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DATA EVALUATION RECORD

TRICLORFON (DYLOX TECHNICAL)

Study Type: SPECIAL STUDIES, CHOLINESTERASE INHIBITION [NON-GUIDELINE]
MRID 46647404 (peak effect - preweaning); 46647403 (acute - preweaning); 46635601 (repeated - preweaning)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Prepared by
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Task Order No. 124-2006C

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DATA EVALUATION RECORD

STUDY TYPE: Non-guideline special study, Effects on Cholinesterase in Preweaning Rats (Companion Study to Developmental Neurotoxicity Study 870.6300)

PC CODE: 057901 **DP BARCODE:** DP322591
SUBMISSION NO.: none

TEST MATERIAL (PURITY): Trichlorfon (100% a.i.)

SYNONYMS: Dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate; Dylox Technical

CITATION: Langewische, F.W. (2005) Study to determine the time of peak cholinesterase inhibition in preweaning Wistar rats treated by gavage with an acute dose of technical grade trichlorfon. Bayer HealthCare AG, PH-R&D-PD Toxicology International, 42096 Wuppertal, Germany. Report No. AT02017, Study No. T4073932. April 15, 2005. MRID 46647404. Unpublished.

Langewische, F.W. (2005) Study to determine cholinesterase inhibition in postnatal day 11 Wistar rats treated by gavage with an acute dose of technical grade trichlorfon. Bayer HealthCare AG, PH-R&D-PD Toxicology International, 42096 Wuppertal, Germany. Report No. AT02064, Study No. T8073936. May 30, 2005. MRID 46647403. Unpublished.

Klaus A.-M. (2005) Study to determine cholinesterase inhibition in postnatal day 11 Wistar rats treated by gavage for eleven days with technical grade trichlorfon. Bayer HealthCare AG, PH-R&D Toxicology, 42096 Wuppertal, Germany. Report No. AT02252, Study No. T5073357. August 5, 2005. MRID 46635601. Unpublished.

SPONSOR: Bayer CropScience AG, 40789 Monheim, Germany

EXECUTIVE SUMMARY: In a series of special non-guideline comparative cholinesterase activity inhibition studies, trichlorfon (Dylox technical; 100% a.i., lot #1030228) was administered by oral gavage to groups of preweaning Wistar rats. For time-course evaluation (MRID 46647404) 9-10 animals/sex/group were given a single oral dose of 0 or 50 mg/kg on post-natal day (PND) 11 and sacrificed 1, 2, 4, 8, or 24 hours later. In an acute study (MRID 46647403) groups of 10 rats/sex were given a single oral dose of 0, 5, 10, or 30 mg/kg on PND 11 and sacrificed 2 hours post-dosing, at the time of peak effect. Finally, repeated administration was studied (MRID 46635601) by giving eleven daily doses of 0, 5, 10, or 20 mg/kg/day to

groups of 10 rats/sex on PNDs 11-21; animals were sacrificed 1 hour after the last dose. Plasma, red blood cell (RBC), and brain cholinesterase (ChE) activity was measured in all animals in each study.

No adverse clinical signs of toxicity or treatment-related deaths were observed in any animal in any study.

During time-course investigations following a single oral dose of 50 mg/kg on PND 11, maximum ChE inhibition occurred at 1-2 hours post-dosing. In male pups, the highest levels of inhibition of plasma and RBC cholinesterase activity were 82 and 75%, respectively, observed at 1 hour after dosing, and the greatest inhibition of brain cholinesterase activity was 58%, observed at 2 hours after dosing. In female pups, the highest level of cholinesterase activity inhibition was observed at 2 hours for all compartments with inhibition for plasma, RBC, and brain, at 81, 65, and 66%, respectively. Overall, the greatest level of inhibition was observed in plasma cholinesterase activity in both males and females. After 24 hours, there was still significant inhibition of plasma (38%) and RBC (23%) enzyme activity in males, while brain enzyme activity recovered to control levels. In females after 24 hours, there was significant inhibition of plasma ChE (34%), while RBC and brain enzyme activity recovered to control levels. The time of peak effect of cholinesterase inhibition after acute trichlorfon administration was determined to be 2 hours post dosing.

