DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: OPPTS 6200a [§81-8], Neurotoxicity Screening Battery in Rats

Work Assignment No. 4-01-128 A (MRID 46808217)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
2777 South Crystal Drive
Arlington, VA 22202

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

Primary Reviewer
David A. McEwen, B.S.

Signature: David A. McEwen
Date: 12/19/06

Secondary Reviewer
Stephanie E. Foster, M.S.

Signature: Stephanie E. Foster
Date: 12/19/06

Program Manager:
Michael E. Viana, Ph.D., D.A.B.T.

Signature: Michael E Viana
Date: 12/19/06

Quality Assurance:
Mary L. Menetrez, Ph.D.

Signature: Mary L Menetrez
Date: 12/20/06

Disclaimer

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

EPA Reviewer: Karlyn J. Bailey, M.S. **Signature:** [signature]
Registration Action Branch 2, Health Effects Division (7509P) **Date:** 5/31/07
EPA Secondary Reviewer: Myron Ottley, Ph.D. **Signature:** [signature]
Registration Action Branch 3, Health Effects Division (7509P) **Date:** 5/31/07
Template version 02/06

DATA EVALUATION RECORD

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [' 81-8]; OECD 424.

PC CODE: 129108 **DP BARCODE:** D331116
TXR#: 0054348

TEST MATERIAL (PURITY): XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714)

SYNONYMS: XR-570, XRD-570, DE-570, N-(2,6-diflurophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-*c*)pyrimidine-2-sulfonamide

CITATION: Mattsson, J.L., R.J. McGuirk, and B.L. Yano (1997) XDE-570: Acute neurotoxicity in Fischer 344 rats. The Toxicology Research Laboratory, The Dow Chemical Company, Midland, MI. Laboratory Project Study ID: DR-0312-6565-022, January 6, 1997. MRID 46808217. Unpublished.

SPONSOR: Dow AgroSciences Canada, Inc. , 2100- 450 1 St. SW, Calgary, AB, Canada

EXECUTIVE SUMMARY - In an acute neurotoxicity study (MRID 46808217), groups of 10 fasted young adult Fischer 344 rats/sex/dose were given a single oral gavage dose of XDE-570 (Florasulam; 99.3% a.i.; Lot # 940714) in aqueous methylcellulose at dose levels of 0, 200, 1000, or 2000 mg/kg (limit dose) and were observed for 15 days. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in all rats at one week prior to dosing and on Days 1 (approximately 6-7 hours post-dosing), 8, and 15. At study termination, 5 rats/sex/dose were euthanized and perfused *in situ* for neuropathological examination. The brain and peripheral nervous system tissues collected from the perfused animals in the control and 2000 mg/kg groups were subjected to histopathological evaluation. Positive control data were provided.

There were no compound-related effects on mortality, clinical signs, body weight, and gross or neuropathology observed at any dose.

In the 2000 mg/kg males, overall (Days 0-15) body weight gain was decreased by 21%, although body weight at termination was comparable to controls. This was attributed to a lower body weight gain (decr. 33%) in these animals during Week 1. Additionally in these animals, there was a slight transient decrease in motor activity, increased incidence of minimal activity in the open-field, and decreased reactivity to sharp noise on Day 1. However, the differences from control values did not exceed the historical controls and complete recovery occurred by the next test session (Day 8). When the FOB and motor activity findings were combined they were considered to be a treatment-related effect. As there were no corroborative gross or neuropathological findings to suggest a neurotoxic effect, this pattern of decreased activity was considered to be likely due to general malaise.

No treatment-related effects were observed in the females at any dose and the males at 1000 mg/kg or below.

No evidence of neurotoxicity was observed at any dose in either sex.

The systemic LOAEL is 2000 mg/kg (limit dose), based on decreased body weight gain (21%) and general malaise (slight transient decrease in motor activity, minimal activity in open field, and reactivity) in the males. The systemic NOAEL is 1000 mg/kg.

The neurotoxicity LOAEL was not observed. The neurotoxicity NOAEL is 2000 mg/kg (limit dose).

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for Test Guideline OPPTS 870.6200a; OECD 424 for an acute neurotoxicity study in the rat.

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

NOTE: This DER summarizes EPA conclusions regarding effects observed in the acute neurotoxicity study in rats. A detailed DER completed by the Canadian Pest Management Regulatory Agency (PMRA) is attached.

COMMENTS: EPA concurs with the PMRA toxicology evaluation, no conclusions have been changed.

46808217.PMRA.der
.pdf

Reviewer: Tom Morris , Date May 26, 2000.

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200; OECD 424.

TEST MATERIAL (PURITY): XDE-570 (Purity - 99.3%).

SYNONYMS: XR-570, XRD-570, DE-570, florasulam.

CITATION: Mattsson, J. L., McGuirk, R. J. and Yano, B. L. January 6, 1997. **XDE-570; Acute Neurotoxicity in Fischer 344 Rats.** Performing Laboratory: The Toxicology Research Laboratories, The Dow Chemical Company, Midland, Michigan, 48674. Laboratory Project Study ID: DR-0312-6565-022. Unpublished

SPONSOR: Dow AgroSciences Canada Inc. (DAS).

EXECUTIVE SUMMARY: In an acute neurotoxicity study, groups of 10 fasted young-adult Fischer 344 rats/sex/dose were given a single dose (oral gavage) of XDE-570 (Purity - 99.3%) in aqueous methylcellulose at dose levels of 0, 200, 1,000 or 2,000 mg/kg bw and observed for 15 days. Neurobehavioural assessment (functional observational battery [FOB] and motor activity testing) were performed one week prior to treatment and on days 1 (≈6 to 7 hours post-dosing), 8 and 15 following treatment. At study termination, 5 animals/sex/group were euthanised and perfused *in situ* for neuropathological examination. All control and high-dose perfused animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

There were no treatment-related effects on mortality or adverse clinical signs. In the high-dose males, overall body-weight gain was approximately 21% lower compared to controls, although body weight at the termination of the study was comparable between the controls and the high-dose males. This was attributed to a lower body-weight gain (≈33%) in the high-dose males during the first week. On the day of treatment (day 1), there was a slight transient decrease in motor activity, increased incidence of minimal level of activity in the open field and decreased responsiveness to sharp noise in males at 2,000 mg/kg bw. However, the difference from control values did not exceed the range of normal variability for animals of this age and strain from this laboratory and complete recovery occurred by the next test occasion, seven days following treatment (day 8). When the FOB and motor activity findings were combined they were considered to be a treatment-related effect, although minimal. The overall pattern suggests a slight transient decreased activity and reactivity in the high-dose males on the day of dosing which was most likely due to general malaise rather than to neurotoxicity. Fore-limb and hind-limb grip strength, landing foot splay and rectal temperature, were not affected by treatment in either sex at any dose level. There were no treatment-related gross pathological or histopathological findings and no neuropathological findings in the central or peripheral nervous system in either sex up to and including 2,000 mg/kg bw. In the absence of any corroborating treatment-related gross pathological or histopathological findings or neuropathological findings in the central or peripheral nervous system, the FOB and motor activity findings in males at 2,000 mg/kg bw on the day of dosing were not considered to be due to neurotoxicity *per se*.

