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WASHINGTON, D.C. 20460

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#342

JAN 6 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No.: 057801. Diazinon. Review of the series 81-8ss acute neurotoxicity screen study and a special study to assess for ChE/AChE inhibition following acute administration.

TOX CHEM No.: 342
PC No.: 057801
Barcode No.: D200167
Submission No.: S459921

FROM: John Doherty, Ph.D. *John Doherty* 12/9/94
Section IV, Toxicology Branch I
Health Effects Division (7509C)

TO: Larry Schnaubelt/Robert Richards
Product Manager #72
Special Review and Reregistration Division (7505C)

THROUGH: Marion Copley, DVM, Section Head *Marion Copley*
Section IV, Toxicology Branch I
Health Effects Division (7509C) 12/9/94

I. CONCLUSION

431322-04

Two separate studies (MRID No.: ~~431332-04~~ for the main study and 431322-02 for the special ChE/AChE study) were reviewed (refer to DERS attached). The main study satisfies the requirement for a series 81-8ss acute neurotoxicity study and no additional acute neurotoxicity study data are required at this time. The combined data indicate that the LEL for inhibition of plasma ChE and RBC AChE is < 2.5 mg/kg and the NOEL and LEL for inhibition of brain AChE is 2.5 and 150 mg/kg. The NOEL and LEL for neurotoxicity symptoms is also 2.5 and 150 mg/kg based largely on abnormal and ataxic gait and decreased body temperature. Other symptoms also occurred in the 150, 300 and 600 mg/kg dose groups.

The special study which attempted to correlate enzyme



inhibition with symptoms indicated that only limited correlation exists in the rat. In particular, although inhibition of plasma ChE and RBC and brain AChE in excess of 70% appeared to be necessary for expression of symptoms at 9 hours, this level of inhibition or higher was still present after the symptoms subsided at 24 hours.

II. Action Requested

The Ciba-Geigy Corporation has submitted a series 81-8ss acute neurotoxicity study and an addendum that assesses the effects of diazinon on plasma ChE and RBC and brain AChE (refer to the letter from Carolyn B. Bussey dated February 14, 1994). These studies were submitted as a part of the reregistration requirements for diazinon. The addendum was provided to assess the time course for ChE/AChE inhibition and attempt to correlate enzyme inhibition with the symptoms.

III. Toxicology Branch Comments

1. The main study (MRID No.: 431332-04) was classified as CORE GUIDELINE. No additional series 81-8ss acute neurotoxicity study data are required at this time. Refer to table below for additional details.
2. The addendum study (MRID No.: 431322-03) was classified as SUPPLEMENTARY since it did not follow the prescribed protocol for a series 81-8 acute neurotoxicity study. The study, however, provided an insight into the correlation or lack thereof between inhibition of the three subtypes of ChE or AChE. In particular, inhibition of activity remained high in the brain and blood long after the symptoms subsided.
3. The main study indicated that RBC AChE had a NOEL and LEL of 2.5 and 150 mg/kg. The addendum especially designed to assess for ChE and AChE inhibition indicated significant RBC AChE inhibition at 2.5 mg/kg. Since the second study was specifically designed to assess for AChE inhibition, the dose level of 2.5 mg/kg is considered an effect level for RBC AChE inhibition.

IV. Studies Reviewed

Study Identification	Material	Results
<p>81-8ss Acute neurotoxicity screen - rats Ciba-Geigy Environmental Health Center. Study No.: F-00175, January 20, 1994</p> <p>MRID No.: 431322-04 (3 volumes) 431322-01 and -02 (range finding and addendum).</p> <p>Classification: MINIMUM</p>	<p>D*Z*NR Technical grade diazinson 87% purity, lot No.: FL-880045</p>	<p>In an acute neurotoxicity screening study, groups of 15/sex rats (Sprague-Dawley) were dosed as control 2.5, 150, 300 or 600 mg/kg of diazinson (D-Z-N technical 88% purity) in corn oil by gavage. 10/sex/group were assigned to the main phase of the study to assess for clinical signs, FOB and motor activity; the other five were assessed for ChE/AChE activity.</p> <p>Plasma ChE was inhibited at all dose levels (27% for males and 47% for females in the 2.5 mg/kg dose group) and RBC AChE was inhibited at 150 mg/kg (83% for males and 76% for females) at the time of peak effect (about 9 hours postdosing). ChE was equivalent to the controls at day 15 but RBC AChE still remained inhibited for both males and females especially at the higher dose levels. Brain AChE was unaffected when assessed at day 15. The LEL for RBC AChE inhibition is 150 mg/kg. The NOEL for RBC AChE inhibition is 2.5 mg/kg. The LEL for plasma ChE inhibition is < 2.5 mg/kg.</p> <p>Based on the FOB assessments, effects at 150 mg/kg included <u>abnormal gait</u> (3/10 males, 7/10 females), <u>ataxic gait</u> (3/10 females), <u>decreased body temperature</u> (-2.1%, females), <u>decreased rearing counts</u> (-33% females), <u>stereotypy</u> (3/10 females) and <u>fecal consistency and stained fur</u> (3/10 males). Numerous other FOB parameters were affected at 300 mg/kg and above, of these <u>tremors</u> (6/10 females and 5/10 males at 300 mg/kg) were noted and <u>dehydration</u> (6/10 females) were noted. Refer to DER for additional parameters affected. <u>Motor activity</u> was decreased for males (27%, not significant) and females (46% p < 0.01) at 150 mg/kg and above. <u>Body weight gain</u> in males was decreased in the 300 (25%) and 600 (29%) mg/kg dose groups. Deaths (2 males and 1 female) resulted at 600 mg/kg. No histopathological lesions attributed to treatment were indicated. The LEL for neurotoxicity is 150 mg/kg based mainly on <u>ataxic gait</u> and supported by other effects believed to be related to ChE/AChE inhibition. The NOEL for neurotoxicity is 2.5 mg/kg.</p>

81-8ss Special study to assess
ChE/AChE inhibition-rats.
Ciba-Geigy Environmental Health
Center, Study No.: F-00185,
January 12, 1994

MRID No.: 431322-03

Classification: Supplementary

D*Z*N
Technical
grade
diazinon
87% purity.
Lot No.:
FL- 880045

Five groups of 15 Sprague-Dawley rats/sex were dosed as control, 2.5, 150, 300 or 600 mg/kg diazinon MG87% (D*Z*N, 88% purity) by gavage in corn oil and were sacrificed in groups of 5/sex after 3, 9 or 24 hours. These intervals were designated as pre-peak, peak and post-peak for effects. The rats were assessed for clinical signs and for plasma ChE, RBC and brain AChE.