After an acute dose of trichlorfon, there was significant inhibition of plasma (68-75%), RBC (24-37%), and brain (39-45%) ChE activity in males and females at the high dose (30 mg/kg). After an acute dose of 10 mg/kg, there was significant inhibition in male and female plasma (26-29%) and brain (9-13%) ChE activity, but no significant effects on RBC enzyme activity. After an acute dose of 5 mg/kg, plasma ChE activity was inhibited by 12% in both males and females.

Following repeated dosing with 20 mg/kg/day, plasma ChE activity was significantly inhibited in both males (24%) and females (39%). RBC enzyme activity was inhibited in high-dose females by 34% although statistical significance was not attained. Brain ChE activity was significantly inhibited in males at the high dose (17%), and in females at all doses (6, 11, and 26% at 5, 10, and 20 mg/kg/day, respectively).

For acute exposure of preweaning rats to trichlorfon:

the preweaning LOAEL for brain ChEI is 10 mg/kg
the preweaning NOAEL for brain ChEI is 5 mg/kg;

the preweaning LOAEL for plasma ChEI is 10 mg/kg
the preweaning NOAEL for plasma ChEI is 5 mg/kg;

the preweaning LOAEL for red blood cell ChEI is 30 mg/kg
the preweaning NOAEL for red blood cell ChEI is 10 mg/kg;

For acute oral exposure to trichlorfon, the overall LOAEL for cholinesterase activity inhibition in PND 11 rats is 10 mg/kg based on enzyme inhibition in plasma and brain in males and females; the preweaning NOAEL is 5 mg/kg.

For repeated exposure of preweaning rats to trichlorfon:

the preweaning LOAEL for brain ChEI 5 mg/kg/day (females)
the preweaning NOAEL for brain ChEI is not identified;

the preweaning LOAEL for plasma ChEI is 20 mg/kg/day
the preweaning NOAEL for plasma ChEI is 10 mg/kg/day;

the preweaning LOAEL for red blood cell ChEI is 20 mg/kg/day (females)
the preweaning NOAEL for red blood cell ChEI is 10 mg/kg/day;

For repeated oral exposure to trichlorfon, the overall LOAEL for cholinesterase activity inhibition in PND 11 rats is 5 mg/kg/day based on enzyme inhibition in brain in females; the preweaning NOAEL is not identified.

The ChE activity measurements following acute oral dosing with trichlorfon did not demonstrate a difference in susceptibility between preweaning male and female rat pups. By 24 hours post-dosing females showed a greater recovery in RBC activity, but no differences between the sexes were seen in the other compartments. Following repeated dosing, however, females appeared slightly more susceptible than males. Compared to plasma or brain enzyme activity in males and females, the RBC ChE activity was the least sensitive compartment after acute and repeated trichlorfon exposure.

Taken together these studies are classified **Acceptable/Nonguideline** for the determination of plasma, RBC, and brain ChE activity inhibition following treatment with trichlorfon in PND 11 rats.

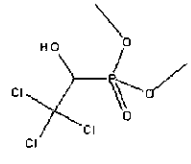
COMPLIANCE: Signed and dated GLP, Quality Assurance, Flagging, and Data Confidentiality statements were provided for all studies.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Trichlorfon

Description:	whitish powder; $C_4H_8Cl_3O_4P$
Lot/Batch #:	1030228 (Bayer CropScience AG)
Purity:	100% a.i.
Compound Stability:	room temperature, 8 days
CAS # of TGAI:	52-68-6
Structure:	



2. **Vehicle and/or positive control:** Demineralized water was used as a vehicle. No positive control was used.

