8-11-97

DATA EVALUATION RECORD

SAN 835H

Study Type: 81-8: Acute Neurotoxicity Study -Rats
Work Assignment No. 3-01M (MRID 44170145)

Prepared for

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DATA EVALUATION RECORD

STUDY TYPE: Acute Oral Neurotoxicity Study in Rats

OPPTS Number: 870.6200

OPP Guideline Number: §81-8

DP BARCODE: D232811
P.C. CODE: 005107

SUBMISSION CODE: S516012
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): SAN 835 H Technical (96.4% a.i.)

SYNONYMS: None

CITATION: Hughes, E.W. and D.P. Meyers (1996) San 835 H Neurotoxicity to rats by acute oral administration. Huntington Life Sciences Ltd., P.O. Box 2, Huntington, Cambridgeshire, PE18 6ES, England. Project Number SNC/186. May 30, 1996. MRID 44170145. Unpublished.

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EXECUTIVE SUMMARY:

In an acute neurotoxicity study (MRID 44170145), SAN 835 H technical (96.4% a.i.) was administered by gavage to Crl:CD BR rats (10/sex/group) at dose levels of 0, 125, 500 or 2000 mg/kg. The rats were evaluated for reactions in functional observations and motor activity measurements at 3 hours, 7 days, and 14 days postdosing. Histopathological evaluation on the brain and peripheral nerves was assessed after day 14.

San 835 H had no definite impact on neurotoxic responses. Although a few abnormalities were observed in the functional battery on the day of dosing. A decrease in immediate righting responses that was observed in several males in all treatment groups was not concentration-dependent. Nasal staining was observed in more rats in the 2000 mg/kg treatment groups (6 males; 3 females), but was not considered a definite or significant response to treatment. Lower mean brain weights in all female treatment groups lacked associated macroscopic and microscopic histopathological changes, and were only 4-5% lower than the control brain weight. Mean locomotor activities for the 2000 mg/kg female treatment groups was decreased on Days 7

(~ 27%, $p < 0.05$) and 14 (~15%, not significant) after dosing, but the pattern of activity for the individual animals was similar to the individual controls over time. There were no definite treatment-related differences in body weights or food consumption in any of the treatment groups. There was no evidence of treatment-related neuropathology in the 2000 mg/kg treatment group. **A LOAEL was not established. The NOAEL for acute neurotoxicity is 2000 mg/kg (the limit dose).**

This study is classified **ACCEPTABLE** and satisfies the guideline requirement for an acute neurotoxicity study in rodents (§81-8).

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

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: SAN 835 H Technical
   Description: Beige powder
   Lot/Batch #: 6500-19
   Purity: 96.4% a.i.
   Stability of compound: Reported to expire in March 1997 [page 12]
   CAS #: Not provided
   Structure: Not provided

2. Vehicle: 1% w/v Aqueous methylcellulose

3. Test animals: Species: Rat
   Strain: Crl:CD BR
   Age (approximate) at study initiation: males, 47 days; females, 47 days
   Weight at study initiation: Males, 206-208 g; females, 145-150 g
   Source: Charles River Breeding Laboratories, Margate, Kent, England
   Housing: Individually housed in suspended cages with wire mesh floors
   Diet: Pelleted SDS Rat and Mouse Maintenance Diet, ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
      Temperature: 22 ± 2 C
      Humidity: 47 ± 17%
      Air changes: Not reported
      Photoperiod: 12-Hour light/dark cycle
   Acclimation period: 12 Days for males; 19 days for females

B. STUDY DESIGN

1. In-life dates - Males: 10/16/95 to 11/03/95
Females: 10/23/95 to 11/10/95

2. Animal assignment

Animals were selected based on health and body weights and were randomly assigned to the test groups shown in Table 1. The groups were stratified by bodyweight so that initial group means were approximately equal.