Clinical signs were first evident in the 300 mg/kg dose group males at 9 hours and at 600 mg/kg at 3 hours. Males were more frequently affected than females. Plasma ChE was inhibited at 2.5 mg/kg by 30% for males and 60% for females after 9 hours and to a lesser extent at the other intervals. 66-91% inhibition was noted for all other intervals at higher doses. RBC AChE was inhibited 40% (p < 0.01) in females dosed with 2.5 mg/kg and 42 to 82% at the higher doses for all other intervals. Four brain regions (cerebellum, cerebral cortex, striatum and hippocampus) and the spinal cord were also assessed. Definite brain AChE inhibition (31 to 68%) was noted at 150 mg/kg in all four regions and the spinal cord. Thus, the LEL for plasma ChE and RBC AChE is < 2.5 mg/kg for both sexes but the NOEL and LEL for brain AChE are 2.5 and 150 mg/kg. Limited correlation between enzyme inhibition with symptoms was apparent since at 9 hours the symptoms were maximal and inhibition (> 77% in brain, >74% in RBC and >77% in plasma at 600 mg/kg) were reported but the enzymes remained inhibited when the symptoms regressed at 24 hours.

Reviewed by: John Doherty, Ph.D., D.A.B.T.
Section IV, Toxicology Branch I (7509C)
Secondary reviewer: Linnea Hansen, Ph.D.
Section IV, Toxicology Branch I (7509C)

John Doherty 11/15/94
Linnea T. Hansen 11/15/94

DATA EVALUATION REPORT

STUDY TYPE: 81-8 - Special ChE/AChE assays - rats

01137

MRID NO.: 431322-03

TOX. CHEM. NO.: 342
PC No.: 057801

TEST MATERIAL: D*Z*N Technical diazinon MG87%, Lot Number FL-880045).

STUDY NUMBER: F-00185

SPONSOR: Ciba-Geigy Corporation

TESTING FACILITY: Ciba-Geigy Environmental Health Center

TITLE OF REPORT: "Acute Cholinesterase Inhibition Time Course Study with D*Z*N Diazinon MG87% in Rats"

AUTHOR: Robert F. Potrepka

REPORT ISSUED: January 12, 1994

In life phase: October 25, 1993 to October 29, 1993]

EXECUTIVE SUMMARY:

Five groups of 15 Sprague-Dawley rats/sex were dosed as control, 2.5, 150, 300 or 600 mg/kg diazinon MG87% (D*Z*N, 88% purity) by gavage in corn oil and were sacrificed in groups of 5/sex after 3, 9 or 24 hours. These intervals were designated as pre-peak, peak and post-peak for effects. The rats were assessed for clinical signs and for plasma ChE, RBC and brain AChE.

Clinical signs were first evident in the 300 mg/kg dose group males at 9 hours and at 600 mg/kg at 3 hours. Males were more frequently affected than females. Plasma ChE was inhibited at 2.5 mg/kg by 30% for males and 60% for females after 9 hours and to a lesser extent at the other intervals. 66-91% inhibition was noted for all other intervals at higher doses. RBC AChE was inhibited 40% ($p < 0.01$) in females dosed with 2.5 mg/kg and 42 to 82% at the higher doses for all other intervals. Four brain regions (cerebellum, cerebral cortex, striatum and hippocampus) and the spinal cord were also assessed. Definite brain AChE inhibition (31 to 68%) was noted at 150 mg/kg in all four regions and the spinal cord. Thus, the LEL for plasma ChE and RBC AChE is < 2.5 mg/kg for both sexes but the NOEL and LEL for brain AChE are 2.5 and 150 mg/kg. Limited correlation between enzyme inhibition with symptoms was apparent since at 9 hours the symptoms were maximal and inhibition ($> 77%$ in brain, $> 74%$ in RBC and $> 77%$ in plasma at 600 mg/kg) were reported but the enzymes

remained inhibited when the symptoms regressed at 24 hours.

Classification: Supplementary (study is a non-guideline study). This study, however, provides information complementary to the definitive series 81-8ss acute neurotoxicity study (MRID No.: 431322-04).

Quality Assurance Statement: Provided.

Good Laboratory Practice Statement: Provided.

Statement of No Data Confidentiality Claims: No claim of confidentiality under FIFRA section 10 (d) (1) (A), (B), or (C).

REVIEW

Experimental Constants:

Test Chemical:

Chemical:	Technical diazinon, D*Z*N MG87%
Lot Number:	FL-880045 (EHC Code No.: 0173-05)
Purity:	88.0%
Storage:	Room temperature, in dark
Structure:	

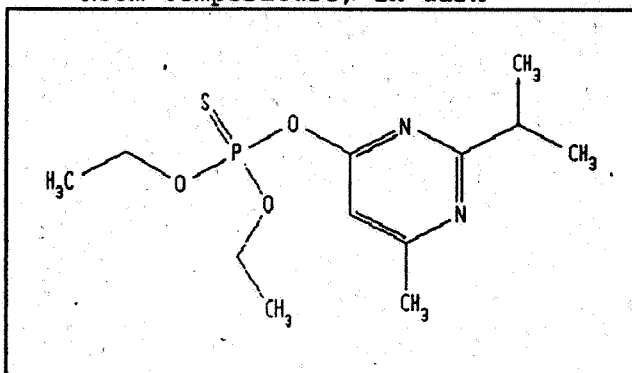


Figure 1. Structure of diazinon.

Analytical Chemistry: Analysis of the dosing solutions resulted in samples ranging from 98 to 105.8% of the nominal dose levels.

Test System.

Species:	Rats
Strain:	Sprague-Dawley
Supplier:	Harlan Sprague-Dawley, Frederick, Maryland
Age:	Approximately 7 weeks at a start of study.
Weight:	Males: 174.3 to 212.5, females: 120.6 to 153.6
Housing:	Individually.
Feed:	PMI ^R Feeds Certified Rodent Diet #5002.

Basic Experimental Design:

This experiment was specially designed to complement the series 81-8ss acute neurotoxicity study with diazinon (MRID No.: 431332-04) and to investigate the time course for inhibition

of plasma ChE and RBC and brain AChE. Thus, the rationale for dose levels and time of assay selections were based on the previously mentioned study.