3. **Test animals:**

Species:	Rat	
Strain:	SPF-bred Wistar (Crl:GL x Brl Han:WI)	
Age and wt. at study initiation:	Postnatal day 11; body weight not reported	
Source:	Charles River Wiga (Deutschland) GmbH, 97633 Sulzfeld, Germany	
Housing:	Dams with litter in Type IIIh Makrolon® cages	
Diet:	Kliba mouse and rat maintenance diet (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 times/hr
	Photoperiod:	12 hrs light/12 hrs dark
Acclimation period:	Adult females at least 7 days prior to mating	

B. PROCEDURES AND STUDY DESIGN

1. **In life dates:** MRID 46647404: Start: December 14, 2004; End: December 17, 2004
MRID 46647403: Start: January 12, 2004; End: January 12, 2004
MRID 46635601: Start: June 19, 2005; End: June 29, 2005

2. **Study design:** Table 1 shows the treatment groups allocated for the study.

TABLE 1. Study design for cholinesterase activity inhibition studies

MRID	Dose(s) (mg/kg/day)	Sex; No. of animals/ group	Treatment and termination
46647404	0, 50	M: 10 F: 9-10	Single oral dose on PND 11; animals terminated 1, 2, 4, 8, or 24 hours post-dosing; control animals terminated 2 hours post-dosing
46647403	0, 5, 10, 30	M&F: 10	Single oral dose on PND 11; animals terminated 2 hours post-dosing
46635601	0, 5, 10, 20	M&F: 10	Eleven daily oral doses beginning on PND 11; terminated 1 hour after the last dose on PND 21

3. **Mating procedure:** Animals were mated by placing two females in a cage with one male overnight. On the morning after mating, if vaginal smears indicated a vaginal plug or sperm, the day was considered day 0 of gestation.

4. **Animal assignment:** Using a within-litter treatment design, pups were consecutively allocated to the dose groups described in Table 1. In the peak effect study (MRID 46647404), 60 males and 59 females were allocated to six experimental groups. In the acute study (MRID 46647403), a total of 40 males and 40 females were allocated to four experimental groups. In the repeated dose study (MRID 46635601), 40 males and 40 females were allocated to four experimental groups.

5. **Dose selection rationale:** The dose levels used in all studies were selected as requested by the sponsor. Treatment should result in inhibition of ChE activity but not induce overt toxicity.

6. **Dosage administration:** The animals were treated with trichlorfon by oral gavage in a dose volume of 10 mL/kg body weight at dose levels described in Table 1. The control animals received only vehicle (demineralized water) at the same volume. The body weight of the animals was determined prior to dosing. Gavage was selected since oral exposure is a possible route of exposure for humans.

7. **Dosage preparation and analysis:** The test material was dissolved in demineralized water and stored at room temperature for the duration of use. Stability analyses were performed in 0.1 mg/mL and 20 mg/mL samples prior to the start of these studies. Analysis of concentration of the active ingredient in samples was carried out a few days before first day of dosing for each study. For the repeated dose study, the frequency of preparation was not stated; however, it was noted that the dosing solutions were stored for a maximum of 8 days. Homogeneity of the dosing solutions was not measured. The results for each study are given below.

   Results: For all studies, absence of test article was confirmed in the vehicle. Stability data confirmed stability over a period of 8 days at room temperature. After 4 days of storage at room temperature, 0.1 and 20 mg/mL solutions were 95 and 97% of the initial measured concentration, respectively. After 8 days of storage at room temperature, 0.1 and 20 mg/mL solutions were 96 and 94% of the initial measured concentration, respectively.

   MRID 46647404: The mean concentration was 104% of nominal for the 5 mg/mL solution and 97% of nominal for the 20 mg/L solution.

   MRID 46647403: The mean concentrations were 99, 99, and 101% of nominal for the 0.5, 1.0, and 3.0 mg/mL solutions, respectively.

   MRID 46635601: The mean concentrations were 97, 101, and 99% of nominal for the 0.5, 1.0, and 2.0 mg/mL dose preparations, respectively.

   The analytical data indicated that the difference between nominal and actual dosage to the study animals was acceptable for all studies.

