD)IGS BR	
Age at study initiation:	males & females: Young adults (42 days old) and 11-day old pups	
Wt. at study initiation:	Not important	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	Individually or with litter in plastic shoe boxes	
Diet:	LLC certified rodent LabDiet 5002, *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	18-26°C
	Humidity:	30-70%
	Air changes:	Not given
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	About 4 days	

PROCEDURE & STUDY DESIGN: Study initiated 1/31/05 and experiment started 2/1/05 and terminated 2/17/05.

Pups on arrival were assigned cross-fostering lactating dams at 5/sex/dam. Whether pups from the same litter were assigned to a dam is not clear, but there was no indication that litter mates were assigned to different dams. Young adults were assigned to groups by computerized, stratified random selection.

Peak time and recovery time were previously determined for young adults and 11-Day old pups [30 minutes for both young adults and 11-Day old pups]. All dosed were administered by a single gavage dose based on the animal's weight at dosing. At the indicated time pups were killed by intraparenteal injection of Beuthansia and blood collected by cardiac puncture. Young adult rats killed by CO2 asphyxiation and blood collected from *vena cava* puncture.

Blood was centrifuged, erythrocytes hemolyzed 5-10 seconds and analyzed within 15 minutes after blood was collected. Brains were weighed and snap frozen until homogenized and analyzed. Cholinesterase activity was measured by a modified [SOP CP124-p; Roche Reagent 124117] on a Roche Behringer-Mannheim Hitachi 717 chemistry analyzer.

Subset 1: Time to peak inhibition and recovery of ECHE and BCHE in 11-Day old pups at 30 minutes post dose. 11-Day old pups were administered a single dose of 0 or 0.1 mg/kg by gavage. [The recovery data at 60, 90, 120, 180 and 360 minutes is not shown in the current DER.] The pups were returned to the litters/dams and killed at indicated times. Blood and brain were collected after dosing for CHE activity. Data obtained from Page 13 of MRID# 46615301.

Table 1: Subset 1: Treatment Groups and Dose levels						
Males	Females	Number	Dose vol. ml/kg	Dosage mg/kg	Conc. mg/ml	Sacrifice Time [min.]
I	II	5	2	0.0	0.0	60
III	IV	5	2	0.0	0.0	120
V	VI	5	2	0.0	0.0	240
VII	VIII	5	2	0.1	0.050	30
IX	X	5	2	0.1	0.050	60
XI	XII	5	2	0.1	0.050	90
XIII	XIV	5	2	0.1	0.050	120
XV	XVI	5	2	0.1	0.050	180
XVII	XVIII	5	2	0.1	0.050	240
XIX	XX	5	2	0.1	0.050	360
XVII	XVIII	5	2	0.1	0.050	240
XIX	XX	5	2	0.1	0.050	360

Subset 2: Dose vs. response of ECHE and BCHE in 11-Day old pups. 11-Day old pups were dosed as indicated, returned to litters/dams, killed 30 minutes post dosing and blood and brains collected for CHE determination. Data obtained from Page 13 of MRID# 46615301.

Table 2: Subset 2: Treatment Groups and Dose levels						
Males	Females	Number	Dose vol. ml/kg	Dosage mg/kg	Conc. mg/ml	Sacrifice Time [min.]
I	II	10	2	0.0	0.0	30
III	IV	10	2	0.075	0.0375	30
V	VI	10	2	0.1	0.05	30
VII	VIII	10	2	0.125	0.0625	30
IX	X	10	2	0.15	0.075	30

Subset 3: Dose response at peak inhibition and recovery for young adult rats. Young adult rats approximately 42 days old were administered a single dosed as indicated, and killed 30 minutes and 240 minutes post dosing [Data on the reversibility of cholinesterase at 240 minutes not shown in the current DER]. Blood and brains were collected for CHE. Data obtained from Page 14 of MRID# 46615301.