Five randomly assigned groups of 15 rats/sex (fasted for 12 hours before dosing) were dosed with either corn oil or dose levels of 2.5, 150, 300 or 600 mg/kg of diazinon in corn oil in a dosing volume of 5 ml/kg. Following dosing 5 rats /sex were assessed for clinical signs and for ChE/AChE activity (from blood obtained by bleeding from the orbital sinus and sacrificing to obtain the brain) at 3, 9 and 24 hours. The 3 hour time interval is considered a pre-clinical signs interval, the nine hour interval is regarded as the time of peak effect and the 24 hour time interval is regarded as the post-peak effect time. It should be noted that the FOB and motor assessments in the series 81-8ss study were made using the 9 hour interval for time of peak effect.

Statistics: The study report asserts that the following statistical tests were performed.

Statistical Test	Parameter Investigated
<p>One-way analysis of variance (ANOVA) followed by Dunnett's t-test when overall F-statistic was significant ($p \leq 0.05$) to detect treatment differences from control.</p> <p>Bartlett's test for homogeneity of variance for body weight assessed before ANOVA.</p>	<p>Body weight and ChE/AChE parameters</p>

Specific Methods and Results

1. Deaths. No deaths resulted. It should be noted that in the definitive acute neurotoxicity study, deaths attributed to treatment occurred in the 600 mg/kg dose group on days 2, 4 and 5, indicating that the high dose is potentially lethal.

2. Clinical Reactions. Tables 9.3 (data for males) and 9.4 (data for females) photocopied from the study report are attached to summarize the clinical signs. Table 1 below illustrates the frequency of clinical signs reported. This table shows that there were no treatment related clinical signs at any time interval for dose levels of 150 mg/kg and below. Clinical signs first become apparent for males and females at 300 mg/kg after 9 hours with the males having a higher frequency for effects. Males, but not females displayed clinical signs after only three hours when dosed with 600 mg/kg. Clinical signs were less evident for the 300 mg/kg after 24 hours indicating recovery for

both sexes. There was also an indication of recovery for the male groups dosed with 600 mg/kg but the females actually had a higher frequency of clinical signs after 24 hours indicating no recovery in this sex.

Table 1. Frequency of clinical signs in male and female rats dosed with diazinon.

Dose (mg/kg)	Males			Females		
	Time interval (hours)			Time Interval (hours)		
	3	9	24	3	9	24
0	0	0	0	0	0	0
2.5	0	0	0	0	0	0
150	0	0	0	0	0	0
300	0	16/5 ¹	1/1	0	2/2	0
600	8/3	27/5	17/5	0	10/5	21/5

Data are from Tables 9.4 and 9.5 (attached, refer to these tables for the description of the clinical signs) and from Appendix 10.3.1 and 10.3.2 (for individual animal data).

1. Data are total number of clinical signs/total number of rats with one or more of the clinical signs noted (not all rats had all clinical signs).

TB-I notes that there were no reports of eye effects such as pupil changes (miosis) which are recognized as a common sign of ChE/AChE inhibition for some organophosphates.

3. Body Weight and Gain. No differences in body weight were reported.

4. ChE/AChE data. Plasma ChE and AChE in the brain regions and spinal cord were assessed using an IL MonarchTM Chemistry Analyzer and Boehringer Mannheim Diagnostics (BMD) Cholinesterase reagent. RBC AChE was assessed using the method of Ellman et al (1961) as modified for use with a Centrifichem^R 500 Analyzer. The methods used for preparing each tissue sample for assay were fully described in the report.

A. Plasma ChE. Plasma ChE inhibition data are illustrated in Table 2 below. This species of enzyme was significantly inhibited at all dose levels at each time interval for both sexes. Consistent with previous studies, females were more sensitive than males (refer to FSTS for Diazinon). Inhibition was near maximal at 150 mg/kg but greater degrees of inhibition were noted at the higher dose levels. The extent of inhibition at 9 hours was slightly more than that at 3 hours for nearly all groups. In the 2.5 mg/kg dose group the least depression in activity was noted at 24 hours suggesting a recovery. For higher dose levels there was in some cases slightly more inhibition at

24 hours when compared to 9 hours.

The inhibition of plasma ChE at 2.5 mg/kg (30% in males and 60% in females) is consistent with the 27% in males and 53% in females inhibition obtained at about 9 hours post-dosing in the main study (MRID No.: 431322-04).

Table 2. Plasma ChE inhibition data at 3, 9 and 24 hours post dosing.

Dose Level (mg/kg)	Males			Females		
	3'	9	24	3	9	24
Control	522±36 ²	576±61	595±80	1254±172	1249±135	1173±128
2.5	21**	30**	17**	57**	60**	42**
150	66**	79**	76**	75**	82**	89**
300	71**	80**	85**	77**	85**	89**
600	72**	77**	88**	79**	83**	91**

Data are from Tables 9.7 (males) and 9.8 (females) of the study report and are based on 5 rats/sex/group.

1. Time of assay following diazinon administration.
2. Data are for the control the mean value in IU/L ± the standard deviation and for the groups dosed with diazinon the percent inhibition relative to the control is presented. For the dosed groups the standard deviations were similar.

** p < 0.01.

B. RBC AChE. RBC AChE inhibition data are illustrated in Table 3 below.

Table 3. RBC AChE inhibition data at 3, 9 and 24 hours post dosing.

Dose Level (mg/kg)	Males			Females		
	3'	9	24	3	9	24
Control	1396±144	1340±32	1256±213	1164±305	1192±265	1356±149
2.5	0	+1	11	1	40**	11
150	66**	76**	68**	42**	68**	70**
300	82**	78**	77*	50**	78**	68**
600	75**	81**	76**	73**	74**	71**

Data are from tables 9.9.7 and 9.8 and are the means of 5 rats/sex/group.

1. Time of assay following diazinon administration.
2. Data are for the control the mean value in U/L PRBC ± the standard deviation and for the groups dosed with diazinon the percent inhibition relative to the control. For the dosed groups the standard deviations were similar.

+ slight increase in activity noted.

At 150 mg/kg and above, RBC AChE was significantly inhibited at all time intervals. There was little difference between the 3, 9 and 24 hour intervals for males other than that the 150 mg/kg dose group appeared slightly less inhibited at 3 hours (66%) than at 9 hours (76%) and 24 hours (68%) indicating a possible maximum inhibition at 9 hours and a later partial recovery.

Among the females, there was a trend for maximum inhibition at 9 hours for the 2.5 mg/kg dose group only. At 150 and 300 mg/kg the least amount of inhibition was at 3 hours but the 9 and 24 hour values were similar. At 600 mg/kg, all three time intervals had similar degrees of inhibition.