C. OBSERVATIONS:

1. **In-life observations:** Dams were observed once daily for clinical signs, mortality and moribundity. Body weight gain, and feed and water consumption were not determined. The numbers of live and stillborn pups were recorded for each litter. Pups were observed once daily for clinical signs from birth until sacrifice. If a clinical sign was observed, the pup was removed from the cage for more detailed observation. On PND 4 litters were culled using a computer-generated randomization plan, to yield 4 males and 4 females. Litters with less than 8 pups were excluded. If there were less than 4 males or females, litters were adjusted to yield 3 of one sex and 5 of the other. Pup body weight was recorded after birth, on PND 4, and on each dosing day for determination of dose volume.

2. **Termination schedule and sample collection**: Pup blood samples were taken for cholinesterase determination at the timepoints specified in Table 1. Following decapitation, blood was collected in K-EDTA tubes for analysis of erythrocyte and plasma cholinesterase levels. Immediately following blood collection, the whole brain was removed, weighed, and stored at ≤18°C until analysis. After the last pup was sacrificed, dams were sacrificed by cervical dislocation while under deep carbon dioxide anesthesia. Gross pathological examination of dams and pups was not performed.

3. **Cholinesterase activity determination**: Cholinesterase assays were performed on all blood and brain samples using a modified Ellman method with 6,6'-dithiodinicotinic acid as the coupling reagent and measuring the change in absorbance at 340 nm.

D. DATA ANALYSIS: Statistical analyses of ChE activity data was performed using SAS routines on the actual data, not on the percent inhibition values. An adjusted Welch test was used for statistical evaluation. In order to control the familywise type-one error rate within each sex × date constellation, Holm's sequentially rejective multiple test was applied. Benchmark dose levels of 10% and 20% inhibition of ChE activity were calculated using the National Center for Environmental Assessment Benchmark Dose Software (version 1.3.2), the ChE data and the analytically confirmed doses. Statistical significance at $p \leq 0.05$ and $p \leq 0.01$ were designated by * and **, respectively.

II. RESULTS:

A. Mortality and clinical observations: In the acute dose studies, no clinical signs or mortality were observed in the dams or the pups. In the repeated dose study, two female pups in the control group were found dead. One was found cannibalized on postnatal day 14 and another was found dead on postnatal day 16.

B. Body weight: Body weight data were not reported.

C. Brain weight: Brain weight data were not reported.

D. Cholinesterase activity: The plasma, RBC, and brain ChE activity data for treated preweaning male and female rats are shown in Tables 3, 4 and 5 for time-course, acute, and repeated dose studies, respectively.

1. **Time-course of inhibition (MRID 46647404):** ChE activity data for rat pups treated on PND 11 are shown in Table 2. In male pups, the highest levels of inhibition of plasma and RBC enzyme activity were 82 and 75%, respectively, observed at 1 hour after dosing, and the greatest inhibition of brain ChE activity was 58%, observed at 2 hours after dosing. In female pups, the highest level of cholinesterase activity inhibition was observed at 2 hours for all compartments with inhibition for plasma, RBC and brain enzyme activity, at 81, 65, and 66%, respectively. Overall, the greatest level of inhibition was observed in plasma cholinesterase activity in both males and females. At 24 hours, there was still significant inhibition of plasma and RBC enzyme activity in males, while brain ChE activity recovered to control levels. In females after 24 hours, there was significant inhibition of plasma ChE activity, while erythrocyte and brain enzyme activity recovered to control levels. The time of

peak effect of cholinesterase inhibition after acute trichlorfon administration was determined to be 2 hours post dosing.

TABLE 2. Plasma, RBC, and brain ChE activity in PND 11 rats treated with trichlorfon:
Acute exposure with termination 1, 2, 4, 8, and 24 hours post-dosing