TABLE 1: STUDY DESIGN

Test Group	Dose (mg/kg)	Males	Females
Control	0	10	10
Low (LDT)	125	10	10
Mid (MDT)	500	10	10
High (HDT)	2000	10	10

Rats were orally administered, via gastric intubation, a single dose of San 835 H dissolved in 1% methylcellulose at a dosing volume of 1 mL/100 g bodyweight (10/mL/kg). Animals were fasted overnight prior to dosing. Control animals received vehicle alone. The dosage volume administered to individual rats (10 mL/kg) was adjusted according to the most recently recorded bodyweight and to the nearest 0.1 mL. During dosing, the suspensions were stirred with a magnetic stirrer. Animals were dosed using a graduated syringe and a rubber catheter (Ch 8 or 10) inserted into the stomach.

The high dose of 2000 mg/kg is the limit dose as specified in Subdivision F guidelines. The low and intermediate doses were selected to give a geometric progression of dosages.

3. Dosing solution preparation and analysis

The test substance was prepared for oral dosing by grinding the powder in a mortar with a small amount of 1% w/v aqueous methylcellulose, and adding additional vehicle to bring the suspension to the desired concentration. The suspension was mixed using a high shear homogenizer. A series of suspensions was made by serial dilution to yield a constant dose volume of 10 mL/kg body weight. Fresh dosing solutions were prepared daily for each group to be treated that day.

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In order to establish the adequacy of the preparation methods, homogeneity, concentration, and stability tests were conducted prior to the start of the study. Bulk formulations containing the test substance at nominal concentrations of 1 or 200 mg/mL were thoroughly mixed by shaking and magnetic stirring. Samples from the top, middle, and bottom portion of each formulation were collected after 5 minutes, 0.5 hours, and 1 hour of magnetic stirring. Additional samples were collected for analysis after the formulation was stored at 21°C for 4 hours, and at 4°C for 24 hours. The solutions were remixed by inversion and magnetic stirring, then sampled at intervals as described.

Results:

Homogeneity (0 hour):

1 mg/mL: 95.2-96.7% of nominal
200 mg/mL: 98.5-99.5% of nominal

The homogeneity of the test solutions was confirmed following 0.5 and 1 hour of magnetic stirring was confirmed; recoveries were 91.7-92.5% of nominal for the 1 mg/kg solution and 96.5-99% of nominal for the 200 mg/kg solution. In addition, the test solutions were successfully resuspended after 4 hours of storage at ambient temperature, and after 24 hours of refrigeration; recoveries were 89-92% of nominal for the 1 mg/kg solution and 98-99% of nominal for the 200 mg/kg solution.

Concentration:

12.5 mg/mL: 87.2-88% of nominal
50 mg/mL: 92.2-93% of nominal
200 mg/mL: 95-96.5% of nominal

Stability:

storage at room temperature, 4 hours:

1 mg/mL: 88.1-91.5% of nominal
200 mg/mL: 98.5-99.5% of nominal

storage at 4°C, 24 hours:

1 mg/mL: 90.4-90.8% of nominal
200 mg/mL: 96.5-97.0% of nominal

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

4. Statistics

Bodyweight, bodyweight gain, and food consumption recorded during the functional observation battery (FOB), grip strength, hindlimb splay, activity and rearing counts, rectal temperature, and brain measurements were analyzed using a one-way analysis of variance. With the exception of predose data, analyses of variance were followed by the Student's t test and William's t test for a dose-related response. Kruskal-Wallis analyses

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were followed by the nonparametric equivalents of the t test and Shirley's test. For predose data, analyses of variance were followed by the Student's t test. When a difference between the control and treated groups was indicated, the data were analyzed using the Linear by Linear Association test. A one-tailed test was applied for abnormal gait, palpebral closure and tremors. A two-tailed test was applied for all other parameters.

5. Positive Control Data Base.

The positive control data base from the Huntingdon Laboratory was previously reviewed by HED and determined to be acceptable (refer to HED Doc. No.: 012567, dated April 9, 1998).

C. METHODS

1. Observations

Animals were observed and palpated at least once daily for signs of behavioral change, reaction to treatment or ill health. Animals were observed twice daily, once in the morning and once in the afternoon, for moribundity and mortality.

