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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUL 2 2 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Barium Metaborate - Draft Report of a Range-finding Acute Neurotoxicity Study in Rats; **6(a)(2)**

TO: Barry O'Keefe
PM Team Reviewer (72)
Reregistration Branch, SRRD (H7508C)

FROM: Linda L. Taylor, Ph.D. Linda Lee Taylor 7/20/92
Toxicology Branch II, Section II,
Health Effects Division (H7509C)

THRU: K. Clark Swentzel K. Clark Swentzel 7/20/92
Section II Head, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia van Gemert, Ph.D. Marcia Gemert 7/21/92
Chief, Toxicology Branch II/HFAS/HED (H7509C)

Registrant: Buckman Laboratories International, Inc.
Chemical: Barium metaborate
Synonym: Busan 11-M1
Case No.: 818581
Caswell No.: 071
Submission No.: S421051
Identifying No.: 011101
DP Barcode: D180239
MRID No.: 423436-01
Action Requested: Please review MRID 42343601 for Guideline 81-8-SS. As per the 6(a)(2) screening team, this study is to be reviewed under a normal time schedule of 90 days.

Comment: The Registrant submitted this draft report under FIFRA 6(a)(2) "for the following possible adverse effect: Gait abnormalities (rocking, lurching and swaying) and reduced or absent forelimb/hindlimb grasp were consistently the major clinical findings in males and females at dose levels of 50.0, 100.0, 200.0, 400.0 and 600 mg/kg. ... The dose levels of 400 and 600 mg/kg produced mortalities in females." Additionally, it was stated in the cover letter that this effect has not been previously reported for this chemical.

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TB II disagrees with this latter statement. The Registrant submitted the results of this range-finding study previously in connection with the protocol for the acute neurotoxicity study on Busan 11-M1 and dose selection.

The "AUDITED DRAFT" of the study: A Range-Finding Acute Study of Busan 11-M1 in Rats has been reviewed, and the DER is appended. Under the conditions of the study, administration of a single dose of Busan 11-M1 via gavage to rats at dose levels of 12.5, 25, 50, 100, 150, 200, 400, and 600 mg/kg resulted in death at the 400 and 600 mg/kg dose levels in females only and several clinical signs indicative of neurological involvement, which included gait abnormalities, reduced/absent forelimb/hindlimb grasp reflex, and reduced/absent surface righting reflex. A no-effect dose was observed at 25 mg/kg. Dose levels of 175, 200, and 250 mg/kg were administered similarly to clarify selection of a benchmark dose level and estimate the time of peak neurologic effect for a subsequent acute neurotoxicity study. It was determined that the peak effect was reached at 3-5 hours post dose and the benchmark dose level was estimated to be 200 mg/kg. Doses of 25, 50, 100 and 200 mg/kg were selected for the acute neurotoxicity study with Busan 11-M1 in rats, and the time to peak effect was estimated to be ≈ 4 hours following dosing.

A quality assurance statement was provided in this DRAFT report, but it was not signed. It stated that the "findings from review of the final report were documented and reported to the study director." It is not apparent to this reviewer why a draft of the final report, which is not signed either, was submitted instead of the final report since, according to the quality assurance statement, there is a final report. Additionally, the results of this study were reported to the Agency previously in relation to the protocol for the acute study. Since the findings of this study have been reported to the Agency in this DRAFT, the final report, when submitted, should not be submitted as 6(a)(2) data.

CONCLUSION

This study is a range-finding study, which does not satisfy any guideline requirement per se (nor was it intended to), but the report is apparently a DRAFT, which is not signed, and the purity of the test material and analysis of the test material formulations were not provided. This study is classified not acceptable, but it may be upgraded with the submission of information on the test material purity/formulation analyses, a final **signed** study report, and a **signed** quality assurance statement. Additionally, a summary table of the clinical findings should be provided.

NOTE: The "bean sheet" indicated that this study is to be reviewed under a normal time schedule of 90 days; however, TB II notes that on the "bean sheet" the study was received on 06/08/92 and was sent to TB II on 07/02/92; the Admin due date is 07/27/92.

Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 7/20/92
Tox. Branch II, Section II (H7509C)
Secondary Reviewer: K. Clark Swentzel K. Clark Swentzel 7/20/92
Tox. Branch II, Head Section II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Range-finding acute neurotoxicity - rats

TOX. CHEM. NO.: 071

MRID NO.: 423436-01

TEST MATERIAL: BUSAN 11-M1

SYNONYMS: barium metaborate

STUDY NUMBER: WIL-94045/WIL-94045A

SPONSOR: Buckman Laboratories International, Inc.

TESTING FACILITY: WIL Research Laboratories, Inc., Ashland, OH

TITLE OF REPORT: A Range-Finding Acute Study of BUSAN 11-M1 in Rats

AUTHOR: IC Lamb

REPORT ISSUED: October 15, 1991

QUALITY ASSURANCE: A quality assurance statement was provided (page 24), but it was not signed. It states that the "findings from review of the final report were documented and reported to the study director." It is to be noted that the title page (only) indicates that this report is an AUDITED DRAFT, which is not signed either. It is not apparent to this reviewer why a draft of the final report was submitted instead of the final report since, according to the quality assurance statement, there is a final report.

CONCLUSIONS: Under the conditions of the study, administration of a single dose of Busan 11-M1 via gavage to rats at dose levels of 12.5, 25, 50, 100, 150, 200, 400, and 600 mg/kg resulted in death at the 400 and 600 mg/kg dose levels in females only and several clinical signs indicative of neurological involvement, which included gait abnormalities, reduced/absent forelimb/hindlimb grasp reflex, and reduced/absent surface righting reflex. A no-effect dose was observed at 25 mg/kg. Dose levels of 175, 200, and 250 mg/kg were administered similarly to clarify selection of a benchmark dose level and estimate the time of peak neurologic effect for a subsequent acute neurotoxicity study. It was determined that the peak effect was reached at 3-5 hours post dose and the benchmark dose level was estimated to be 200 mg/kg. Doses of 25, 50, 100 and 200 mg/kg were selected for the acute

neurotoxicity study with Busan 11-M1 in rats, and the time to peak effect was estimated to be ≈ 4 hours following dosing.

Classification: Not acceptable. This study is a range-finding study, which does not satisfy any guideline requirement per se (nor was it intended to), but the report is apparently a DRAFT, which is not signed, and the purity of the test material and analysis of the test material formulations were not provided. This study may be upgraded with the submission of information on the test material purity/formulation analyses, a final **signed** study report, and a **signed** quality assurance statement.

A. MATERIALS:

1. Test Compound: BUSAN 11-M1; Description: white powder; Batch #: Lot # 1-9769; Purity: % not provided; stated that it was the Sponsor's responsibility, 100% was assumed for purposes of dose preparation.

2. Test Animals: Species: rat; Strain: Sprague-Dawley Crl:CD®BR; Age: ≈ 6/7 weeks old at randomization; Weight: males 167-178/203-266 g, females 151-160/166-209 g; Source: Charles River Breeding Laboratories, Inc., Portage, Michigan.

3. Statistics: None.

B. STUDY DESIGN

1. Methodology: This study consisted of two phases: the initial phase incorporated eight dose levels and the second phase 3 (to clarify selection of a benchmark dose and the time to peak effect of dose administration). Twenty-six males and 26 females were assigned (computer randomization procedure-body weight stratification in a block design) to one of eight/three groups as shown below, each composed of the # rats/sex indicated, and administered the test material as a single dose (gavage; dosing volume: 5 mL/kg). Appropriate amounts of the test material were mixed with the vehicle (0.5% aqueous methylcellulose), prior to dosing. The formulations were stirred continuously throughout the dosing procedure and visually inspected for homogeneity prior to dosing. Dosages were calculated based on the animal's body weight [not fasted], which was measured prior to dosing. Following dosing, the animals were observed for 7 days.

animals in each group

Study/Dose Levels	MALES	FEMALES
WIL-94045		
12.5	2	2
25.0	2	2
50.0	2	2
100.0	2	2
150.0	2	2
200.0	2	2
400.0	1	1
600.0	1	1
WIL-94045A		
175.0	4	4
200.0	4	4
250.0	4	4

The rats were housed individually during the study and were fed a basal ration of Purina® Certified Rodent Chow® 5002, which along with tap water were available ad libitum.