The LOAEL for systemic toxicity was 2,000 mg/kg bw based on decreased body-weight gain, slight transient decreased motor activity, increased incidence of minimal level of activity in the open field and decreased responsiveness to sharp noise in males on the day of dosing. The NOAEL for systemic toxicity was 1,000 mg/kg bw.

The LOAEL for neurotoxicity was not determined. The NOAEL for neurotoxicity was 2,000 mg/kg bw, the highest dose tested.

The study is classified as acceptable / guideline as an acute neurotoxicity study in rats (870.6200; OECD 424).

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

I. MATERIALS AND METHODS

A. MATERIALS:

1 **Test Material:** XDE-570 as named in the study. Chemical Name (CA nomenclature): N-(2,6-diflurophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-c)pyrimidine-2-sulphonamide

Description: White powdery solid

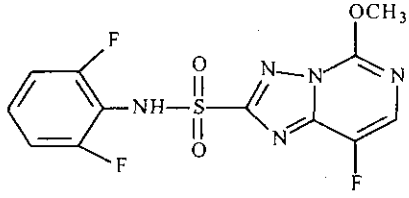
Lot/Batch #: Batch # TSN100511 / Lot # 940714

Purity: 99.3 % a.i. (determined by HPLC).

Compound Stability: The test substance was re-assayed after study determination and was confirmed at 99.3% (Knowles, et al., 1997, Lab Report Code GHE-P-6448)

CAS #: 145701-23-1

Structure



2. **Vehicle and/or positive control:** The test substance was prepared in aqueous methylcellulose (MC). The solution was stable for 2 weeks (Kropscott, B.E., 1995, Dose Confirmation, Analytical Report Number 95-33, The Dow Chemical Company Internal Report, Midland, MI).

3 **Test animals:**

Species: Male and female rats

Strain: Fischer 344

Age/weight at dosing: At dosing, the animals were ≈8 weeks of age with a body weight range of 137.1 to 178.2 g for males and 90.8 to 112.2 g for females.

Source: Charles River Laboratories, Kingston, NY.

Housing: Animals were housed 2/cage (same sex) during the acclimation period and, after randomization, 1/cage in suspended stainless steel cages with wire mesh floors.

Diet: Certified Laboratory Diet #5002 (Purina Mills, St. Louis, MO) *ad libitum* (except during the overnight fast prior to dosing and the overnight fast prior to each FOB).

Water: Municipal tap water *ad libitum* (except during the overnight fast prior to dosing and the overnight fast prior to each FOB).

Environmental conditions:
Temperature: 21-23.1 °C
Humidity: 40-60%
Air changes: Not provided in study report
Photoperiod: 12 hrs dark/12 hrs light

Acclimation period: At least 1 week.

B. STUDY DESIGN:

1. **In life dates** - Start: ≈February 13, 1995 (Feb 6/95 - test day -7). End: March 1, 1995 (necropsy date).

2. **Animal assignment and treatment** - Animals (10 animals/sex) were stratified by weight and randomly assigned to the test groups, as noted in Table 1, using a computer program. The numerous observations to be made in this acute neurotoxicity study made it necessary to stagger-start the study over 4 days. Therefore, the animals were divided into 4 subsets of 20 rats each, fully counterbalanced over the different dose levels and sexes, each replicate

starting one day apart. Each replicate had 5 rats/dose level, either 3 males and 2 females/dose, or 3 females and 2 males/dose, such that over 4 days all rats had been dosed and had begun the 2 week evaluation. Following an overnight fast, rats were given a single dose by oral gavage at a dosing volume of 10 mL/kg bw. After completion of the in-life portion of the study at 2 weeks, a gross pathological examination was conducted on all rats and a neuropathological evaluation of perfusion-fixed central and peripheral nervous tissues was conducted on 5 animals/sex/dose.

TABLE 1: STUDY DESIGN

Test Group	Dose Level (mg/kg bw)	Number of Animals							
		Initial		Neurobehavioural Studies (b)		Necropsy		Neuropathology	
		M	F	M	F	M	F	M	F
Control (a)	0	10	10	10	10	10	10	5	5
Low	200	10	10	10	10	10	10	5	5
Mid	1,000	10	10	10	10	10	10	5	5
High	2,000	10	10	10	10	10	10	5	5

(a) Control animals received the vehicle at the same volume as the treated animals (10 mL/kg bw)
(b) Motor activity was determined pretest (day -7), day 1 (at 6 to 7 hours post-dosing), and at 8 and 15 days following treatment. FOB assessments were performed pretest (day -7), day 1 (at 6 to 7 hours post-dosing), and at 8 and 15 days following treatment. Animals were fasted overnight prior to each FOB and motor activity evaluation.

3. Dose selection: A gavage range-finding study was carried out to determine the benchmark dose, which is defined by EPA as the highest non-lethal dose that shows some neurotoxic or other toxic effects, and the time to peak effect (within 8 hours after dosing) for XDE-570. Based on the lack of clinical observations on an acute oral toxicity study, the benchmark dose study was conducted (oral gavage) at 0 and 2,000 mg/kg bw/d (limit dose). Three rats/sex were observed about 30 minutes post-dosing, and hourly for the next 7 hours. No effects were noted at any time point (data provided in study report). Based on these findings, the high dose for this acute neurotoxicity study was set at 2,000 mg/kg bw/d, the limit dose as indicated in OECD Guideline 424 (Neurotoxicity Study in Rodents) and EPA Guideline OPPTS 870-6200 (Neurotoxicity Screening Battery). The lower dose levels were set at 1,000 and 200 mg/kg bw/d to provide dose-response information and to ensure definition of a NOAEL for the test material.