Table 3: Subset 3: Treatment Groups and Dose levels

Males	Females	Number	Dose vol. ml/kg	Dosage mg/kg	Conc. mg/ml	Sacrifice Time [min.]
I	II	10	2	0.0	0.0	30
III	IV	10	2	0.0	0.0	240
V	VI	10	2	0.15	0.075	30
VII	VIII	10	2	0.15	0.075	240
IX	X	10	2	0.20	0.10	30
XI	XII	10	2	0.20	0.10	240
XIII	XIV	10	2	0.25	0.125	30
XV	XVI	10	2	0.25	0.125	240

Verification Dose administered:

Doses were analyzed and found within acceptable variation of nominal.

STATISTICAL METHODS:

No statistical analyses was reported.

B. RESULTS:

1. Observations: Observations were stated to have been made, but no data was presented. Weight data was not collected.

2. Control Data:

For Subset 1: Controls for time to peak inhibition and recovery [recovery data not shown in the current DER] of erythrocyte and brain cholinesterase activity in pre-weanling rat pups, minimized the number of animals used by analyzing fewer points for control pups than pups dosed with 0.10 mg/kg. Therefore, cholinesterase data from pups dosed with 0.10 mg/kg were compared to most appropriate control (0.0 mg/kg) value, and if time point fell between two control time points, the mean of the two closest time points was used according to the following Table:

Subset 1: Time points for comparison for determination of peak inhibition and recovery. Data obtained form page 19 of MRID#46615301.

Time-point; Dosed Pups (min.)	Compared to Control Data from time-point (min.)
30	60
60	60
90	Mean of 60 and 120
120	120
180	Mean of 120 and 240
240	240
360	240

The control data for erythrocyte cholinesterase [ECHE] pups and young adults showed overlapping standard deviations such that there is some doubt about whether the control data at different times differed and should be separated. Pooling the control data may yield better control information than attempting to use control relative to time after administration of the vehicle to compare data from dosed groups from the respective times. Table 4 presents control data for erythrocyte cholinesterase [ECHE] for male and female 11-Day old pups from various times relative to post dosing and Table 5 presents data for brain cholinesterase [BCHE] for male and female 11-Day old pups for various times relative to post dosing.

However, in all inhibition data from doses were compared with 30 minute controls in Table 6, 7, 8 and 9. Combined control data at various times is presented for information purposes, but not used.

Table 4: ECHE data from control groups of male and female 11-Day old pups. Data obtained from page 39, Table 1, page 40, Table 2, page 41, Table 3 and page 42, Table 4 of MRID# 466153021.				
	Subset 1			Subset 2
Time post dosing (min.)	60	120	240	30
	Group I 0.0 mg/kg	Group III 0.0 mg/kg	Group V 0.0 mg/kg	Group I 0.0 mg/kg
Males				
ECHE	2760	2864	2935	2968
STD	411 [5]	338 [5]	719 [4]	413 [8]
CV%	15	12	24	14
All time frame mean = 2845.455	All time frame STD=442.7697	All time frame CV%=15.6%		
Females				
	Subset 1:			Subset 2
	GroupII 0.0 mg/kg	Group IV 0.0 mg/kg	Group VI 0.0 mg/kg	Group II 0.0 mg/kg
ECHE	2876	3072	2590	2938
STD	634 [5]	108 [5]	549 [4]	413 [10]
CV%	22	4	21	10
All time frame mean = 2895	All time frame STD= 413.5635	All time frame CV%=14.3%		

9

Table 5: BCHE control data from males and female 11-Day old pups. Data obtained from page 39, Table 1, page 40, Table 2, page 41, Table 3 and page 42, Table 4 of MRID# 46615301.