In the main acute neurotoxicity study there was 7% inhibition in males and 4% in females after nine hours in the 2.5 mg/kg dose group comparing favorably for males which in this study did not show inhibition. There was, however, 40% inhibition ($p < 0.01$) in the 2.5 mg/kg dose group females. Since the 24 hour reading for females dosed with 2.5 mg/kg was only 11% (not significant) it is suggested that the 40% decrease is not real. The 76% in males and 68% in females compares favorably with the 82% in males and 76% in females percent inhibition obtained for the 150 mg/kg dose group in the main study (MRID No.: 431322-04).

C. Brain AChE.

Four regions of brain (cerebellum, cerebral cortex, striatum and hippocampus) and a part of the thoracic spinal cord (T7 through T10) were assessed for AChE activity at each of three time intervals. The results of the assays for brain AChE activity are illustrated in Table 4 below.

Although some inhibition was noted at 2.5 mg/kg (up to 7%), only the cerebral cortex reached statistical significance (20% inhibition at 9 hours, $p < 0.05$). Brain AChE for the cerebral cortex was also 16% at 3 hours and 23% at 24 hours (neither value was statistically significant) raising the possibility that the 20% decrease is assay artifact. Since there were no symptoms at this dose level, TB-I does not consider the difference at this dose level to be toxicologically significant.

Time dependent changes in inhibition were noted for some of these regions, with there being generally lesser inhibition at 3 hours especially for the 150 mg/kg dose group males but to a lesser extent for the higher doses. Time course effects were more noted for the females at all dose groups. Evidence suggestive of recovery from inhibition was present by there being lesser inhibition for the 150 and 300 mg/kg dose groups at 24 hours but not for the 600 g/kg dose group.

[81-8ss(ChE/AChE only)Diazinon/1994]

Table 4. Brain and spinal cord AChE, and its inhibition in rats dosed with diazinon.

Region	Hour /sex	Dose Level				
		Control	2.5	150	300	600
Cerebellum	3/ M	3.12±0.25	--	51**	76**	80**
	F	3.51±0.44	7	54**	48**	66**
	9/ M	3.81±0.32	6	59**	78**	84**
	F	3.91±0.17	2	65**	79**	77**
	24/M	3.07±0.29	+3	45**	60**	80**
	F	3.41±0.20	--	68**	74**	82**
Cerebral Cortex	3/ M	6.70±2.60	+16	31(ns)	67**	75**
	F	7.07±0.91	4	34*	35**	56**
	9/ M	5.91±1.04	20*	62**	82**	85**
	F	6.20±1.04	5	63**	75**	78**
	24/M	6.90±1.03	+23(ns)	44**	60**	80**
	F	6.11±2.28	1	73**	77**	85**
Striatum	3/ M	31.44±7.99	--	28*	69**	75**
	F	30.80±1.93	+13	26*	31**	50**
	9/ M	28.56±6.70	+10	65**	77*	85**
	F	31.40±5.59	+9	66**	81**	83**
	24/M	26.96±5.37	+12	43**	58**	85**
	F	32.36±6.35	5	68**	84**	87**
Hippocampus	3/ M	6.03±0.69	+5	40**	70**	80**
	F	5.53±1.67	10	46**	47**	56**
	9/ M	6.37±0.65	5	57**	76**	84**
	F	5.73±0.52	+5	68**	81**	83**
	24/M	5.16±0.61	+25	45*	62**	85**
	F	5.38±1.18	1	65**	74**	81**
Thoracic spinal cord	3/ M	4.88±1.22	+10	27ns	65**	77**
	F	4.86±0.79	+8	39**	33*	49**
	9/ M	5.02±1.10	+8	51**	76**	85**
	F	5.00±1.28	+4	63**	73**	77**
	24/M	5.14±0.19	+9	42**	50**	81**
	F	5.38±1.18	+3	51*	46*	81**

Data are from Tables 9.7 (males) and 9.8 (females) of the study report and represent the results from 5/sex/group. Data are the mean plus the standard deviation for the controls in U/gm tissue. The percentage inhibition is presented for the dosed groups. + Some increase in activity was noted. -- Activity was the same as the controls.
* p < 0.05, ** p < 0.01.

Based on the 9 hour assays and the data at 150 mg/kg only for males, the order of sensitivity of the 5 structures was spinal cord (51%), hippocampus (57%), cerebellum (59%), cerebral cortex (62%) and striatum (65%). Although some indication for the striatum being the most sensitive in males is evident, the females were all within 68 to 63% inhibited for all five structures. At 300 mg/kg, the males were 76 to 82% inhibited and at 600 mg/kg they were 85 and 86% inhibited. Thus, TB-I agrees with the study author that there is no strong evidence that one brain area or the spinal cord is more susceptible than other areas to the inhibitory effects of diazinon.

CONCLUSION/DISCUSSION. This is a special study specifically designed to assess ChE/AChE inhibition with time and does not follow a specific guideline and is thus classified as SUPPLEMENTARY. This study, however, provides information complementary to the definitive series 81-8ss acute neurotoxicity study (MRID No.: 431322-04).

Correlations between the inhibition of plasma ChE or RBC and brain AChE with the symptoms (made by cage side observation) noted in this study were not considered evident by this reviewer. The only symptoms noted at cage side observation in this study were at 300 mg/kg (only a two females affected) but all three species of enzyme were inhibited to nearly the same degree at 300 mg/kg and higher dose levels. Moreover, the enzymes were still inhibited to the same degree or more at 24 hours after many of the symptoms were no longer observable. On this basis correlation between symptoms and inhibition is considered limited.

There were, however, several parameters noted to be affected at 150 mg/kg in the FOB and motor activity assessments made in the acute neurotoxicity study (MRID No.: 431322-04). Thus, if the clinical signs and FOB data from the first study and the enzyme inhibition data from the special study are compared it can be implied that inhibition of RBC or brain AChE (i.e. probably > 70% inhibition) are correlated with the symptoms. Since these enzymes stay inhibited after the symptoms regress, it would be expected that the symptoms would persist while the inhibition remained > about 70%. There is, however, no evidence for this in the data generated in this study or the acute neurotoxicity study. Females demonstrated more inhibition of ChE/AChE than did males, but the males developed the symptoms sooner and had a higher frequency than did the females provided additional indications of lack of correlation between ChE/AChE inhibition data and clinical signs.

Diazinon Tox.R 11375

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Pages 13 through 14 are not included.