4. Test substance preparation and analysis The test substance was prepared in aqueous methylcellulose immediately prior to use. Homogeneity, stability and concentration were tested prior to dosing.

Results - Homogeneity Analysis: Dosing suspensions had a relative standard deviation (RSD) of 4 to 10% (Kropscott, B.E., 1995, Dose Confirmation, Analytical Report Number 95-33, The Dow Chemical Company Internal Report, Midland, MI). Generally, an RSD of approximately 10% or less is considered a homogenous mixture.

Stability Analysis: The solution was stable for 2 weeks (Kropscott, 1995).

Concentration Analysis: The dosing solutions were analysed for concentration prior to treatment with a range of 94-113% of the target concentration (Kropscott, 1995).

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. Statistics - Statistical analyses were conducted on body weights, grip performance, rectal temperatures, landing

foot splay and motor activity. The average of 3 grip performance trials and the average of 3 landing food splay values were used for statistical analyses. Motor activity counts were reported as their square roots to minimize problems of heterogeneity of variance and departure from normality that occur from treatment. For overall FOB summarization and subjective evaluation, the data are the average ranks for each FOB observation (for males and females at each dose level). For statistical analyses, the incidence of ranked FOB observations, between control and each treated group (for each sex separately), were evaluated by a test of proportions (Bruning and Kintz, 1997). Means and standard deviations were calculated and homogeneity of variance was confirmed with the F-max test (α = 0.01). The study design had 2 sexes and four major data collection periods: pre-exposure, days 1, 8 and 15. Initial statistical analyses, therefore, were factorial repeated-measure analyses to account for data from both sexes at all time periods in one statistical analyses. By using sex as a factor, the statistical power of the test was increased. In factorial repeated-measure tests (a dependent variable repeated over time, i.e., pre-exposure, days 1, 8 and 15), the inclusion of pre-exposure data in the analysis makes only the analyses which include factors of both treatment and time. The following interactions were studied:

Treatment x time - a significant p value indicates that, taken together, both males and females were affected by treatment at some time interval.

Treatment x time x sex - a significant p value indicates that treatment effects were different between males and females at some time interval.

Treatment x time x epoch - a significant p value indicates that treatment effects were different amongst the different epochs at some time interval. (motor activity only)

To reduce the rate of false declarations, the Type I error rate (α) per comparison was set at 0.02. The corrections for multiple statistical analyses were applied to alpha only, and the probability was reported without correction.

Number and Type of Statistical Tests (a)

Dependent Variable		Number of Primary Tests	Type of Test (b)
Body weight		2 (T x D & T x D x S)	Rep-ANOVA
Grip performance	- forelimb - hindlimb	2 (T x D & T x D x S) 2 (T x D & T x D x S)	Rep-ANOVA
Temperature		2 (T x D & T x D x S)	Rep-ANOVA
Landings food splay		2 (T x D & T x D x S)	Rep-ANOVA
Motor activity	- total counts - Epochs (nested by day)	2 (T x D & T x D x S) 1 (T x D x E)	Rep-ANOVA
FOB observations		~384 (T)	Z-test of proportions

Factors: T = treatment; D = day; S = sex; E = Epoch. Repeated across days. For motor activity, repeated across days and across epochs.
(a) Table extracted from page 17 of the study report.
(b) Rep-ANOVA (repeated-measure analysis of variance) was calculated by rep=MANOVA with the multivariate model. This format avoids the requirement of sphericity of the variance / covariance matrix of the Rep-ANOVA. The multivariate index was the Pillai Trace statistic.

C. METHODS:

1. Clinical Observations: A visual evaluation for morbidity, moribundity and mortality, the availability of food and water and treatment-related effects was performed twice daily for 14 days. Animals found dead were refrigerated until necropsy. When the FOB, motor activity evaluation or clinical exams were conducted, a cage-side observation was not necessary for that corresponding time of day. Clinical observations were comparable to the hand-held portion of the FOB and were conducted once a day (pm) on days 2, 3 and 4.

2. Neurobehavioural Studies: The neurobehavioural evaluation consisted of a Functional Observational Battery (FOB) and determination of motor activity (MA). The FOB and determination of motor activity were conducted in such a manner that the observer did not know the treatment status of the animal.

a. Motor Activity Evaluation: A motor activity evaluation was carried out in all animals (10 animals/sex/dose) prior to dosing (day -7), on the day of dosing (day 1), and on days 8 and 15 post-dosing. The motor activity evaluation was started before the FOB at approximately 5-6 hours post-dosing on day 1 and at approximately the same time of day for pre-exposure, day 8 and day 15. Each animal was tested individually for motor activity. Animals were fasted overnight prior to each motor activity evaluation. All test sessions consisted of six 8-minute epochs, totalling 48 minutes of testing for each animal. The duration was chosen based on the results of a validation study indicating that performance of the control animals approached asymptote in 30-40 minutes. Total activity counts for each epoch were recorded. Each beam break lasting for more than 100 msec constituted an activity count (minimum duration was set to discount activities such as tail-flicking, rearing, head-bobbing, etc). Motor activity was monitored by a computerized system located in an adjoining room.