Males				
	Subset 1			Subset 2
Time post dosing (min.)	60	120	240	30
	Group I 0.0 mg/kg	Group III 0.0 mg/kg	Group V 0.0 mg/kg	Group I 0.0 mg/kg
BCHE	5.3	6.8	6.5	6.0
STD	0.7 [5]	0.5 [5]	0.2 [5]	0.5 [10]
CV%	13	7	3	8
All time frame mean=6.11	All time frame STD=0.692411	All time frame CV%=11.3%		
Females				
	Subset 1			Subset 2
Time post dosing (min.)	60	120	240	30
	Group II 0.0 mg/kg	Group IV 0.0 mg/kg	Group VI 0.0 mg/kg	Group II 0.0 mg/kg
BCHE	5.2	6.3	6.7	5.9
STD	0.2 [5]	0.6 [5]	0.2 [5]	0.5 [10]
CV%	4	10	3	8
All time frame mean=5.99	All time frame STD=0.662898	All time frame CV%=11.1%		

3. Cholinesterase Data for 11-Day Old Pups

Dose vs. response in ECHE and BCHE activity and % inhibition for 11-Day old male pups is presented in Table 6. Cholinesterase is depressed and % inhibition is increased at all dose levels, but especially at 0.15 mg/kg. Dose related response in ECHE and BCHE activity and % inhibition for 11-Day old female pups is presented in Table 7. Cholinesterase activity is depressed at all dose levels and % cholinesterase inhibition is increased at all dose levels, but the values were greater at 0.15 mg/kg.

Cholinesterase [ECHE and BCHE] values were lower than control, but showed essentially no change with dose for dose levels 0.075, 0.10, 0.125 mg/kg for male and female 11-Day old pups. This may have been due to the narrow separation of the doses administered and variation in the individual values. Cholinesterase [ECHE and BCHE] appeared more definitively changed at 0.15 mg/kg.

10

Since no statistical analyses were conducted, the significance of the cholinesterase depression and % inhibition increase has not been determined. However, a comparison of these data by a "t" test, which is an inadequate method for these data, shows that the data at the various dose levels appears to be significantly different from control values. Comparison of cholinesterase data from each dose level consecutively with control values by a "t" test for male and female ECHE and BCHE showed a $p<0.05$. However, this data is best handled by a Benchmark dose calculation to establish an endpoint for regulation.

Table 6: Summary of ECHE, BCHE values and % Inhibition versus dose for male 11-Day old pups compared with control Group I at 30 minutes.. Data obtained from page 41, Table 3 of MRID# 46615301.

	Subset 2	Subset 1 & 2	Subset 2			
Time post-dose (min)	30	Combined 30, 60, 120 & 240 min	30	30	30	30
	Group I 0.0 mg/kg	Mean of all controls 0.0 mg/kg	Group III 0.075 mg/kg	Group V 0.10 mg/kg	Group VII 0.125 mg/kg	Group IX 0.15 mg/kg
Male 11-Day old pups						
ECHE [U/L]	2968	2845	2428	2478	2528	1854
STD [N]	413 [8]	442 [22]	375 [10]	396 [9]	517 [10]	251 [10]
CV%	14%	15.4%	15%	16%	20%	14%
% inhibition	0%	4.1%	18%	17%	15%	38%
STD	14 (8)	ND	13 (10)	13 (9)	17 (10)	8 (10)
BCHE [U/g]	6.0	6.11	5.3	5.3	5.3	4.6
STD [N]	0.5 [10]	0.692 [25]	0.5 [10]	0.5 [10]	0.6 [10]	0.6 [10]
CV%	8	11.1%	9%	9%	11%	13%
% inhibition	0%	-1.8%	11%	12%	12%	23%
STD	8 (10)	ND	8 (10)	9 (10)	11 (10)	10 (10)

ND = Not determined

Table 7: Summary of ECHE, BCHE, % inhibition of ECHE and BCHE for female 11-Day old pups compared with control Group II at 30 minutes. Data obtained from page 42, Table 4 of MRID#46615301 and calculated by the reviewer.