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 - Description of quality control procedures.
 - Identity of the source of product ingredients.
 - Sales or other commercial/financial information.
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 - The document is not responsive to the request.
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Reviewed by: John Doherty, Ph.D., D.A.B.T. *John Doherty 11/15/94*
Section IV, Toxicology Branch I (7509C)
Secondary reviewer: Linnea Hansen, Ph.D. *Linnea Hansen 11/14/94*
Section IV, Toxicology Branch I (7509C)

DATA EVALUATION REPORT

STUDY TYPE: 81-8. Acute neurotoxicity - rats

MRID NO.: 431322-04 (3 volumes) - Main Study
431322-01 and 02, Range finding study and addendum.

Tox Chem No.: 342 **PC No.:** 057801

TEST MATERIAL: D-Z-N^R Diazinon technical grade stabilized, 87%

STUDY NUMBER: F-00175

SPONSOR: Ciba-Geigy Corporation.

TESTING FACILITY: Ciba-Geigy Corporation Plant Protection
Division Environmental Health Center, Farmington, Conn.

TITLE OF REPORT: "Acute Neurotoxicity Study with D-Z-N^R Diazinon
MG87% in Rats"

AUTHOR: Edward Chow and Alexander G. Richter

REPORT ISSUED: January 20, 1994
Study initiated on February 4, 1993.

EXECUTIVE SUMMARY:

In an acute neurotoxicity screening study, groups of 15/sex rats (Sprague-Dawley) were dosed as control 2.5, 150, 300 or 600 mg/kg of diazinon (D-Z-N technical 88% purity) in corn oil by gavage. 10/sex/group were assigned to the main phase of the study to assess for clinical signs, FOB and motor activity; the other five were assessed for ChE/AChE activity.

Plasma ChE was inhibited at all dose levels (27% for males and 47% for females in the 2.5 mg/kg dose group) and RBC AChE was inhibited at 150 mg/kg (83% for males and 76% for females) at the time of peak effect (about 9 hours postdosing). ChE was equivalent to the controls at day 15 but RBC AChE still remained inhibited for both males and females especially at the higher dose levels. Brain AChE was unaffected when assessed at day 15. The LEL for RBC AChE inhibition is 150 mg/kg. The NOEL for RBC AChE inhibition is 2.5 mg/kg. The LEL for plasma ChE inhibition is < 2.5 mg/kg.

Based on the FOB assessments, effects at 150 mg/kg included abnormal gait (3/10 males, 7/10 females), ataxic gait (3/10 females), decreased body temperature (-2.1%, females), decreased rearing counts (-33% females), stereotypy (3/10 females) and fecal consistency and stained fur (3/10 males). Numerous other

FOB parameters were affected at 300 mg/kg and above, of these tremors (6/10 females and 5/10 males at 300 mg/kg) were noted and dehydration (6/10 females) were noted. Refer to DER for additional parameters affected. Motor activity was decreased for males (27%, not significant) and females (46% p < 0.01) at 150 mg/kg and above. Body weight gain in males was decreased in the 300 (25%) and 600 (29%) mg/kg dose groups. Deaths (2 males and 1 female) resulted at 600 mg/kg. No histopathological lesions attributed to treatment were indicated. The LEL for neurotoxicity is 150 mg/kg based mainly on ataxic gait and supported by other effects believed to be related to ChE/ACHE inhibition. The NOEL for neurotoxicity is 2.5 mg/kg.

Classification: MINIMUM. The study satisfies the requirement for a series 81-8ss acute neurotoxicity screen study. No additional series 81-8ss acute neurotoxicity study data are required at this time. The limiting factor considered in classifying this study as MINIMUM is that no NOEL was established for plasma ChE inhibition.

Quality Assurance Statement: Provided
Good Laboratory Practice Statement: Provided
Statement of No Data Confidentiality Claims: Provided

REVIEW

Experimental Constants:

Test Chemical:

Chemical:	D-Z-N ^R diazinon MG87%
Purity:	88%
Lot Number:	FL-880045, EHC Code No.: 0173-05
Source:	Ciba-Geigy's Plant Protection Division Greensboro, North Carolina
Description:	Amber liquid
Vehicle:	Corn oil

Analytical Chemistry:

A preliminary study indicated that diazinon concentrations of 0.4 and 200 mg/ml were stable in corn oil for 16 days. No more than 1.5% decomposition (if any) could have occurred. The concentrations of 0.5, 30, 60 and 120 mg/ml nominal dosing preparations yielded 0.452 (90.4%), 28.36 (94.53%), 55.8 (93%) and 118 (98%) with relative standard deviations (an index of homogeneity) of 2.4%, 1.5%, 2.2% and 3.4% respectively. The dosing solutions are considered by TB-I to be acceptable. Data establishing the stability of triadimefon in corn oil were also presented.

Positive Control:

Chemical:	Triadimefon
Purity:	99.0%
Lot Number:	30-107A
Source:	Chem Services Inc., West Chester, Pa.

Test System:

Species/strain:	Rat/Hsd:Sprague-Dawley ^R SD TM
Source:	Harlan Sprague Dawley, Frederick, Maryland.

Weight:	Males 168.8 to 209.5 g, females 124.7 to 145.7 g.
Age:	Approximately 8 weeks of age at initiation of dosing.
Randomization:	By body weight such that no statistical differences in weight among groups was noted at start of dosing.
Housed:	Individually
Diet:	Purina Certified Rodent Chow

Basic Experimental Design:

Five groups of 15 rats/sex were dosed by gavage with 0, 2.5, 150, 300 or 600 mg/kg of diazinon in corn oil. A sixth group of 10/sex was dosed with 150 mg/kg of triadimefon¹ a positive control for neurobehavioral assessments. The first ten animals from each diazinon group were subjected to a battery of FOB and motor activity assessments starting at 9-11 hours and on days 7 and 14 postdosing. The remaining five/sex/group were assessed for blood ChE/AChE at the estimated time of peak effect (9-11 hours) and on study day 15. On study day 15, the rats were sacrificed and 5/sex were prepared for histopathology and 5/sex from the satellite group were prepared for assessment of AChE activity. FOB and motor activity for the triadimefon treated animals was done starting at 1 hour post dosing.

Diazinon was administered unadjusted for purity. Administration of the test material was in corn oil and at a rate of 5 ml/kg to animals that were fasted approximately 12 hours prior to dosing (16 hours for triadimefon). Food was withheld for four hours after dosing for diazinon animals but not for triadimefon animals. The rats were dosed in the night between 10 PM and 5 AM under red lighting to minimize potential effects on the rats' circadian rhythms.