Twenty-four motor activity cages, visually isolated from each other, were located in a quiet dimly lit room. Each motor activity cage consisted of a clear plastic circular alley. An infra-red photo-beam dissected the cage so that the beam crossed the alley in 2 locations. The cages were calibrated prior to testing each day. Calibration was performed with a rod (attached to a rotary motor) that broke the infra-red beam. The time of beam interruption average for all test units was recorded, and any photocell showing a difference exceeding 4 centi-seconds was readjusted to ensure equivalence of devices. The animals were allocated to the motor activity cages in such a way that counterbalancing of treatment groups and sexes across cages and across times was maximized.

b. FOB Evaluations: A functional observation battery (FOB) was carried out in all animals (10 animals/sex/dose), prior to dosing (day -7), on the day of dosing (day 1) at approximately 6 to 7 hours post-dosing, and on days 8 and 15 post-dosing. Animals were fasted overnight prior to each FOB evaluation. The animals were tested at the time of peak effect (approximately 6-7 hours after dosing), and at the same time of day for each subsequent FOB evaluation. The following FOB parameters were evaluated:

HOME CAGE OBSERVATIONS	**OPEN FIELD OBSERVATIONS**
Posture	Piloerection
Piloerection	Respiration abnormalities
Gait abnormalities	Posture
Clonic / clonic movements	Clonic / tonic movements
Vocalizations	Stereotypic / bizarre behaviour
Other abnormal observations	Gait abnormalities
HAND-HELD OBSERVATIONS	Vocalizations
Ease of removal from cage	Arousal
Reaction to handling	Rearings / 2 minutes
Muscle tone	Defecation
Palpebral closure	Urination
Pupil size	Other abnormal observations
Lacrimation	***MEASUREMENTS***
Salivation	Hindlimb grip strength
Staining (eyes, oral, nasal, anal, urine)	Forelimb grip strength
Other abnormal observations	Landing footsplay
REFLEX / PHYSIOLOGICAL OBSERVATIONS	Body weight
Approach response	Body temperature (rectal temperature)
Touch response	

Auditory response
Righting reflex
Tail pinch response

3. Body weight: Body weights were determined pre-exposure and on days 1 (prior to dosing), 8 and 15 (prior to sacrifice) of the study.

4. Food consumption: Not determined.

5. Sacrifice and Pathology: After completion of the in-life portion of the study at 2 weeks, a gross pathological examination was conducted on all rats. Necropsy consisted of an examination of the external tissues and orifices. The head was removed, the cranial cavity opened and the brain, pituitary and the adjacent cervical tissues were examined. The nasal cavity was flushed with phosphate buffered solution of 1.5% glutaraldehyde - 4% formaldehyde. The skin was reflected from the carcass, the thoracic and abdominal cavities were exposed and the viscera were examined *in situ*. All visceral tissues were dissected from the carcass and re-examined. The brain, spinal column with spinal cord, fore- and hind-limbs and tail were trimmed and immersed in fixative (phosphate buffered solution of 1.5% glutaraldehyde - 4% formaldehyde). Muscles from the hind-limb were reflected to expose the nerves. Thoracic and abdominal viscera were also saved in fixative. Tissues marked with an (X) in the following table were collected and preserved during necropsy. No organ weight data was obtained in this study.

	DIGESTIVE SYSTEM		*CARDIOVASC./HAEMAT.*		NEUROLOGIC
X	Tongue	X	Aorta	X	Brain
X	Salivary glands	X	Heart	X	Peripheral nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	X	Spleen	X	Eyes (optic n.)
X	Jejunum	X	Thymus		GLANDULAR
X	Ileum		UROGENITAL	X	Adrenal gland
X	Cecum	X	Kidneys	X	Lacrimal gland
X	Colon	X	Urinary bladder	X	Mammary gland
X	Rectum	X	Testes	X	Parathyroids
X	Liver	X	Epididymides	X	Thyroids
	Gall bladder	X	Prostate	X	Auditory sebaceous glands
X	Pancreas	X	Seminal vesicle		OTHER
	RESPIRATORY	X	Ovaries	X	Bone (including joint)
X	Trachea	X	Uterus	X	Skeletal muscle
X	Lung	X	Cervix	X	Skin
X	Nose	X	Coagulating glands	X	All gross lesions and masses
X	Pharynx	X	Oviducts		
X	Larynx	X	Vagina		

A neuropathological evaluation of perfusion-fixed central and peripheral nervous tissues was conducted on 5 animals/sex/dose. Five randomly selected animals/sex/dose were heparinized approximately 10 minutes prior to perfusion (0.2 mL heparin 10,000 USP/mL/100 g bw, IP) and were anaesthetized by methoxyflurane vapour inhalation. Animals were perfused intracardially with 0.05 M phosphate buffer containing 0.7% sodium nitrate, followed by a phosphate buffered solution of 1.5% glutaraldehyde - 4% formaldehyde. Tissues for neuropathological evaluation, marked with an (X) in the following table, were prepared from all perfusion-fixed animals in the control and high-dose groups. Tissues from the central nervous system and sections of skeletal muscle were embedded in paraffin, sectioned approximately 6 µm thick and stained with haematoxylin and eosin. Peripheral nerves and dorsal root ganglia with roots were osmicated, embedded in plastic, sectioned approximately 2 µm thick and stained with toluidine blue. All tissues were examined by a veterinary pathologist using a light microscope.

258

Nervous System Tissue Collection and Disposition			
Paraffin		**Plastic**	
Olfactory epithelium	X	**Dorsal root ganglia**	
Olfactory bulb	X	- cervical swelling (C_3 - C_6)	X
Cerebrum, anterior	X	- lumbar swelling (L_1 - L_4)	X
Cerebrum, middle	X	**Dorsal and ventral roots**	
Pituitary gland	X	- cervical swelling (C_3 - C_6)	X
Trigeminal ganglia	X	- lumbar swelling (L_1 - L_4)	X
Midbrain and posterior cerebrum	X	**Peripheral nerves (cross and *longitudinal section*)***	
Cerebellum and pons	X	- proximal sciatic	X
Cerebellum and medulla (2 levels)	X	- tibial	X
Nucleus gracilis	X	- peroneal (saved)	X
Spinal cord (cross and oblique section) - cervical swelling (C_3 - C_6)	X	- sural	X
- Lumbar swelling (L_1 - L_4)	X	- caudal (saved)	X
Eyes	X	- optic (longitudinal only)	X
Skeletal muscle - anterior tibial and gastrocnemius	X		
* Peripheral nerves from the right hind-limb were examined histologically.			