	Subset 2	Subset 1 & 2	Subset 2			
Time post-dose (min)	30	Combined 30, 60, 120 & 240 min	30	30	30	30
	Group II 0.0 mg/kg	Mean of all controls 0.0 mg/kg	Group IV 0.075 mg/kg	Group VI 0.10 mg/kg	Group VIII 0.125 mg/kg	Group X 0.15 mg/kg
Female 11-Day old pups						
ECHE [U/L]	2938	2895	2480	2340	2502	1876
STD [N]	302 [10]	414 [22]	239 [9]	642 [9]	310 [9]	590 [10]
CV%	10%	14.34%	10%	27%	12%	31%
% inhibition	0%	1.5%	16%	20%	15%	36%
STD [N]	10 [10]	ND [22]	8 [9]	22 [9]	11 [9]	20 [10]
BCHE [U/g]	5.9	6.11	5.5	5.3	5.3	4.5
STD [N]	0.5 [10]	0.692 [25]	0.1 [10]	0.5 [10]	0.3 [10]	0.8 [10]
CV%	8	11.1%	2%	9%	6%	18%
% inhibition	0%	-3.6%	7%	10%	9%	23%
STD [N]	8 [10]	ND	3 [10]	8 [10]	6 [10]	14 [10]

ND = Not determined

4. Cholinesterase Data for Young Adult Rats.

A dose related response in ECHE and BCHE activity and % inhibition for young adult male rats are presented in Table 8. Cholinesterase is depressed and % inhibition is elevated at all dose levels, but especially at 0.25 mg/kg. Treatment related response in ECHE and BCHE activity and % inhibition for young adult female rats is presented in Table 9. The dose relationship was more definitive in the adult rats than in the 11-Day old pups. This may have due in part to the wider separation of doses with the young adults than in with the 11-Day old pups.

Since no statistical analyses were conducted, the level of significance of the cholinesterase depression and % inhibition increase has not been determined. However, comparison by the a "t" test, which is an inadequate statistical comparison for these data, shows that the data at the various dose levels appears to be significantly different from control values, $p<0.5$ for each dose level, except BCHE in females at 0.15 mg/kg, $p>0.05$. However, this data is best handled by a Benchmark dose calculation to establish an endpoint for regulation.

Table 8: Summary of young adult male cholinesterase activity and inhibition compared with control Group I at 30 minutes. Data obtained from page 43, Table 5 of MRID# 46615301 and calculated by the reviewer.

	Subset 3				
Time post-dose (min)	30	30&240	30	30	30
	GroupI 0.0 mg/kg	Group I&III 0.0 mg/kg	GroupV 0.15 mg/kg	Group IX 0.20 mg/kg	Group XIII 0.25 mg/kg
ECHE (U/L)	2292	2294.1	1718	1176	1248
STD	439 (10)	481.0 (17)	307 (10)	353 (10)	326 (326)
CV%	19%	21%	18%	30%	26%
% inhibition	0	-4.4%	25%	49%	46%
STD	19 (10)	ND	13 (10)	15 (10)	14 (10)
BCHE	9.1	9.49	8.2	8.0	7.2
STD	1.2 (10)	1.05 (17)	0.9 (10)	1.0 (10)	1.3 (10)
CV%	13%	11%	11%	13%	18%
% inhibition	0	-4.3	10%	13%	22%
STD	13 (10)	ND	10 (10)	11 (10)	14 (10)

Table 9: Summary of young adult female cholinesterase activity and inhibition compared with control Group II at 30 minutes. Data obtained form page 44, Table 6 of MRID# 46615301 and calculated by the reviewer.