RESULTS

No information was provided regarding the homogeneity other than as noted above. No data on the analysis of the test material formulations were provided. The expiration date on the label of the test material was 4/22/93.

2. Clinical Observations: The animals were observed twice daily for mortality and moribundity. Prior to dosing, approximately every hour for 8 hours subsequent to dosing, and once a day thereafter, each animal received a detailed clinical examination, which, in addition to changes in the overall general appearance and condition of the animal, consisted of placing the animal in an open field arena (2 feet x 2 feet x 0.5 feet) for ≈ one minute and arousal, surface righting reflex, and gait were assessed (see below).

Surface righting reflex - animal placed supine in open field arena, and the ability to return to a normal position was recorded as present or absent (both phases).

Posture and gait abnormalities - assessed as present or absent in WIL-94045; gait abnormalities ranked in WIL-94045A:

0 = absence of gait abnormalities
1 = gait abnormalities present
2 = gait abnormalities slight
3 = gait abnormalities moderate
4 = gait abnormalities severe
5 = animal prostrate

Forelimb and hindlimb grasp reflexes - animal allowed to grasp an object and any impairment was recorded as present or absent in WIL-94045 and ranked in WIL-94045A:

0 = forelimb/hindlimb grasp normal
1 = slight reduction in forelimb/hindlimb grasp
2 = moderate reduction in forelimb/hindlimb grasp
3 = severe reduction in forelimb/hindlimb grasp
4 = forelimb/hindlimb grasp absent

Additionally, individual body weights were recorded one day prior to study and on days 0, 7, and 8 of study.

RESULTS

Survival and Clinical Observations - WIL-94045

The two females at the two highest dose levels were found dead (400 mg/kg on day of treatment, approximately 6 hours post dose; 600 mg/kg on day 1), and each had displayed (prior to death) the same clinical signs observed in the survivors. The predominant clinical signs were gait abnormalities (rocking, lurching, or swaying) initially observed at one hour post dose in rats of both sexes at 100, 150, 200, 400, and 600 mg/kg. Two hours after dosing, the 50 mg/kg females also displayed gait abnormalities, as did one female at 12.5 mg/kg. The greatest incidence of gait abnormalities in these groups occurred at ≈ 4 hours post dose and persisted in all groups through 8 hours following dosing. The 400 mg/kg male and the 600 mg/kg male were both prostrate beginning at the 5- and 7-hour post dose observation periods, respectively. Reduced forelimb/hindlimb grasp was observed initially in the 600 mg/kg female one hour post dose. Reduced or absent forelimb/hindlimb grasp was noted in one 150 mg/kg female at 3 hours post dose only, in one 200 mg/kg female at 2-7 hours post dose, in both 200 mg/kg males at 4 and 6 hours post dose and in one at 5 and 7 hours post dose. Absent forelimb/hindlimb grasp persisted in the 400 mg/kg male and in the 600 mg/kg male and female through the last observation period (8 hours post dose). Surface righting reflex was impaired or absent from 3 hours on in one 200 mg/kg female and in the 400 mg/kg and 600 mg/kg animals. Splayed hindlimbs were observed in one 150 mg/kg females at one hour post dose and in one 600 mg/kg female at 3 hours post dose. At ≈ 24 hours post dose, the following clinical signs were still evident: gait abnormalities in the 200 mg/kg females and in the 400 and 600 mg/kg males; and reduced/absent forelimb/hindlimb grasp reflex, hypoactivity/prostration, and absent surface righting reflex in the 600 mg/kg male.