6. *Positive Controls:*

FOB - Positive control studies for FOB evaluations were conducted with saline (0.15 mL, i.p.), chlorpromazine (4 mg/kg i.p.), d-amphetamine (8 mg/kg i.p.) or atropine + physostigmine sulfate (2 mL/kg atropine i.p. followed in 5 min with 0.75 mg/kg physostigmine s.c.) to establish the sensitivity, reliability, and validity of these test procedures, the adequacy of training of technical personnel and to serve as a historical control. Head weaving and piloerection were observed in animals treated with d-amphetamine. Chlorpromazine treated animals were observed to hold fixed postures. Atropine-physostigmine treated animals exhibited tremors and decreased response to tail pinch. Similar appropriate observations were made for ranked observations, and for measurements of temperature, grip performance and landing foot splay. Positive control studies with untreated animals and with animals treated with reference substances that evaluate FOB proficiency, adequately established the sensitivity, reliability and validity of these test procedures. It was determined subjectively that D.A. Myers made the appropriate observations for the specific pharmacologic syndromes. Objectively, the Pearson's cross-correlation coefficient of Myers' observational scores vs template (expected) scores yielded r = 0.944, and Pearson's r for measurements of temperature, grip and splay was 0.941. These high correlations demonstrated objectively that Myers' observation and measurements were a high match to those expected. The combination of subjective and objective evaluations of FOB proficiency for Myers indicate a high degree of FOB proficiency with positive control substances. The proficiency demonstration for D.A Meyers (FOB observer) and the FOB positive control study and data were provided on pages 307-369 of the study report. The raw data and supporting documentation were filed under laboratory ID: HET T1.05-022-000-007.

Motor activity - Positive control studies with untreated animals (0.5 mL physiological saline, i.p. and a non-injected control group) and with rats treated with reference substances that increase (d-amphetamine at final concentrations of 0.06, 0.196 or 0.65 mg/mL) and decrease (chlorpromazine at final concentrations of 0.3, 1.33 or 3.0 mg/mL) motor activity established the sensitivity, reliability and validity of these test procedures. Motor activity positive control study and data were provided on pages 287-306 of the study report. Raw data and supporting documentation were filed under laboratory ID: HET T1.05-018-002-REV.

Neuropathology - Three groups of 5 male Fischer 344 rats were each treated with either: a single oral gavage of 7 mg/kg bw of trimethyltin (TMT) in water on day 1, repeated oral gavage with 35 mg/kg bw/d of acrylamide 5 times/week for 3 weeks or distilled water by gavage 5 times/week for 3 weeks. Tissues for neuropathological evaluation were prepared from all rats. The most common spontaneous microscopic neurologic lesions consisted of axonal degeneration in the trapezoid body of the medulla oblongata and caudal nerve. In addition, the majority of the rats, regardless of treatment, had mineralization of the cornea and nasal mucosa which were considered to be common non-neurological lesions in Fischer 344 rats. Lesions specific to rats treated with acrylamide were observed primarily in the peripheral nerves, but also in the cerebellum. Very slight axonal degeneration occurred in the sural nerve and moderate degeneration occurred in the tibial nerves of rats given 35 mg/kg bw/d acrylamide. Other lesions included very slight axonal degeneration in the peroneal nerves (3/5 rats), lumbar spinal cord (2/5 rats), the cervical spinal cord (3/5 rats) and dorsal root ganglia (2/5 rats). These lesions may not be treatment-related due to limited severity and low incidence and similarity to the controls (cervical spinal cord). Purkinje cells in the cerebellum demonstrated degenerative changes which were primarily characterized by isolated cell pyknosis and hypereosinophilia. The lesions attributed to treatment with acrylamide were consistent with published findings. Lesions attributed to trimethyltin included degenerative neuronal lesions in the hippocampus and piriform cortex of the CNS. These lesions were characterized primarily by neuronal loss and the presence of occasional necrotic cells. This also included an increase in glial cell density which was observed in some of the affected areas. These lesions are consistent with published toxic effects of trimethyltin. Other lesions not generally associated with trimethyltin included degenerative axonal lesions in the sciatic, peroneal sural and tibial nerves. The etiology of these peripheral neve lesions may be due to treatment with trimethyltin since similar lesions were not observed in the controls. The pathological changes produced by the two known neurotoxicants, acrylamide and trimethyltin, and those changes which occurred spontaneously were generally consistent with respective published neuropathologic findings. It was concluded the methods, skills and judgement exercised by the study personnel were adequate to detect significant neurotoxic effects of these chemicals when administered to rats. The neuropathology positive control study and data were provided on pages 370-396 of the study report. Raw data and supporting documentation were filed under laboratory ID: T2.08-001-012-001A.

II. RESULTS

A. Observations :

1. Clinical signs of toxicity - There were no significant adverse treatment-related clinical signs of toxicity. The only clinical observation was perineal urine soiling in females at ≥1,000 mg/kg bw/d on day 2 (not dose related) and at 2,000 mg/kg bw/d on day 3. This was completely resolved by day 4. Perineal soling was not observed in males at any time. Perineal soiling was considered to be a secondary or indirect effect and was considered to be due to lack of grooming possibly due to urine acidification or the presence of excretory products of the test substance in the urine.

TABLE 2: Clinical observations (expressed as incidence/number examined). (a)

Observation	Dose Level (mg/kg bw)	Day 2	Day 3	Day 4
Perineal soiling (females only)	0	0/10	0/10	0/10
	200	0/10	0/10	0/10
	1,000	7/10	0/10	0/10
	2,000	4/10	2/10	0/10

(a) Data obtained from pages 55-62 of the study report.

2. Mortality - There were no mortalities.

B. Body weight and weight gain: No significant differences were attained in body weight in any treatment group

when compared to controls for both sexes (Table 3). Overall body-weight gain (days 1-15) was comparable between the controls and the treated animals at 200 and 1,000 mg/kg bw/d for males and at all dose levels for females. In the high-dose males, overall body-weight gain was approximately 21% lower compared to controls. This was attributed to a lower body-weight gain (≈33% lower) in the high-dose males during the first week.