Dose	0 mg/kg	50 mg/kg	50 mg/kg	50 mg/kg	50 mg/kg	50 mg/kg
Time after treatment (hr)	2	1	2	4	8	24
Males						
Plasma (kU/L)	0.71±0.074	0.13**±0.024 (82)	0.17**±0.034 (76)	0.26**±0.080 (63)	0.33**±0.087 (54)	0.44**±0.040 (38)
RBC (kU/L)	2.13±0.367	0.54**±0.158 (75)	0.60**±0.185 (72)	0.86**±0.438 (60)	0.96**±0.318 (55)	1.63**±0.397 (23)
Brain (U/g)	5.93±0.2.34	2.74**±0.656 (54)	2.52**±0.278 (58)	3.18**±0.591 (46)	4.15**±0.557 (30)	5.74±0.239
Females						
Plasma (kU/L)	0.70±0.082	0.15**±0.044 (79)	0.13**±0.031 (81)	0.24**±0.087 (66)	0.42**±0.039 (40)	0.46**±0.082 (34)
RBC (kU/L)	1.56±0.333	0.64**±0.213 (59)	0.55**±0.222 (65)	0.85**±0.290 (46)	0.99**±0.149 (37)	1.63±0.276
Brain (U/g)	6.21±0.351	3.04**±0.614 (51)	2.14**±0.360 (66)	3.01**±0.537 (52)	4.41**±0.652 (29)	5.95±0.211

Data extracted from Annex pp. 33-36, MRID 46647404.
N = 10/sex/group
Numbers in parenthesis are percent inhibition relative to control from Table 6-2, p. 28.
Significantly different from control: **p ≤ 0.01.

2. **Acute exposure (MRID 46647403)**: Cholinesterase activity data for rats treated with a single dose of the test article are shown in Table 3. After an acute dose of trichlorfon, there was significant inhibition of plasma, RBC and brain ChE activity in males and females at the high dose (30 mg/kg). After an acute dose of 10 mg/kg, there was significant inhibition in male and female plasma and brain cholinesterase activity, but no significant effects on RBC cholinesterase activity. After an acute dose of 5 mg/kg, there was significant inhibition (12%) in plasma cholinesterase activity in both males and females.

   Benchmark dose estimates for 10% inhibition (BMD_{10}) of plasma, RBC, and brain ChE activity were 4.00, 8.82, and 10.72 mg/kg, respectively for males and 4.42, 16.25, and 7.75 mg/kg, respectively for females. Benchmark dose estimates for 20% inhibition (BMD_{20}) of plasma, RBC, and brain ChE activity were 8.01, 17.64, and 17.68 mg/kg, respectively for males and 8.85, 26.53, and 15.49 mg/kg, respectively for females. The reviewer did not verify the benchmark calculations presented in the study.

TABLE 3. Plasma, RBC, and brain ChE activity in PND 11 rats treated with trichlorfon:
Acute exposure with termination 2 hours post-dosing

Dose (mg/kg bw)	0	5	10	30
Males				
Plasma (kU/L)	0.68±0.062	0.60*±0.061 (12)	0.48**±0.079 (29)	0.17**±0.075 (75)
RBC (kU/L)	1.93±0.344	1.60±0.250	1.58±0.347	1.22**±0.287 (37)
Brain (U/g)	5.89±0.279	5.78±0.248	5.34**±0.347 (9)	3.25**±0.336 (45)
Females				
Plasma (kU/L)	0.69±0.070	0.61*±0.080 (12)	0.51**±0.114 (26)	0.22**±0.0.96 (68)
RBC (kU/L)	1.66±0.352	1.64±0.351	1.57±0.423	1.26*±0.235 (24)
Brain (U/g)	5.66±0.223	5.36±0.409	4.90**±0.462 (13)	3.46**±0.763 (39)

Data extracted from Annex pp. 33-34, MRID 46647403.
N = 10/sex/group
Numbers in parenthesis are percent inhibition relative to control from Table 6-2, p. 27.
Significantly different from control: *p≤ 0.05, **p ≤ 0.01.

3. **Repeated Exposure (MRID 46635601):** Cholinesterase activity data for repeatedly treated preweaning rats are shown in Table 4. Plasma cholinesterase activity was significantly inhibited at 20 mg/kg/day only, in both males and females. RBC enzyme activity was inhibited in high-dose females by 34% although statistical significance was not attained. Brain cholinesterase activity was significantly inhibited in males at the high dose (20 mg/kg/day), and in females at all doses.