The dose levels were selected based on preliminary range finding studies (no separate DER has been prepared for these studies). In the first study (Ciba-Geigy Study No.: 7679-90, November 9, 1993) oral doses of 600, 1000, 1200, 1400 or 1800 mg/kg of diazinon undiluted were administered by gavage to groups of rats 5/sex. In this study, deaths occurred at 1200 (2/10), 1400 (10/10) and 1800 (9/10) mg/kg with a resulting combined LD₅₀ of 1290 mg/kg. In another study (Ciba-Geigy Study No.: F-00174, MRID No.: 431322-01) 6 rats/sex were dosed with 0, 250 (males only), 750, 1000 (females only) and 1400 mg/kg and 1/12, 2/6, and 12/12 deaths occurred at the 750, 1000 and 1400 mg/kg dose levels respectively. Since 500 mg/kg was the lowest non-lethal dose for female rats, the selection of 600 mg/kg was considered an appropriate high dose. The 300 and 150 mg/kg dose levels were expected to produce intermediate effects and no or minimal effects respectively. The 2.5 mg/kg dose group was previously established to be a NOEL for inhibition of brain AChE (Study No.: HWI 6117-221) and was expected to produce no toxic effects. A discussion of the time to onset, time to maximum symptoms or duration of effects was provided in the range finding study. Onset of toxic symptoms was as early as 3 hours, but maximum response was at 9 to 11 hours with many of the findings reportedly abating by 21 to 24 hours. In some cases the ataxia and abnormal gait persisted beyond 24 hours. It was also noted that the average time to onset of symptoms for the 600 mg/kg dose group was 6

¹Reactions and results with triadimefon are discussed in Part 8.

hours.

Statistics: The study report asserts that the following statistical tests were performed.

Statistical Test	Parameter Investigated
One way ANOVA followed by Dunnett's t-test (two tailed when significant differences were detected. Homogeneity of data were first assessed using Bartlett's test (alpha 0.001).	Body weight and gains and food consumption, ChE data Figure 8 maze activity body temperature grip strength foot splay.
Ranking of data followed with analysis of variance and Dunnett's t-test	<u>Quantitative data</u> FOB parameters: fecal consistency, respiration, lacrimation, salivation, fur appearance, pupil size, ataxic gait, righting reflex, hindlimb extensor strength, rearing counts, tremors, ease of handling, ease of removal, arousal, tail pinch response and touch response.
Fisher's Exact test (two tailed) with Bonferroni correction	<u>Qualitative data</u> FOB parameters: stereotypic behavior, bizarre behavior, staining, abnormal gait, posture, pupil response, body tone-dehydration, position of the hindlimb when held by tail and clinical observations.

All statistics test except for Bartlett's test were evaluated at 0.05.

Specific Methods and Results

1. Deaths and clinical reactions. The rats were reportedly observed for clinical signs twice daily.

Two males and one female died in the high dose group as a result of treatment. Their deaths occurred on days 2, 4 and 5.

Clinical signs were noted only in the male rats dosed with 300 mg/kg and above and are illustrated in Table 1. These signs were not reported in either the control, 2.5 or 150 mg/kg dose groups or in the females at 300 mg/kg. Most symptoms in males were noted on the first day. In females the same symptoms were noted by day two or three. It should be noted that only reduced activity reached statistical significance.

Table 1. Selected clinical signs in rats dosed with diazinon.

Symptom	Dose Level (mg/kg)			
	Males		Females	
	300	600	300	600
reduced activity	3 ¹	13*	0	9*
tremors	1	3	0	4
chromodacryorrhea (eye)	1	4	0	4
dacryorrhea (eye)	0	1	-	-
dyspnea	2	1	0	1
salivation	2	1	0	1
chromorhinorrhea (nose)	1	4	0	2
pallor	0	3	0	2
diarrhea	0	2	-	-

Data are from Tables 9.3 and 9.4 of the study report.

- Not reported.

* Significantly different from control $p < 0.01$ by Fisher's Exact test with Bonferroni correction.

1. Data are number of rats affected out of 15 available for assessment.

2. Body Weight and Gain. Body weight was assessed at predosing, at initiation (eight hours before dosing) and at weeks 1 and 2.

Only the male body weight gain was affected in the 300 and 600 mg/kg dose groups when measured at week 1. For example,

-the 300 mg/kg dose group gained only 32.18 gms (compared to 43.05 gms for the control or 25.2% less, $p < 0.01$)

-the 600 mg/kg dose group gained only 30.38 gms (or 29.4% less, $p < 0.01$).

Terminal body weights were also reduced for the 300 mg/kg (17.6%, not significant, data have large standard deviation of 35%) and 600 mg/kg (7.2%, not significant). Male body weight was also decreased in the 300 and 600 mg/kg dose groups (about 9% for both groups, $p < 0.01$) at the time of peak effect (during FOB assessment at day 1).

Females did not have obvious body weight or weight gain effects at weeks 1 or 2. At day 1, the 300 mg/kg dose group was decreased 7.5%. All of the 600 mg/kg and some of the 300 mg/kg dose groups showed evidence of dehydration and were not weighed.

TB-I notes that in order to better assess an effect on body weight, the body weight should have been assessed daily.

3. Food Consumption.

Males consumed less feed in the first week in the 300 and 600 mg/kg dose groups (16% for both groups, $p < 0.01$) and females in the 600 mg/kg dose (10%, $p < 0.05$). This is possibly an indirect neurotoxicity effect.

4. Functional Observational Battery.

A. Qualitative Observations.

Observations in Home Cage:

Posture
Tremors
Convulsions
Bizarre or stereotypic behavior
Fecal color
Fecal consistency
Gait

Manipulative measurements

Ease of removal from cage
Respiration character
Position of hindlimbs when held by tail
Pupillary size
Lacrimation
Eye prominence
Palpebral closure
Staining
Piloerection
Fur appearance
Salivation
Vocalization
Ease of handling in hand.

Open field tests

Arousal level
Number of rears
Number of defecations
Number of pools of urine
Head position
Tremors
Convulsions
Bizarre or stereotypic behavior
Gait

Reflex tests

Approach response
Touch response
Click response
Pupil response
Eye blink response
Tail pinch response
Placing reflex
Righting reflex

Neuromuscular tests

Hindlimb extensor strength
Grip strength (both forelimb and hindlimb)
Hindlimb foot splay

Physiological measurements

Body tone
Body weight
Rectal temperature
Muscle tone

Numerous parameters were affected and these are illustrated in Tables 9.11 and 9.12 photocopied from the study report and appended. These signs are considered to be related to ChE/AChE inhibition. Since the study was designed to determine a NOEL and LEL for neurotoxicity effects, the following discussion addresses the parameters affected to aid toward this end.