TABLE 3: Mean body weight and body-weight gain (g ± SD). (a)

Dose Level (mg/kg bw)	Pre-dosing	Day 1 (b)	Day 8	Day 15	Body-Weight Gain (c)		
					days 1-8	days 8-15	days 1-15 (% control)
	Males (10 animals/dose)						
0	132.0 ± 9.4	153.2 ± 10.0	172.2 ± 10.9	182.4 ± 12.8	19.1 ± 4.8	10.1 ± 3.4	29.2 ± 6.2
200	134.4 ± 9.9	156.9 ± 10.8	174.7 ± 12.2	187.7 ± 12.3	17.8 ± 4.6	13.0 ± 3.0	30.8 ± 6.5 (105)
1,000	133.1 ± 10.2	155.1 ± 10.9	171.5 ± 10.4	183.6 ± 10.8	16.4 ± 2.9	12.1 ± 1.9	28.5 ± 2.9 (98)
2,000	135.1 ± 10.5	158.1 ± 8.9	170.9 ± 12.8	181.3 ± 14.2	12.8 ± 5.3	10.4 ± 5.2	23.2 ± 8.5 (79)
	Females (10 animals/dose)						
0	91.6 ± 4.7	104.2 ± 3.2	114.2 ± 5.8	118.0 ± 6.2	10.0 ± 3.6	3.8 ± 1.9	13.7 ± 4.1
200	90.4 ± 3.9	104.4 ± 4.6	114.5 ± 6.6	119.4 ± 7.1	11.1 ± 4.7	3.9 ± 1.9	15.0 ± 4.7 (109)
1,000	90.8 ± 4.0	104.3 ± 4.8	113.2 ± 7.3	117.8 ± 7.1	8.9 ± 4.0	4.6 ± 2.2	13.5 ± 4.5 (99)
2,000	91.0 ± 5.1	102.8 ± 5.3	111.7 ± 6.8	117.2 ± 7.6	8.9 ± 3.7	5.5 ± 2.5	14.4 ± 5.1 (103)

(a) Data obtained from page 79 in the study report.
(b) Fasted body weight.
(c) Body-weight gain calculated by reviewer from individual body weight data on pages 202-203 of the study report, no statistical analysis done.

C. Food Consumption: Not determined.

D. Motor Activity: There were no significant treatment-related differences in motor activity at any time during the study (Table 4). However, on the day of treatment (day 1) there was a slight decreased motor activity in the high-dose males compared to controls, although, the difference from control values did not exceed the range of normal variability for animals of this age and strain from this laboratory. Complete recovery occurred by the next test occasion, seven days following treatment (day 8). The slight decrease in motor activity in the high-dose males correlate with an increased incidence of minimal level of activity in the open field and decreased responsiveness to sharp noise observed in these animals during the FOB evaluation. When the motor activity and FOB findings were combined they were considered to be a treatment-related effect, although minimal. The overall pattern suggest a slight transient decreased activity and reactivity in the high-dose males on the day of dosing which was most likely due to general malaise rather than to neurotoxicity. In the absence of any corroborating treatment-related gross pathological or neuropathological findings, the slight decreased motor activity on the day of dosing was not considered to be due to neurotoxicity *per se*.

TABLE 4: Motor Activity (a)

Sex	Day	Dose Level (mg/kg bw)			
		0	200	1,000	2,000
	Motor Activity (square root of total beam breaks ± SD)				
Male	Pre-treatment	9.88 ± 1.73	9.15 ± 1.64	9.15 ± 0.96	8.86 ± 1.58
	Day 1 (treatment)	8.60 ± 2.57	8.02 ± 1.51	8.21 ± 1.81	**6.16 ± 1.86**
	Day 8	8.11 ± 1.87	9.57 ± 2.98	8.94 ± 2.44	8.88 ± 2.09
	Day 15	8.18 ± 1.52	8.76 ± 1.63	8.15 ± 1.89	7.97 ± 2.05
Female	Pre-treatment	10.51 ± 1.50	10.47 ± 1.85	8.87 ± 1.31	9.18 ± 1.61
	Day 1 (treatment)	9.67 ± 2.12	9.00 ± 1.96	8.83 ± 1.00	8.46 ± 2.46
	Day 8	8.08 ± 2.45	9.97 ± 2.90	10.14 ± 3.81	10.20 ± 2.24
	Day 15	7.97 ± 2.77	10.00 ± 2.78	10.05 ± 2.50	10.86 ± 1.84

(a) Data obtained from pages 88-93 in the study report for motor activity and pages for locomotor activity. All test sessions consisted of six 8-minute epochs, totalling 48 minutes of testing for each animal.

E. FOB Evaluations: There were no significant treatment-related differences in FOB evaluations at any time during the study (Tables 5 and 6 for males and females, respectively). However, on the day of treatment (day 1) there was a slight increased incidence of minimal level of activity in the open field and decreased responsiveness to sharp noise in males at 2,000 mg/kg bw, although, the difference from control values did not exceed the range of normal variability for animals of this age and strain from this laboratory. Complete recovery occurred by the next test occasion, seven days following treatment (day 8). These FOB findings correlate with a slight decrease in motor activity in these animals. When the FOB and motor activity findings were combined they were considered to be a treatment-related effect, although minimal. The overall pattern suggest a slight transient decreased activity and reactivity in the high-dose males on the day of dosing which was most likely due to general malaise rather than to neurotoxicity. In the absence of any corroborating treatment-related gross pathological or neuropathological findings, the slight decreased level of activity in the open field and decreased responsiveness to sharp noise on the day of dosing were not considered to be due to neurotoxicity *per se*. Fore-limb and hind-limb grip strength, landing foot splay and rectal temperature, were not affected by treatment in males or females at any dose level (Table 7).

TABLE 5: FOB Incidence Summary - males (expressed as # animals with specified observation/# animals examined) (a)

Day	Observation		Dose Level (mg/kg bw)			
			0	200	1,000	2,000
Pre-treatment	Level of activity	- moderate	1/10	3/10	1/10	2/10
		- pronounced	9/10	7/10	9/10	8/10
	Responsiveness to sharp noise	- moderate	10/10	9/10	10/10	10/10
		- pronounced	0/10	1/10	0/10	0/10
Day 1 (treatment)	Level of activity	- minimal	3/10	4/10	2/10	7/10
		- moderate	5/10	6/10	7/10	3/10
		- pronounced	2/10	0/10	1/10	0/10
	Responsiveness to sharp noise	- minimal	0/10	2/10	1/10	4/10
		- moderate	9/10	8/10	9/10	6/10
		- pronounced	1/10	0/10	0/10	0/10
Day 8	Level of activity	- minimal	7/10	5/10	9/10	7/10
		- moderate	3/10	5/10	1/10	3/10
		- pronounced	0/10	0/10	0/10	0/10
	Responsiveness to sharp noise	- minimal	1/10	2/10	0/10	1/10
		- moderate	9/10	8/10	10/10	9/10
		- pronounced	0/10	0/10	0/10	0/10
Day 15	Level of activity	- none	0/10	1/10	0/10	0/10
		- minimal	8/10	9/10	10/10	9/10
		- moderate	2/10	0/10	0/10	1/10
		- pronounced	0/10	0/10	0/10	0/10
	Responsiveness to sharp noise	- minimal	2/10	4/10	0/10	3/10
		- moderate	8/10	6/10	10/10	7/10

(a) Data obtained from pages 67-77 in the study report.