   Benchmark dose estimates for 10% inhibition (BMD_{10}) of plasma, RBC, and brain ChE activity were 12.3, 20.6, and 12.4 mg/kg/day, respectively for males and 9.2, 8.4, and 9.1 mg/kg/day, respectively for females. Benchmark dose estimates for 20% inhibition (BMD_{20}) of plasma, RBC, and brain ChE activity were 18.0, 31.7, and 21.6 mg/kg/day, respectively for males and 13.7, 14.0, and 16.2 mg/kg/day, respectively for females. The reviewer did not verify the benchmark calculations presented in the study.

TABLE 4. Plasma, RBC, and brain ChE activity in preweaning rats treated with trichlorfon: Repeat exposure on PNDs 11-21 with termination 1 hour post-dosing on PND 21

Dose (mg/kg/day)	0	5	10	20
Males				
Plasma (kU/L)	0.55±0.133	0.54±0.078	0.51±0.085	0.42*±0.079 (24)
RBC (kU/L)	1.11±0.234	1.25±0.367	1.03±0.168	1.06±0.376
Brain (U/g)	10.13±0.953	9.91±0.408	9.30±0.416	8.36**±0.772 (17)
Females				
Plasma (kU/L)	0.57±0.104	0.56±0.053	0.50±0.121	0.35*±0.174 (39)
RBC (kU/L)	1.75±0.599	1.60±0.345	1.54±0.567	1.15±0.664
Brain (U/g)	10.60±0.362	9.93**±0.259 (6)	9.43**±0.357 (11)	7.82**±0.962 (26)

Data extracted from Annex pp. 37-38, MRID 46635601.
N = 10/sex/group
Numbers in parenthesis are percent inhibition relative to control from Table 6-2, p. 30.
Significantly different from control: *p≤ 0.05, **p ≤ 0.01.

III. DISCUSSION and CONCLUSIONS:

A. **INVESTIGATOR'S CONCLUSIONS:** The study author concluded that after an acute dose of trichlorfon (50 mg/kg), the greatest cholinesterase activity inhibition was observed in male pups after 1 hour (plasma and erythrocytes) and after 2 hours (brain), and in female pups, the greatest cholinesterase inhibition was observed after 2 hours in all three compartments. Therefore, 2 hours after administration was recommended as the optimal time for sample collection in subsequent investigations.

   Two hours after an acute dose of trichlorfon, cholinesterase activity was decreased in both males and females in a dose dependent manner, at doses up to 30 mg/kg, inclusive, in all three compartments (plasma, erythrocytes, and brain). Treatment related effects did not result in clinical signs at any dose level.

   After treatment of pups for 11 consecutive days, with 0, 5, 10, or 20 mg/kg/day trichlorfon, at approximately 1 hour following the last dose, female brain ChE activity was significantly

inhibited at all dose levels and male brain ChE activity was inhibited at 20 mg/kg only. Significant inhibition of plasma cholinesterase activity was observed only at the high dose level (20 mg/kg) in both males and females. At all dose of ≤10 mg/kg in both sexes, inhibition of cholinesterase activity was ≤12% in all compartments. Clinical signs were not observed at any dose level. In male pups at 20 mg/kg, ChE activity inhibition was ≤24% in all compartments, thus toxicological relevance is questionable. In female pups at 20 mg/kg, cholinesterase activity inhibition was ≥26% and toxicological relevance is assumed.

The US EPA has stated that comparisons based on NOAELs/LOAELs may under or overestimate relative sensitivity. Therefore, Bench Mark Dose (BMD) levels were calculated for each compartment. These BMD estimates are also useful for comparison of ChE activity inhibition between adult and preweaning rats.

B. DISCUSSION AND REVIEWER COMMENTS: A series of studies was conducted to determine ChE activity inhibition resulting from acute or repeated oral exposure of preweaning rats to trichlorfon.

No clinical signs were observed in any study and survival was not affected by treatment with the test article.