2. Body weight

Animals were weighed one week prior to dosing, on the day of dosing, and at weekly intervals following dosing. Animals were also weighed on each occasion that the functional observational battery and motor activity assessment was performed.

3. Food consumption

Food consumption for each animal was measured weekly beginning 6 days (Week -1) prior to dosing through Week 2 following dosing. Food intake per rat (g/rat/week) was calculated based on the amount of food given to and left by each rat for each period of recording. Food efficiency (food consumption/body weight gain) was calculated for each test group during weeks 1 and 2 following dosing.

4. Neurobehavioral Studies

Motor Activity - Motor activity of all animals was measured at approximately the same time of day, before initiation of treatment (not further defined), and on days 0 (3 hours after dosing), 7 and 14 after dosing. Three hours was the estimated time of peak effect based in an acute study (SNC 188a/951596/AC). The placement of each animal within a cage was balanced as much as possible across groups. The test session was initiated when all animals were placed in cages, and lasted one hour for each animal. Motor activity was monitored using a Colbourn Infra-Red Activity Monitoring System which

uses an infra-red detector. For each animal, the time and number of events spent in no movement, locomotor, and non-locomotor activity were recorded. Data were collected every 2 minutes.

Functional Observational Battery - A functional observational battery (FOB) was performed on all animals at approximately the same time of day, before initiation of treatment and on study days 0 (3 hours post dosing), 7, and 14. The following parameters were evaluated:

	HOME CAGE OBSERVATIONS		OBSERVATIONS IN THE ARENA
X	Posture in cage	X	Convulsions, tremors, twitches
X	Convulsions, tremors, twitches	X	Level of activity in arena
X	Spontaneous vocalizations	X	Level of arousal
X	Palpebral closure	X	Rearing count
		X	Grooming
		X	Assessment of gait
	OBSERVATIONS IN THE HAND	X	Presence of fecal boluses, urine
X	Ease of removing rat from cage		MANIPULATIONS
X	Ease of handling rat		
X	Salivation/lacrimation	X	Approach response
X	Palpebral closure	X	Touch response
X	Exophthalmus	X	Startle response
X	Piloerection	X	Righting reflex
X	Vocalization on handling	X	Pupil response
		X	Grip strength; fore and hindlimb
		X	Landing foot splay
		X	Body temperature
		X	Body weight

5. Sacrifice and Pathology

All animals were sacrificed on day 15 by intraperitoneal injection of sodium pentobarbital and perfused *in situ* with heparinized 0.7% sodium nitrite followed by a glutaraldehyde/paraformaldehyde solution. Neuropathological examination was

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conducted on tissues from five rats/sex from the control and high dose groups. The following tissues were examined:

	CENTRAL NERVOUS TISSUES		PERIPHERAL NERVOUS TISSUES
X	Forebrain[a]	X	Gasserian ganglia
	Center of cerebrum	X	Cervical dorsal root ganglia
X	Midbrain[a]	X	Lumbar dorsal root ganglia
X	Cerebellum[a]	X	Dorsal and ventral fibers (cervical level)[c]
X	Pons[a]	X	Dorsal and ventral root fibers (lumbar level)[c]
X	Medulla oblongata[a]	X	Proximal sciatic nerve
X	Lumbar spinal cord[b]	X	Sural nerve
X	Cervical spinal cord	X	Tibial nerve
X	Lumber dorsal root ganglia		

[a] Cross sections of these tissues were evaluated.
[b] Cross and longitudinal sections of these tissues were evaluated.
[c] Longitudinal sections of these tissues were evaluated.

Brains, spinal cords, ganglia, and dorsal and ventral root fibers were embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin. Peripheral nerves from the right side were embedded in epon, sectioned, and stained with toluidine blue.

III. RESULTS

A. Observations

1. Mortality - No rats died during the study.

2. Clinical signs - No treatment-related differences in clinical signs were observed in any of the test groups immediately following dosing or during the 2-week observation period.

B. Body weight and body weight gain

No differences in body weights or body weight gains were observed between the treatment and corresponding control groups. Final mean body weights for all test groups were 301-312 g for males and 204-209 g for females.