TABLE 6: FOB Incidence Summary - females (expressed as # animals with specified observation/# animals examined) (a)

Day	Observation		Dose Level (mg/kg bw)			
			0	200	1,000	2,000
Pre-treatment	Level of activity	- moderate	2/10	0/10	2/10	1/10
		- pronounced	8/10	10/10	8/10	9/10
	Responsiveness to sharp noise	- moderate	10/10	9/10	10/10	9/10
		- pronounced	0/10	1/10	0/10	1/10
Day 1 (treatment)	Level of activity	- minimal	0/10	0/10	2/10	0/10
		- moderate	8/10	5/10	6/10	4/10
		- pronounced	2/10	5/10	2/10	6/10
	Responsiveness to sharp noise	- minimal	2/10	1/10	2/10	0/10
		- moderate	8/10	9/10	8/10	10/10
		- pronounced	0/10	0/10	0/10	0/10
Day 8	Level of activity	- minimal	3/10	4/10	4/10	1/10
		- moderate	7/10	5/10	3/10	4/10
		- pronounced	0/10	1/10	3/10	5/10
	Responsiveness to sharp noise	- minimal	1/10	2/10	1/10	0/10
		- moderate	8/10	8/10	9/10	10/10
		- pronounced	1/10	0/10	0/10	0/10
Day 15	Level of activity	- none	0/10	0/10	0/10	0/10
		- minimal	5/10	3/10	5/10	3/10
		- moderate	5/10	7/10	5/10	6/10
		- pronounced	0/10	0/10	0/10	1/10
	Responsiveness to sharp noise	- minimal	1/10	1/10	0/10	0/10
		- moderate	9/10	9/10	10/10	10/10

(a) Data obtained from pages 67-77 in the study report.

TABLE 7: FOB Measurements. (a)

Sex	Day	Dose Level (mg/kg bw)			
		0	200	1,000	2,000
Hind-limb Grip Strength (g ± SD)					
Male (n = 10 rats/dose)	Pre-treatment	172.0 ± 41.4	211.6 ± 41.8	184.7 ± 46.7	213.4 ± 63.2
	Day 1 (treatment)	216.3 ± 43.2	238.1 ± 46.1	196.3 ± 27.2	230.1 ± 36.5
	Day 8	281.5 ± 60.4	267.6 ± 39.2	245.5 ± 48.1	288.5 ± 40.1
	Day 15	273.5 ± 57.1	308.4 ± 39.7	259.9 ± 31.3	318.7 ± 60.6
Female (n = 10 rats/dose)	Pre-treatment	133.8 ± 21.1	141.7 ± 13.7	138.6 ± 26.6	147.4 ± 19.1
	Day 1 (treatment)	152.0 ± 22.6	155.5 ± 25.5	170.7 ± 18.4	160.1 ± 23.2
	Day 8	193.0 ± 33.6	191.0 ± 20.8	180.0 ± 38.1	183.7 ± 31.6
	Day 15	191.3 ± 27.5	184.1 ± 40.3	197.1 ± 30.2	191.9 ± 33.6
Fore-limb Grip Strength (g ± SD)					
Male (n = 10 rats/dose)	Pre-treatment	283.8 ± 62.5	286.2 ± 46.7	286.9 ± 71.5	315.8 ± 76.6
	Day 1 (treatment)	364.9 ± 94.3	410.9 ± 75.2	340.4 ± 44.4	393.7 ± 65.3
	Day 8	419.1 ± 98.8	398.2 ± 40.0	399.9 ± 103.8	404.6 ± 36.0
	Day 15	390.7 ± 92.1	395.0 ± 53.4	415.4 ± 88.0	406.9 ± 76.9
Female (n = 10 rats/dose)	Pre-treatment	214.2 ± 44.8	217.3 ± 52.3	225.2 ± 37.7	254.4 ± 57.4
	Day 1 (treatment)	255.7 ± 64.8	272.7 ± 74.7	268.1 ± 59.4	288.1 ± 26.7
	Day 8	282.7 ± 67.0	303.2 ± 73.9	300.3 ± 80.2	282.5 ± 56.0
	Day 15	287.8 ± 62.2	269.0 ± 70.4	315.2 ± 70.8	312.1 ± 77.5
Landing Foot splay (cm ± SD)					
Male (n = 10 rats/dose)	Pre-treatment	6.21 ± 0.67	6.22 ± 1.11	6.21 ± 0.92	6.13 ± 0.85
	Day 1 (treatment)	6.85 ± 1.00	6.70 ± 1.14	6.18 ± 0.49	6.38 ± 1.04
	Day 8	5.97 ± 0.55	6.17 ± 0.72	6.01 ± 0.77	6.18 ± 1.08
	Day 15	6.03 ± 0.64	6.22 ± 0.85	5.73 ± 0.50	5.97 ± 0.66
Female (n = 10 rats/dose)	Pre-treatment	4.75 ± 1.07	5.05 ± 0.77	5.10 ± 0.61	4.79 ± 0.57
	Day 1 (treatment)	5.73 ± 0.83	5.48 ± 0.73	5.30 ± 0.76	5.35 ± 0.44
	Day 8	5.39 ± 0.45	5.12 ± 0.77	5.21 ± 0.82	5.25 ± 0.39
	Day 15	4.82 ± 0.58	5.03 ± 0.44	4.72 ± 0.62	4.99 ± 0.33
Rectal Temperature (°C ± SD)					
Male (n = 10 rats/dose)	Pre-treatment	37.39 ± 0.41	37.50 ± 0.37	37.26 ± 0.49	37.64 ± 0.71
	Day 1 (treatment)	37.23 ± 0.38	37.19 ± 0.54	37.36 ± 0.52	37.12 ± 0.54
	Day 8	37.35 ± 0.35	37.40 ± 0.56	37.37 ± 0.39	37.53 ± 0.39
	Day 15	37.49 ± 0.34	37.55 ± 0.55	37.70 ± 0.37	37.60 ± 0.35
Female (n = 10 rats/dose)	Pre-treatment	37.10 ± 0.49	37.20 ± 0.62	37.28 ± 0.46	36.90 ± 0.46
	Day 1 (treatment)	37.43 ± 0.56	37.20 ± 0.60	37.26 ± 0.41	37.29 ± 0.64
	Day 8	37.68 ± 0.57	37.66 ± 0.59	37.73 ± 0.43	37.91 ± 0.29
	Day 15	37.80 ± 0.57	38.02 ± 0.33	37.79 ± 0.36	38.0 ± 0.39

(a) Data obtained from pages 81-87 in the study report.