Following a single dose of the test article, the greatest inhibition of ChE activity was observed between 1 and 2 hours after dosing. In males, the level of enzyme inhibition in all three compartments peaked at one hour post-dosing with a similar level of inhibition maintained up to two hours post-dosing. However, in females slightly greater inhibition occurred in all three compartments after two hours compared with inhibition measured after one hour. Thus the time of peak effect was chosen as one hour post-dosing. Little difference in enzyme inhibition in any compartment was seen between males and females up to 8 hours post-dosing. At 24 hours post-dosing females had recovered RBC and brain enzyme activity, while males had only recovered brain enzyme activity. Plasma ChE activity remained significantly inhibited through 24 hours.

Following acute exposure, a clear dose-related inhibition of enzyme activity was observed in all compartments in both sexes. Biologically significant enzyme inhibition was seen in plasma and brain in males and females at ≥10 mg/kg, while RBC enzyme activity was significantly inhibited only at 30 mg/kg/day.

After eleven daily doses of 20 mg/kg/day of trichlorfon, biologically significant inhibition of ChE activity was apparent in all three compartments in female rats and in plasma and brain in male rats. No other effects were noted in males from repeated dosing. In females, inhibition of brain ChE activity was seen in all treated groups in a dose-related manner.

The ChE activity measurements following acute oral dosing with trichlorfon did not demonstrate a difference in susceptibility between preweaning male and female rat pups. By 24 hours post-dosing females showed a greater recovery in RBC activity, but no differences between the sexes were seen in the other compartments. Following repeated dosing, however, females appeared slightly more susceptible than males. Compared to plasma or brain enzyme activity in males and females, the RBC ChE activity was the least sensitive

compartment after acute and repeated trichlorfon exposure. In general, benchmark dose estimates reflect this hierarchy of susceptibility.

For acute exposure of preweaning rats to trichlorfon:

the preweaning LOAEL for brain ChEI is 10 mg/kg
the preweaning NOAEL for brain ChEI is 5 mg/kg;

the preweaning LOAEL for plasma ChEI is 10 mg/kg
the preweaning NOAEL for plasma ChEI is 5 mg/kg;

the preweaning LOAEL for red blood cell ChEI is 30 mg/kg
the preweaning NOAEL for red blood cell ChEI is 10 mg/kg;

For acute oral exposure to trichlorfon, the overall LOAEL for cholinesterase activity inhibition in PND 11 rats is 10 mg/kg based on enzyme inhibition in plasma and brain in males and females; the preweaning NOAEL is 5 mg/kg.

For repeated exposure of preweaning rats to trichlorfon:

the preweaning LOAEL for brain ChEI 5 mg/kg/day (females)
the preweaning NOAEL for brain ChEI is not identified;

the preweaning LOAEL for plasma ChEI is 20 mg/kg/day
the preweaning NOAEL for plasma ChEI is 10 mg/kg/day;

the preweaning LOAEL for red blood cell ChEI is 20 mg/kg/day (females)
the preweaning NOAEL for red blood cell ChEI is 10 mg/kg/day;

For repeated oral exposure to trichlorfon, the overall LOAEL for cholinesterase activity inhibition in PND 11 rats is 5 mg/kg/day based on enzyme inhibition in brain in females; the preweaning NOAEL is not identified.

C. **STUDY DEFICIENCIES:** No major deficiencies were identified in the conduct of these studies.

DATA FOR ENTRY INTO ISIS

Special Study

PC code	MRID #	Study type	Species	Duration	Route	Dosing method	Dose range mg/kg/day	Doses tested mg/kg/day	NOAEL mg/kg/day	LOAEL mg/kg/day	Target organ(s)	Comments
057901	46647404 46647403	special ChE study	rats	Acute dose (1 day)	oral	gavage	0-50	0, 5, 10, 30, 50	5	10	Cholinesterase activity inhibition (plasma and brain, males and females)	PND 11
057901	46635601	special ChE study	rats	Repeated dose (11 days)	oral	gavage	0-20	0, 5, 10, and 20	not identified	5	Cholinesterase activity inhibition (Brain, females)	PND 11

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R154897

Chemical:

PC Code:

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