The study report asserts a NOEL and LEL of 2.5 and 150 mg/kg for both sexes for FOB parameters and that the effects were noted only at the time of peak effect and not on assessment made on days 7 and 14. TB-I concurs that there were no indications of effects on FOB parameters noted at the dose level of 2.5 mg/kg or at higher does on days 7 and 14.

150 mg/kg. A total of six parameters affected which had a LEL of 150 mg/kg are listed in the order which TB-I considers of relative importance as follows:

Ataxic gait and abnormal gait. Males (2/10 with abnormal gait) were less affected than females (7/10 with abnormal gait and 3/10 with ataxic gait). Nearly all of the males were affected at 300 and 600 mg/kg and all of the females had ataxic gait.

Body temperature. A 2.1% decrease was noted ($p < 0.05$) and progressively greater decreases (4.7% and 12%) noted at higher doses. Males were affected at 300 and 600 mg/kg (3.4% and 11%).

Rearing counts. A 33% decrease was noted ($p < 0.01$) and progressively larger decreases (60% and 93%) were noted at higher doses. Males became affected at 300 and 600 mg/kg (50% and 95%).

Stereotypy. Three of 10 females were affected and progressively more were affected at the higher doses. Males were affected at 300 and 600 mg/kg (5/10 at each dose level).

Altered fecal consistency/diarrhea and stained fur. Three males were described with these conditions and progressively more were noted at higher doses. Females became affected at 300 and 600 mg/kg.

300 mg/kg. 13 parameters LEL at 300 mg/kg. Most significantly tremors (5/10 for both males and females) were noted. The males (5/10) were reported to have bizarre behavior with all having this symptom at 600 mg/kg. Females (6/10) were described as dehydrated and all had this condition at 600 mg/kg. The rest of the symptoms are considered to be related to symptoms already described in the attached tables.

600 mg/kg. At the highest dose level the rats were reported to have impaired respiration and excess lacrimation as well as other symptoms also noted at lower doses and indicated in Tables 9.11 and 9.12.

TB-I notes that there were no reports of pupil dilation (miosis), a symptom that has been reported for other organophosphates.

5. Motor Activity.

Figure 8 maze activity. The animals were assessed approximately one week prior to treatment, at the estimated time of peak effect (approximately 9-11 hours postdosing) and again on study days 8 and 15.

Locomotor activity in the Figure 8 maze was measured by eight separate pairs of photobeams/photocells at standardized locations. Counts were recorded separately every five minutes in the 60 minute session. Only total counts of all eight photocells at each 5 minute interval were included in the study report. The rats were tested in the presence of white noise (70 Db) and under normal lighting conditions.

The study report maintains that females were affected at 150 mg/kg and above and males were affected at 300 mg/kg and above at the time of peak effect only. No differences were recognized by the study author on days 7 and 14. Figures 8.4 and 8.8 photocopied from the study report are attached to illustrate

the findings at the time of peak effect. These figures illustrate the total counts per time interval and the habituation of the rats to the activity chambers.

The 150 mg/kg dose group for males is visibly lower than the low dose and control group but the study author does not consider the decrease an effect of treatment. Inspection of the mean total count data (from Table 9.15) indicates that the mean total count for the control and 2.5 mg/kg dose groups were 310.1 ± 101.6 and 305.1 ± 124.5 while that of the 150 mg/kg dose group was only 227.4 ± 112.6 or 27% less than the control. The 300 and 600 mg/kg dose groups were 76% and 97% less than the control value. By comparison, the females were 46%, 77% and 95% decreased for the 150, 300 and 600 mg/kg dose groups respectively. In conclusion, TB-I considers that the 150 mg/kg dose in males was affected by treatment to result in reduced motor activity. Although the actual data do not reach statistical significance, the biological interpretation of the trend is considered more important. For both males and females, the mean values for the control and low dose groups are very similar and the pretreatment group was also had little variation among the study groups.

5. ChE/AChE determinations. Blood was taken from the orbital sinus for the satellite group of 5 rats/group/sex at the time of peak effect. Although the rats were fasted prior to dosing their feed jars were returned five hours prior to blood collection. Blood samples were again taken on the 14th day. Also on the 14th day, the rats were anesthetized with sodium pentobarbital (i.p. injection) and the whole brain was removed and assessed for brain AChE activity.

Table 2 below illustrates the plasma ChE and RBC AChE inhibition data at day 1 (sample at the time of peak affect) and day 15.

Table 2. Plasma ChE and RBC AChE inhibition following acute diazinon administration in rats at time of peak behavioral effect and after 15 days.

Dose Level	Males ¹				Females			
	Plasma ChE		RBC AChE		Plasma ChE		RBC AChE	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
Control	542±40	586±66	1256±149	1092±119	1232±157	1405±191	1344±145	1288±206
2.5 mg/kg	27%***	5%	7%	+1%	53%***	+5%	4%	11%
150 mg/kg	76%***	6%	82%***	9%	84%***	+5%	76%***	43%***
300 mg/kg	76%***	2%	83%***	34%	85%***	+6%	77%***	26%***
600 mg/kg	78%***	+1%	85%***	46%***	84%***	+2%	76%***	35%***

Data are from Tables 9.19 and 9.20 of the study report.

1. Data are the mean ± the standard deviation for the control group in IU/L for plasma ChE and IU/L PRBC for RBC AChE. For the dosed groups, the percentage differences relative to the control are presented.

+ Activity higher than the control was noted.

These data indicate significant plasma ChE inhibition at 2.5

mg/kg, the lowest dose level tested. The NOEL and LEL for RBC AChE inhibition is 2.5 and 150 mg/kg. The RBC enzyme inhibition persists to day 15 in the females for the groups dosed with 150 mg/kg and above but only for the 300 (although data are not significant) and 600 mg/kg for males.

Brain AChE which was assessed at day 15 only did not indicate treatment related inhibition although the 150 mg/kg dose group females were slightly decreased (6%, $p < 0.05$).