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Clinical Findings*

Sign/dose/hours	1	2	3	4	5	6	7	8
gait abnormalities								
males								
12.5	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
25	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
50	0/2	0/2	0/2	1/2	0/2	0/2	0/2	0/2
100	1/2	2/2	1/2	1/2	1/2	1/2	1/2	1/2
150	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2
200	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2
400	1/1	1/1	1/1	1/1	1/1	1/1	0/1	0/1
600	1/1	1/1	1/1	1/1	0/1	0/1	0/1	0/1
females								
12.5	0/2	1/2	0/2	1/2	1/2	0/2	0/2	0/2
25	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
50	0/2	2/2	1/2	2/2	2/2	0/2	1/2	1/2
100	1/2	0/2	2/2	2/2	2/2	2/2	2/2	2/2
150	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2
200	2/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2
400	1/1	1/1	1/1	1/1	0/1	-	-	-
600	1/1	1/1	1/1	1/1	0/1	0/1	0/1	0/1
reduced/absent forelimb grasp								
males								
12.5	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
25	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
50	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
100	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
150	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
200	0/2	0/2	0/2	2/2	1/2	0/2	1/2	0/2
400	0/1	1/1	0/1	1/1	1/1	1/1	1/1	1/1
600	0/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1
females								
12.5	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
25	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
50	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
100	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
150	0/2	0/2	1/2	0/2	0/2	0/2	0/2	0/2
200	0/2	1/2	2/2	2/2	2/2	2/2	1/2	0/2
400	0/1	0/1	1/1	1/1	1/1	-	-	-
600	0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
reduced/absent hindlimb grasp								
males								
12.5	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
25	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
50	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
100	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
150	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
200	0/2	0/2	0/2	2/2	1/2	2/2	1/2	0/2
400	0/1	1/1	0/1	1/1	1/1	1/1	1/1	1/1
600	0/1	1/1	0/1	1/1	1/1	1/1	1/1	1/1
females								
12.5	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
25	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
50	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
100	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
150	0/2	0/2	1/2	0/2	0/2	0/2	0/2	0/2
200	0/2	1/2	2/2	2/2	2/2	2/2	1/2	0/2
400	0/1	0/1	1/1	1/1	1/1	-	-	-
600	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1

Sign/dose/hours	1	2	3	4	5	6	7	8
impaired/absent righting reflex								
males								
200	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
400	0/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1
600	0/1	0/1	0/1	0/1	1/1	1/1	1/1	1/1
females								
200	0/2	0/2	1/2	1/2	1/2	0/2	0/2	0/2
400	0/1	0/1	1/1	1/1	1/1	-	-	-
600	0/1	0/1	1/1	1/1	1/1	1/1	1/1	1/1
hypoactivity/ prostration								
males								
200	0/2	0/2	0/2	0/2	0/2	0/2	0/2	0/2
400	0/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
600	0/1	0/1	0/1	1/1	1/1	1/1	1/1	1/1
females								
200	0/2	0/2	0/2	1/2	1/2	0/2	0/2	0/2
400	0/1	0/1	1/1	1/1	1/1	-	-	-
600	0/1	0/1	0/1	1/1	1/1	1/1	1/1	1/1

* # displaying finding/# animals in group

Other clinical signs noted (soft stool, diarrhea, staining in anogenital/urogenital area, hair loss, dried material eyes/nose, dyspnea) were noted infrequently and usually at the higher dose levels only.

Survival and Clinical Observations - WIL-94045A

There were no deaths in this phase of the study. Gait abnormalities (rocking, lurching, or swaying) were observed at ≈ 1 hour post dose in females at all dose levels and in males at 200 and 250 mg/kg. By 2 hours post dose, all animals displayed gait abnormalities, and these persisted throughout the observation period.