	Subset 3				
Time post-dose (min)	30	30&240	30	30	30
	GroupII 0.0 mg/kg	Group II&IV 0.0 mg/kg	GroupVI 0.15 mg/kg	Group X 0.20 mg/kg	Group XIV 0.25 mg/kg
ECHE (U/L)	2170	2076	1684	1370	1022
STD	450 (10)	497.5 (20)	412 (10)	386 (10)	176 (10)
CV%	21%	24%	24%	28%	17%
% inhibition	0	4.3%	22%	37%	53%
STD	21 (10)	ND	19 (10)	18 (10)	8 (10)
BCHE (U/g)	10.0	10.1	9.7	8.5	8.1
STD	1.0 (10)	0.81(20)	0.7 (10)	0.9 (10)	1.1 (10)
CV%	10%	8%	7%	11%	14%
% inhibition	0	-1%	3%	15%	19%

STD	10 (10)	ND	7 (10)	9 (10)	11 (10)

DISCUSSION:

Young adult male and female rats and 11-Day old pups were dosed by a single gavage dose of oxamyl technical in water and erythrocyte and brain cholinesterase inhibition was determined at peak cholinesterase levels at 30 minutes and up to 240-360 minutes post gavage when cholinesterase was found to return to normal values. Cholinesterase inhibition at 0.075, 0.10, 0.125, or 0.15 mg/kg was [ECHE: 18%-16%, 17%-20%, 15%-15%, 38%-36%, respectively in males and females at the respective doses] and [BCHE: 9%-7%, 9%-10%, 11%-9, or 13%-23%, respectively in males and females at the respective doses]. In 11-Day old pups erythrocyte and brain cholinesterase was less than control values at all dose levels, however, the three of the four dose levels used essentially did not differ from each other.

In young adult rats, erythrocyte and brain cholinesterase inhibition was greater than control values at all dose levels [0.15, 0.20, or 0.25 mg/kg] and showed a dose relationship [ECHE: 25%-22%, 49%-37%, 46%-53%, respectively in males and females] at the respective doses and [BCHE: 10%-3%, 13%-15%, 22%-14%, respectively in males and females] at the respective doses. Young male and female adult rats showed significantly decreased dose related cholinesterase depression at all doses administered, except BCHE in females at 0.15 mg/kg. Since no statistical analyses were conducted on the data by the study authors, estimates of possible significance were made by the reviewer by comparison of each dose group with 30 minute control data by a "t" test. By a "t" test, all dose levels were significant at $p < 0.05$, except BCHE in young adult females at 0.15 mg/kg.

Extrapolation of the steep dose vs. inhibition line to zero inhibition in a semi-log plot of inhibition vs. dose was seen roughly around 0.04 mg/kg for 11-day old male and female pups and roughly around 0.10 mg/kg for young adult males and females. [Plot not shown in DER.] The difference seen between males and females in young adults or 11-Day old pups appeared to be due to variation rather than a difference in cholinesterase levels. A benchmark dose calculation may raise or lower these zero inhibition endpoints.

The acute neurotoxicity study (MRID#s 44254401 & 44420301 & 44740701) in the same strain of rats and approximate age at peak cholinesterase inhibition at 30-60 minutes post dosing showed data with a NOAEL of 0.1 mg/kg based plasma, erythrocyte and brain cholinesterase depression, while in current study, young adult rats showed a LOAEL at 0.1 mg/kg, LDT. Clearly the current acute study showed effects of cholinesterase at lower doses than the previous acute study. The reason for this difference is unknown, since the same strain of rats were used at the same peak cholinesterase inhibition in both studies, but the difference in the data probably represents factors other than oxamyl induced cholinesterase inhibition.

Although data in the Tables on % inhibition for 11-day old pups and young adults was compared with control values, both 30 minutes post gavage, other control values at other times were included in the report. Control values among the data were values at 30, 60, 120 and 240 minutes post gavage. The data from all these controls appeared not to vary significantly, and thus all control values should be pooled to increase the number of animals in the control group [however, no statistical analyses was conducted in order to prove that the control data from the various times post gavage did not differ].

13544

R122753

Chemical: Thiabendazole

PC Code: 060101
HED File Code: 61400 SRRD DERs
Memo Date: 1/1/2000
File ID: 00000080
Accession #: 412-06-0197

HED Records Reference Center
7/25/2006