C. Food consumption

A statistically significant increase in food consumption was noted in the high dose group for cumulative intake over the 1-2 week period (14 day period) in males. The mean values were 396±21.3, 421±17.4, 413±29.4 and 421±25.5 ($p < 0.05$)for the control, 250, 500 and 2000 mg/kg dose groups meaning that the high dose group may have consumed 6.3% more feed. It is also noted that during pretest, this high dose group also apparently consumed about 4.3% more. This apparent increase in food consumption is being dismissed as an effect because the 250 mg/k or low dose group also had an apparent increase of 6.3% in food intake but this did not reach statistical significance.

In conclusion, does not consider that there is an effect of treatment on food consumption.

D. Functional Observational Battery

A possible effect on the immediate righting response on the day of dosing (3 hours postdose) and on day 7 was noted. For example, this parameter was impaired in 6/10 males in the 125 and 2000 mg/kg groups ($p=0.0305$) compared to no impairment in the controls (Table 2). A slower speed of the righting response was also observed on Day 7 after dosing; 3-5 males in each treatment group were affected compared to no impairment in the controls. Females did not appear to be affected.

Table 2. The incidence of rats with immediate righting response following a single oral dose of SAN 835H Technical at 125, 500 or 2000 mg/kg.[a]

Test Group	Number of rats with immediate righting response	
	Males	Females
0 mg/kg		
Predose	8/10	9/10
3 hour	10/10	10/10
7 day	10/10	9/10
14 day	7/10	8/10
125 mg/kg		
Predose	9/10	10/10
3 hour	4/10[b]	10/10
7 day	5/10	9/10
14 day	6/10	8/10
500 mg/kg		
Predose	10/10	9/10
3 hour	8/10	8/10
7 day	7/10	10/10
14 day	6/10	7/10
2000 mg/kg		
Predose	8/10	10/10
3 hour	4/10[b]	8/10
7 day	6/10	9/10
14 day	8/10	9/10

[a] Data obtained from Table 4, pages 34-36 in the study report.
[b] Significantly difference from the control, p=0.0305[1].

Conclusion (Righting Reflex). HED does not consider that the incidence of slower immediate righting reflex supports an effect of treatment in males. There is no similar support such as other evidence of lethargy or decreased motor activity. At both intervals where there are some apparent decreases (i.e. day 0 and day 7) there is no dose response with the low and high dose groups being equal at day 0 and the low dose actually having more animals affected than the high dose at day 7.

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[1]Secondary review of the study noted that the study report does not indicate that the 125 mg/kg dose group is statistically significant but the contractor reviewer indicates that this is statistically significant. Since both he high dose and low dose response was 6/10, it is a fair assumption that both are statistically significant.

The incidence of nasal staining was significantly increased on the day of dosing in the 2000 mg/kg group males (6/10; p=0.0034) and females (3/10; p=0.0154) compared to the controls (2/10 males; 0/10 females). The low and mid dose groups were equivalent to or less than the control for males but there was also one incident in the 500 mg/kg dose group females.

A significant ($p<0.05$) increase in rearing counts was observed in the 2000 mg/kg males on the day of dosing compared to the controls (3 vs. 0 counts).

Effects observed on the day of dosing (3 hours postdose) that were not clearly treatment-related were

-*hunched posture* in 1/10 of the 500 mg/kg females and 1/10 males and 1/10 females treated at 2000 mg/kg, unsteadiness in the arena in 1/10 males treated at 500 or 2000 mg/kg.

-*soft feces* in 1 or 2 males treated at 500 or 2000 mg/kg. Effects observed in the arena on Day 7 after dosing.

-*increased incidence of defecation* in the 2000 mg/kg group males, The increased incidence of defecation in the 2000 mg/kg group males was significant (p=0.0182; 3/10) compared to the controls (0/10), and was not observed in treated females during any observation period.

-*urination* in the 500 and 2000 mg/kg group males. The increased incidence of urination in the 500 and 2000 mg/kg group males (4-5 rats/group) compared to the controls (0/10) was not concentration-dependent or statistically significant.