Incidence and Rank of Gait Abnormalities*

Group	MALES												FEMALES											
Dose	175 MG/KG				200 MG/KG				250 MG/KG				175 MG/KG				200 MG/KG				250 MG/KG			
Rank/ hrs	P	1	2	3	P	1	2	3	P	1	2	3	P	1	2	3	P	1	2	3	P	1	2	3
Gait																								
1	-	-	-	-	3	-	-	-	4	-	-	-	2	-	-	-	4	-	-	-	2	2	-	-
2	2	1	1	-	-	-	4	-	-	-	4	-	-	1	3	-	-	1	3	-	-	-	4	-
3	-	-	4	-	-	-	4	-	-	-	3	1	-	-	4	-	-	-	4	-	-	-	2	2
4	-	3	1	-	-	-	2	2	-	-	1	2	-	-	4	-	-	-	3	1	-	-	1	2
5	-	-	3	1	-	-	2	2	-	-	1	2	-	-	4	-	-	-	3	1	-	-	-	3
6	-	-	4	-	-	-	3	1	-	-	1	2	-	-	4	-	-	-	2	2	-	-	-	3
7	-	2	2	-	-	-	3	1	-	-	2	1	-	-	4	-	-	-	3	1	-	-	-	3
8	-	4	-	-	-	-	2	2	-	-	3	-	-	-	4	-	-	-	2	2	-	1	1	1

* rank: P=present, 1=slight; 2=moderate; 3=severe; hours-post dose

The other predominant clinical finding was reduced/absent forelimb/hindlimb grasp reflex, which was observed in one high-dose female at the 1-hour post dose period and in all groups, both sexes, beginning at 3 hours post dose and remaining throughout the 8-hour post dose observation period in the majority of the animals. The peak mean scores were said to have been attained at ≈3-5 hours, expressed by the incidence and severity of the finding. By 24 hours post dose, none of the clinical findings noted above were observed in any animal. From day 1 after dosing until study termination, none of the animals displayed gait abnormalities, deficits in any reflexes, or hypoactivity/prostration.

NOTE: No summary table was provided, only separate tables for each hour post dose listing the individual findings.

	MALES											
Dose	175 mg/kg				200 mg/kg				250 mg/kg			
Rank/hrs	P	1	2	3	P	1	2	3	P	1	2	3
reduced/absent forelimb grasp reflex												
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-
3	-	3	-	-	-	2	2	-	-	-	2	1
4	-	1	-	1	-	1	2	-	1	-	2	-
5	-	1	1	-	-	1	1	2	1	1	2	-
6	-	1	1	-	-	1	1	1	1	2	-	1
7	-	-	-	-	-	1	2	-	1	1	-	1
8	-	2	-	-	-	2	1	-	1	2	1	-
reduced/absent hindlimb grasp reflex												
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	1	-
3	-	3	-	-	-	1	2	1	1	1	-	2
4	1	-	-	1	-	1	3	-	1	-	1	1
5	1	1	-	-	-	-	1	3	1	-	2	1
6	-	1	1	1	1	-	3	-	2	-	2	-
7	-	-	-	-	-	1	3	-	1	-	2	1
8	-	2	-	-	-	3	-	-	1	2	1	-
impaired/absent righting reflex												
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	1	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	1	-	-	-
7	-	-	-	-	-	-	-	-	1	-	-	-
8	-	-	-	-	-	-	-	-	1	-	-	-

	FEMALES											
Dose	175 mg/kg				200 mg/kg				250 mg/kg			
Rank/hrs	P	1	2	3	P	1	2	3	P	1	2	3
reduced/absent forelimb grasp reflex												
1	-	-	-	-	-	-	-	-	-	1	-	-
2	-	-	-	-	-	-	-	-	-	-	1	-
3	-	2	1	-	-	-	3	1	-	-	2	2
4	-	1	3	-	-	1	2	1	2	-	2	-
5	0	-	3	1	-	-	4	-	1	-	1	2
6	-	-	2	2	-	-	1	3	-	-	2	2
7	-	2	2	-	-	1	2	1	1	1	1	1
8	-	1	2	-	-	-	4	-	1	-	3	-
reduced/absent hindlimb grasp reflex												
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-
3	-	3	-	-	-	-	2	2	-	-	1	3
4	-	1	2	1	-	-	3	1	2	-	2	-
5	-	-	3	1	1	-	3	-	2	-	-	2
6	-	-	-	4	3	-	-	1	1	-	2	1
7	-	-	4	-	-	1	-	3	1	-	2	1
8	-	2	1	-	-	-	2	2	1	-	2	1
impaired/absent righting reflex												
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	1	-
7	-	-	-	-	-	-	-	-	1	-	-	-
8	-	-	-	-	-	-	-	-	1	-	-	-

Other clinical signs noted (soft stool, diarrhea, staining in anogenital/urogenital area, hair loss, dried material eyes/nose, dyspnea) were noted infrequently and usually at the higher dose levels only.