Since there was little meaningful difference with increasing dose (300 and 600 mg/kg) between RBC AChE inhibition for either males (76 to 78%) or females (84 to 85%) at the time of peak effect but there were a variety of behavioral difference noted as the dose level increased, the correlation between either ChE or AChE inhibition and symptoms is poor. Moreover, the rats appeared to symptom free after a day or two but RBC AChE was still inhibited until day 15. Plasma ChE was inhibited up to 53% in females in the 2.5 mg/kg dose group but these rats did not show symptoms.

6. Histopathology and Perfusion Studies.

The rats in the main phase of the study were anesthetized with sodium pentobarbital (i.p.) and sacrificed by whole body perfusion with 2.5% buffered glutaraldehyde and necropsied. The following tissues were removed and preserved in 10% neutral buffered formalin (NBF). Some tissues (as indicated by BG) were preserved in buffered glutaraldehyde. The tissues were embedded in paraffin.

Nervous system: brain (levels 1-10); spinal cord (with ganglia), cervical, thoracic, lumbar and sacral); peripheral nerves - right sciatic, left sciatic (BG), right fibular, left fibular (BG), right tibial, left tibial (BG), right lateral cutaneous sural, left cutaneous sural (BG), gasserian ganglion (BG), Musculoskeletal: skeletal muscle, right thigh. Special senses: eyes (with optic nerve, BG). And gross lesions and other tissues as specified by the pathologist.

The first five animals in the control and high dose groups and the animals that were found dead were processed histologically. The histopathological methods were described for the brain and spinal cord (including fixation)

Five control/sex and 7 high dose males and 6 high dose females were assessed microscopically. No specific lesions were reported in these animals. The only lesion reported was a single rat from the female controls that had chronic inflammation of the muscle (thigh).

7. Immunochemistry: No assessments for GFAP were made.

8. Validation of methodology. This study included a concurrent

set (10/sex) of rats dosed with triadimefon (150 mg/kg) a known stimulant. Triadimefon produced its expected stimulating effects (refer to Figures 8.4 and 8.8 and tables 9.11 and 9.12 from photocopied from the study report attached.

CONCLUSION/DISCUSSION: This study is classified CORE MINIMUM and satisfies the requirement for a series 81-8ss acute neurotoxicity screen study. Study deficiencies: The study did not establish a NOEL and LEL for inhibition of plasma ChE. The 27% inhibition is considered to be related to treatment and this was confirmed in the special study (MRID No.: 431322-03). Since it is known that plasma ChE is very sensitive to diazinon, additional data to establish a NOEL/LEL is not considered necessary.

In summary, the study demonstrated that diazinon elicits several behavioral reactions that are detected in the FOB at the time of peak effect that are consistent with the expected reactions to organophosphate inhibition of ChE/AChE. The principle signs of toxicity at the LEL were ataxic gait which was supported by other related gait and movement effects. Diazinon did not cause miosis which is a typical response to many organophosphate or other ChE/AChE inhibitors possibly indicating an inability of diazinon to be transported to the critical sites (eye structures). Although the symptoms were consistent with expected inhibition of ChE/AChE there was actually poor correlation between the onset and duration and degree of plasma ChE and RBC AChE inhibition. In particular, there was little or no difference between the extent of inhibition at 300 and 600 mg/kg but the severity and number of symptom types increased between these dose levels. In addition, RBC AChE remained inhibited until day 15 but the symptoms were not evident after 2 or 3 days.

Note: Additional positive control data provided by the Ciba-Geigy Corporation Environmental Health Center is summarized in the Table in Appendix I attached.

Diazinon TOXR 11375

Page _____ is not included in this copy.

Pages 25 through 30 are not included.

The material not included contains the following type of information:

- Identity of product inert ingredients.
 - Identity of product impurities.
 - Description of the product manufacturing process.
 - Description of quality control procedures.
 - Identity of the source of product ingredients.
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 - A draft product label.
 - The product confidential statement of formula.
 - Information about a pending registration action.
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Ciba-Geigy Laboratory

Appendix 1

Chemical	Study Identification	Treatment Information	Results and Comments
Triadimefon (acute)	F-00175 (with diazinon) January 20, 1994 MRID No.: 431322-04 HED Document No.: pending.	150 mg/kg in corn oil by gavage. Hsd Sprague-Dawley SD strain rats.	FOB: increased rearing and arousal, bizarre behavior. Motor activity: Starts only slightly higher than control but remains elevated.
Triadimefon. (acute) F-00166 (with profenofos) Septemebr 1, 1993 MRID No.: 429398-02 HED Docuemnt pending 100 mg/kg males and 150 mg/kg females in corn oil HSD Sprague Dawley strain rats. increased rearing, arousal, tail pinch response, motor activity, compulsive sniffing, Straub tail and exophthalmos.
Propoxur (acute)	F-00166 (with profenofos) September 1, 1993 MRID No.: 429398-02 HED Docuemnt No.: pending	6 mg/kg ip in corn oil. Hsd Sprague Dawley strain rats.	FOB : diarrhea, lacrimation, salivation, miosis, impaired respiration, increased urination, soiled fur, stereotypy (compulsive licking and repeated opening and closing of teh mouth), abnormal gait (ataxic, hunched, crouched, waddling, immobilem or hindlimbs splayed or dragged) impaired rr, decreased forelimb and hindlimb grip strength, impaired extensor reflex, flattened posture, decreased arousal, tremors, muscle increased ease of handling, muscle fasciculations, decreased rearing, impaired tail pinch response, dehydration, decreased body temperature anddecreased m,otor activity.
Acrylamide (subchronic)	F-00167 (with profenofos) March 1, 1994 MRID No.: 432133-03 HED Document: Pending	16 mg/kg in distilled water by gavage 5 days/week for 90 days Hsd Sprague-Dawley strain rats.	

<p>Trimethyltin chloride (subchronic)</p>	<p>F-00167 (with profenofos) March 1, 1994 MRID No.: 432133-03 HED Document: Pending</p>	<p>3 mg/kg in distilled water by gavage once a week for 6 weeks Hsd Sprague-Dalwey strain rats</p>	<p>Deaths, convulsions, other minor singular incidents., sharply decreased body weight, abnormal gait, impaired rr, hindlimb extensor, forelimb grip strength, hypotonia of muscle, tremors, arcus al esae of handling, body tone, dehydration, palpebral closure, piloerection, soiled fur, decreased motor activity.</p> <p>Pathology: hippocampus - necrosis gliosis, nerve cell loss, ganglion- generalized chromatolysis and some nerve degeneration, peripheral and spinal nerves had axonal degeneration and chromatolysis in the spinal cord.</p>
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