-*decreased activity counts* at day 14 in the 2000 mg/kg females (18) compared to the controls (28),

-*decreased rearing counts* in all female treatment groups (15-21/group) compared to the controls (28). Although these decreased counts were statistically significant ($p<0.05$ or $p<0.01$), they were not concentration-dependent, were not observed in the corresponding male treatment groups, and were not supported by any significant changes in large movement locomotor activity.

Conclusion (Other FOB parameters). The presence of nasal staining is considered possibly related to treatment and the NOEL and LOEL are 500 and 2000 mg/kg for both sexes for systemic effects. HED does not consider that nasal staining is a neurotoxic effect. The nature of this nasal staining is not defined. It could be the secondary result of some blood effect (if the

staining was red or brown) or it could be some artifact of the test material itself being somehow migrated to the nasal area (a unlikely possibility since the rats do not have a vomiting or regurgitating reflex). It may be a residue of incomplete intubation of the test material. The presence of this effect and its possible relationship to treatment is noted. It's frequency of occurrence or severity is not considered sufficient for risk assessment purposes and it is not recommended that it be included in the NOAEL and LOAEL statement for this study.

All other parameters that show some possible indications of effects are not considered of sufficient magnitude or consistency to be considered to be related to treatment.

E. Motor Activity Measurements

All test groups, including the controls, exhibited decreased mean locomotor activities at 3 hours postdose compared to their mean predose mean locomotor activities. For example, the control group males had a mean of 750±328.9 (standard deviation of 44%) at pretest and only 306±131.4 or approximately a 60% decrease. On days 7 and 14, the control mean values were again near the value of 770 counts with large standard deviations (i.e. ~35%). It was also noted that the 500 mg/kg dose group females were much lower (30%) than the control group at pretest ($p < 0.01$).

At 3 hours postdosing, there were no statistical differences in the mean large movement counts for either the males or females. The mid dose female group was again about 30% lower but not statistically significant.

At day 7, there was noted a decrease in mean count for the high dose females (27%, $p < 0.05$) but by day 14 there was no statistical difference although the mean was 15% lower.

The individual animal data suggested that the mean locomotor activity value for each group was highly influenced by a few animals. The pattern of activity for the individual animals showed approximately the same degree of decline and increase as was observed in the individual controls.

Conclusion (motor activity): The NOAEL for motor activity is > 2000 mg/kg. There were no effects on motor activity which HED considered related to treatment.

F. Sacrifice and Pathology

Absolute brain weights for all female treatment groups were significantly ($p<0.05$) lower than the control weights; the decrease brain weights were not concentration-dependent, were only 4-5% lower than the controls, and were not observed in treated males (Table 3). There were no intergroup differences in mean brain length and width. HED does not consider that the difference in brain weight were related to treatment.

Table 3. Mean brain weights for control and treatment groups.[a]

Dose Group (mg/kg)	Brain Weight (g)	
	Males	Females
0	1.564±0.0465	1.474 ±0.0655
125	1.576	1.413* (4.13%)
500	1.591	1.397*(5.22%)
2000	1.605	1.416*(3.93%)

[a] Data obtained from Table 13, page 46, of the study report.
* Significantly different from the control, $p<0.05$.

No macroscopic or microscopic findings were observed in any of the nervous system tissues in the treated rats, based on histological examination of the central nervous tissues, spinal cords with ganglia, and the peripheral nerves of the control and high dose (2000 mg/kg) groups (5 rats/sex/group examined). A single treated male exhibited trace focus of necrotic ganglion cells and inflammatory cells in a Gasserian ganglion that was not clearly attributable to treatment. Both control and treated rats exhibited a low incidence of trace axonal degeneration (1 or 2 rats/group) that was reported to be consistent with normal background [page 28].