Body Weight - WIL-94045

The 400 mg/kg and 600 mg/kg males displayed lower body weights compared to the other males at day 8 of the study. The two females at these two dose levels died prior to the first day post dose measurement. Body-weight change was lower at these two dose levels in males also.

Mean Body-Weight Change (g)

Day/Dose	12.5	25.0	50.0	100.0	150.0	200.0	400.0	600.0
MALES								
-1-0	15	13	15	12	14	13	15	12
0-7	58	54	56	58	51	50	41	19
7-8	10	6	6	5	5	3	6	10
0-8	68	60	62	63	57	58	47	29
-1-8	83	73	77	75	70	31	62	41

Day/Dose	12.5	25.0	50.0	100.0	150.0	200.0	400.0	600.0
FEMALES								
-1-0	6	3	8	6	9	10	8	8
0-7	27	24	20	34	21	19	-	-
7-8	-2	-4	4	0	6	11	-	-
0-8	25	20	24	34	27	30	-	-
-1-8	31	23	32	40	36	40	-	-

% Mean Body-Weight Change

Time/dose	12.5	25	50	100	150	200	400	600
MALES 0-8	35.6	32.4	32.6	34.4	30.3	36.2	25.4	15.7
FEMALES 0-8	15.6	12.5	14.8	21.0	16.3	18.2	-	-

Body Weight - WIL-94045A

There was no adverse effect on body weight or body-weight gain in either sex.

% Mean Body-Weight Change

Time/dose	175 mg/kg	200 mg/kg	250 mg/kg
MALES 0-8	17.0	16.7	16.3
FEMALES 0-8	9.0	6.7	7.1

3. Pathology: All animals were sacrificed at study termination and discarded. No macroscopic or microscopic examination were performed.

DISCUSSION

Both females at the two highest dose levels (400 and 600 mg/kg) died within one day of dosing, each displaying clinical findings similar to the surviving animals. Body-weight gains were decreased (dose-related) at these two high dose levels in males; death precluded an assessment of body weight/gain of the females at these doses. Body weight/gains were comparable among the other dose levels in both phases of the study. The two predominant clinical findings were gait abnormalities (rocking, lurching, and swaying) and reduced/absent forelimb/hindlimb grasp reflex. These were observed with varying severity and incidence (dose-related) at dose levels of 50 mg/kg and greater. The occurrence of gait abnormalities in one 12.5 mg/kg female at 2, 4, and 5 hours post dose was considered incidental since the 25 mg/kg animals did not

display this effect. Reduced/absent forelimb/hindlimb grasp reflex was displayed at dose levels of 150 mg/kg and greater.

CONCLUSION

Under the conditions of the study, administration of a single dose of Busan 11-M1 via gavage to rats at dose levels of 12.5, 25, 50, 100, 150, 200, 400, and 600 mg/kg resulted in death at the 400 and 600 mg/kg dose levels in females only and several clinical signs indicative of neurological involvement, which included gait abnormalities, reduced/absent forelimb/hindlimb grasp reflex, and reduced/absent surface righting reflex. A no-effect dose was observed at 25 mg/kg. Dose levels of 175, 200, and 250 mg/kg were administered similarly to clarify selection of a benchmark dose level and estimate the time of peak neurologic effect for a subsequent acute neurotoxicity study. It was determined that the peak effect was reached at 3-5 hours post dose and the benchmark dose level was estimate to be 200 mg/kg. Doses of 25, 50, 100 and 200 mg/kg were selected for the acute neurotoxicity study with Busan 11-M1 in rats, and the time to peak effect was estimated to be ≈ 4 hours following dosing.

This study is classified as not acceptable. This study is a range-finding study, which does not satisfy any guideline requirement per se, but the report is apparently a DRAFT, which is not signed, and the purity of the test material and analysis of the test material formulations were not provided. This study may be upgraded with the submission of information on the test material purity/formulation analyses, a final **signed** study report, and a **signed** quality assurance statement.