F. Sacrifice and Pathology

1. Brain weight - No organ weight data was obtained in this study; therefore, brain weights were not provided in the study report. However, there were no treatment-related gross pathological or neuropathological findings or other correlated findings in the brain to suggest a treatment-related effect on brain weight.

2. Gross pathology - There were no treatment-related gross pathological observations.

3. Microscopic pathology - There were no treatment-related histopathological findings and no treatment-related

neuropathological findings in the central or peripheral nervous system. A low number of spontaneous lesions were identified in the control and high-dose animals (Table 8). These lesions were characterized as very slight degeneration in the trapezoid body (medulla oblongata), the cervical and lumbar spinal cord and trigeminal ganglia and mineralization of the cornea or blood vessels in proximity of the eye. The distribution of these lesions suggest that they were not treatment-related but reflected the occurrence of spontaneous lesions.

TABLE 8: Neuropathological Observations (incidence of specific finding / number of animals examined). (a)

Observation		Dose Level (mg/kg bw)			
		0	200	1,000	2,000
Males					
Brain - medulla oblongata	- degeneration of individual fibres, trapezoid body, very slight	1/5	-	-	2/5
Cranial Nerve - optic	- mineralization of blood vessels, unilateral/bilateral, very slight	3/5	-	-	2/5
Eyes	- mineralization of cornea, unilateral/bilateral, very slight	5/5	-	-	4/5
Spinal Cord - cervical	- degeneration of individual nerve fibres, very slight	1/5	-	-	0/5
Spinal Cord - lumbar	- degeneration of individual nerve fibres, very slight	0/5	-	-	0/5
Trigeminal Ganglia and Nerve	- degeneration of individual nerve fibres, very slight	0/5	-	-	1/5
Females					
Brain - medulla oblongata	degeneration of individual fibres, trapezoid body, very slight	1/5	-	-	0/5
Cranial Nerve - optic	- mineralization of blood vessels, unilateral/bilateral, very slight	3/5	-	-	3/5
Eyes	- mineralization of cornea, unilateral/bilateral, very slight	3/5	-	-	1/5
Spinal Cord - cervical	- degeneration of individual nerve fibres, very slight	1/5	-	-	0/5
Spinal Cord - lumbar	- degeneration of individual nerve fibres, very slight	1/5	-	-	0/5
Trigeminal Ganglia and Nerve	- degeneration of individual nerve fibres, very slight	0/5	-	-	0/5

(a) Data obtained from pages 96-98 in the study report.

III. DISCUSSION

A. Investigators' conclusions (extracted from page 9 of the study report): "XDE-570 caused a minor, transient depression of activity and depression of reactivity to a noise stimulus on the day of dosing (day 1) in male rats given 2000 mg/kg. Perineal soiling occurred in some high- and mid-dose female rats on day 2, and in a few high-dose female rats on day 3. Other minor differences were considered chance events, and not related to treatment. No treatment-related findings were present after day 3. Comprehensive neuropathological examination revealed no treatment-related findings. The no-observed-effect level was greater than 1000 mg/kg for male rats based on decreased activity and reactivity at 2000 mg/kg, and a NOEL of 200 mg/kg for female rats, based on perineal soiling at 1000 and 2000 mg/kg."

B. Reviewer comments: There were no treatment-related effects on mortality or adverse clinical signs. In the high-dose males, overall body-weight gain was approximately 21% lower compared to controls, although body weight at the termination of the study was comparable between the controls and the high-dose males. This was attributed to a lower body-weight gain (≈33%) in the high-dose males during the first week. On the day of treatment (day 1), there

264

was a slight transient decrease in motor activity, increased incidence of minimal level of activity in the open field and decreased responsiveness to sharp noise in males at 2,000 mg/kg bw. However, the difference from control values did not exceed the range of normal variability for animals of this age and strain from this laboratory and complete recovery occurred by the next test occasion, seven days following treatment (day 8). When the FOB and motor activity findings were combined they were considered to be a treatment-related effect, although minimal. The overall pattern suggest a slight transient decreased activity and reactivity in the high-dose males on the day of dosing which was most likely due to general malaise rather than to neurotoxicity. Fore-limb and hind-limb grip strength, landing foot splay and rectal temperature, were not affected by treatment in either sex at any dose level. There were no treatment-related gross pathological or histopathological findings and no neuropathological findings in the central or peripheral nervous system in either sex up to and including 2,000 mg/kg bw. In the absence of any corroborating treatment-related gross pathological or histopathological findings or neuropathological findings in the central or peripheral nervous system, the FOB and motor activity findings in males at 2,000 mg/kg bw on the day of dosing were not considered to be due to neurotoxicity *per se.*

The LOAEL for systemic toxicity was 2,000 mg/kg bw based on decreased body-weight gain, slight transient decreased motor activity, increased incidence of minimal level of activity in the open field and decreased responsiveness to sharp noise in males on the day of dosing. The NOAEL for systemic toxicity was 1,000 mg/kg bw.

The LOAEL for neurotoxicity was not determined. The NOAEL for neurotoxicity was 2,000 mg/kg bw, the highest dose tested.

C. <u>Study deficiencies:</u> No organ weight data was obtained in this study; therefore, brain weights were not provided in the study report. However, currently accepted guidelines for acute neurotoxicity studies, OECD 424 (Neurotoxicity Study in Rodents) and OPPTS 870.6200 (Neurotoxicity Screening Battery), do not indicate that brain weights are required. There were no treatment-related gross pathological or neuropathological findings or other correlated findings in the brain to suggest a treatment-related effect on brain weight. There were no study deficiencies which would impact on the outcome of the study; therefore, this study is classified as acceptable as an acute neurotoxicity study in rats (870.6200; OECD 424).