III. DISCUSSION

A. Investigator's Conclusions

The study authors concluded that a single oral dose of SAN 835 H Technical at 125, 500 or 2000 mg/kg did not cause any neurotoxic effects in rats. The authors concluded (page 10 of the study report) that "there were a few changes on the functional observational battery on the day of dosing but these were interpreted as indicating as acute systemic response and not a neurotoxic response" The authors also noted the decrease in brain weigh in females but in the absence of any treated behavioral changes or neuropathology, this was not considered to be of toxicological importance.
The authors did not assign a NOAEL and LOAEL for systemic effects.

B. Reviewer's Discussion (as provided by the contractor)

The postdosing observations of male or female rats treated with a single dose of SAN 835H technical to rats at 125, 500 or 2000 mg/kg are variable, since the effects were not clearly neurotoxic or acute systemic responses. Differences in righting response, the

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incidence of nasal staining, and absolute brain weights in one or more treatment groups were not clearly attributable to treatment.

Fewer males in all treatment groups had an immediate righting response on the day of dosing that may have been a neurotoxic response in that the equilibrium of the test animals was disturbed. However, the effect was not concentration-dependent, and while a slower righting response was observed in a similar number of males in all treatment groups on Day 7 (3-5/group), it was also observed in 3/10 control males on Day 14 after dosing. Furthermore, no other differences in parameters in the functional observation battery of the male treatment groups suggested neurotoxic effects. The fact that fewer treated males had an immediate righting response could be due to the methods of handling or treating (gavage) the test animals or some other environmental stress. It was also noted that from Day 7 to Day 14, the 125 and 2000 mg/kg male treatment groups showed improvement in terms of the number of males with an immediate righting response, whereas the control and 500 mg/kg male groups showed an increase in the number of males with an impaired righting response.

Other observed effects were not clearly treatment-related. The increased incidence of nasal staining in the 2000 mg/kg males and females on the day of dosing is not considered a neurotoxic or an acute systemic response. Two control males exhibited nasal staining on the day of dosing, which suggests that a factor other than treatment caused nasal staining. Lower mean brain weights (not statistically significant) for the female treatment groups do not appear to be the result of neurotoxicity since there were no associated macroscopic and microscopic histopathological changes, the weights were only 4-5% lower than the control brain weight, and similar decreases were not observed in the male treatment groups. Differences in functional observational battery parameters and locomotor activities observed in the treatment groups appeared to be isolated, rather than treatment-related effects.

In conclusion, none of the effects observed in the treatment groups are clearly treatment-related. There were no treatment-related differences in body weights or food consumption in any of the treatment groups. There was no evidence of neuropathology in the 2000 mg/kg treatment group. Based on these findings, the NOAEL could be established at 2000 mg/kg for this study.

IV. STUDY DEFICIENCIES

No study deficiencies were indicated to compromise the interpretation of the study.

The following Appendix was photocopied from the study report and is attached to the original review and may not be included with the electronic copy of this DER.

Appendix 4. Locomotor Activity (for females).

APPENDIX 4

Locomotor activity

Animal no.	Total time spent in locomotor activity (secs) when tested during:			
	Predose	Day 0	Day 7	Day 14
Group 1	Sex f			
41	641	181	471	503
42	579	336	539	844
43	573	313	453	303
44	754	346	398	629
45	522	342	519	691
46	717	319	496	464
47	974	492	434	1046
48	759	408	615	506
49	605	435	768	466
50	554	185	488	430
Group 2	Sex f			
51	730	278	689	885
52	399	132	408	450
53	647	395	593	509
54	511	156	431	459
55	476	188	523	345
56	618	449	511	613
57	711	321	571	535
58	898	487	633	628
59	360	187	719	509
60	774	445	1136	572
Group 3	Sex f			
61	231	248	369	651
62	355	294	688	758
63	466	414	358	579
64	329	275	335	528
65	711	182	313	329
66	681	117	339	316
67	541	203	279	345
68	593	297	458	368
69	266	56	255	277
70	522	217	377	445
Group 4	Sex f			
71	629	542	289	301
72	486	535	416	703
73	352	187	220	487
74	804	383	624	714
75	800	227	348	701
76	713	606	545	568
77	430	122	271	196
78	671	540	393	681
79	499	106	279	268
80	640	293	406	365