

ACUTE SYSTEMIC TOXICITY
STUDIES
OF NATURAL-PRODUCT HUMATES
FOR

LAUB BIO-CHEMICALS

AND PROVIDED TO

VIRAL THERAPEUTIC TECHNOLOGIES
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BIOLOGICAL REPORT

Report Date: 07/17/98
Date Received: 05/13/98
Date Completed: 06/30/98
Project #: 98300859
Reference #: 533VA,41-70

SUMMARY AND EVALUATION OF TEST RESULTS:

An acute intravenous systemic toxicity was performed on Swiss Webster mice at 0 (saline control), 50, 25, and 12.5 mg/kg doses. The animals were observed for any signs of toxicity and general clinical findings were recorded. No mortalities were observed over the fourteen (14) day observation period, and while some clinical findings were observed, they were not indicative of toxicity.

SAMPLE DESCRIPTION:

ACCESSION #

SAMPLE

LOT # QTY

98300859

Approximately 110 mg of Humic

N/A 01

Acid 150 K powder

TESTS PERFORMED

BTS METHOD:

Acute Intravenous Systemic
Toxicity Test (Multiple Dose)

M806R0

SAMPLE PREPARATION:

The sample powder was dissolved in sterile, pyrogen-free 0.9% sodium chloride injection to yield final concentrations of 1 mg/mL, 0.5 mg/mL, and 0.25 mg/mL (See chemistry notebook 475, p.52)

OBJECTIVE:

To determine the acute intravenous systemic toxicity of the sample doses.

PROCEDURE:

Testing was performed according to the above references and is

Microbiology • Analytical Chemistry • Toxicology

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DOSAGE:

Humic Acid 150K (1 mg/mL), Humic Acid 150K (0.5 mg/mL), Humic Acid 150K (0.25 mg/mL), and 0.9% sodium chloride injection were injected at 50 mL per kilogram. This resulted in the following Humic Acid 150K doses: 50 mg/kg of body weight from 1 mg/mL, 25 mg/kg from 0.5 mg/mL, 12.5 mg/kg from 0.25 mg/mL, and 0 mg/kg from the 0.9% sodium chloride injection.

IACUC:

This toxicity study procedure has been evaluated and approved by the Institutional Animal Care and Use Committee in accordance with the regulations in 9 CFR 2.31.

ANIMAL DATA:

The animals were Swiss Webster mice, which were supplied by Simonsen Laboratories, Inc. They weighed in the range of 17-23 g at the time of testing. A balanced Teklad diet and water were fed ad libitum during the acclimation and testing periods. All test animals were quarantined and checked for signs of disease prior to testing.

ENVIRONMENTAL CONDITIONS:

All test animals were group-housed 5 per cage in plastic cages with stainless steel suspended lids.

DISPOSITION OF SAMPLE AND AVAILABILITY OF RAW DATA AND FINAL REPORT:

The remainder of the sample has been stored at BioScreen Testing Services, Inc. The raw data and the final report will be retained in the archives of BioScreen Testing Services, Inc.

RESULTS:

No deaths occurred at any dose.

Zero Dose (Sodium chloride 0.9%)

During the fourteen (14) day observation period, no toxic effects or deaths were observed in the five (5) male and five (5) female mice.

Humic Acid 150K (1 mg/mL to yield 50 mg/kg)

Days 1,2, and 3; Ptosis, piloerection, and cyanosis were observed in one of the five male mice.

Days 1,2 and 3; Ptosis and piloerection were observed in one of the five female mice. Cyanosis was observed in two of the five female mice.

After the first three days of the observation period, no signs of toxic effects occurred for the rest of the study period.

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RESULTS (cont'd):

Humic Acid 150K (0.5 mg/mL to yield 25 mg/kg)

No toxic effects were observed in any of the five male mice at this concentration level.

Days 1 and 2; Ptosis, piloerection, and cyanosis were observed in one of the five female mice.

After the first two days of the observation period, no signs of toxic effects occurred for the rest of the study period.

Humic Acid 150K (0.25 mg/mL to yield 12.5 mg/kg)

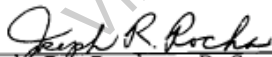
Day 1; Piloerection and aggressive behavior were observed in one of the five male mice.

Initial time and 4 hours; Piloerection was observed in one of the five female mice.

After the first day of the observation period, no signs of toxic effects occurred for the rest of the study period.

DISCUSSION AND CONCLUSION:

Ptosis, piloerection, and cyanosis or blue color effect were observed in one (1) of the five (5) female and one (1) of the five (5) male mice tested for the first three days observation at the highest concentration tested. The number of days of these observations and the number of animals showing these symptoms decrease as the concentration is decreased. The cyanosis was not in fact a true cyanosis but the effect of the pigment in the test article. The ptosis observed was probably due to a slight transient sedative effect. No toxic effect of the administration was evident over the balance of the observation period. The overall clinical findings did not reveal any toxic effects.



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TABLE I CHECKLIST FOR CLINICAL OBSERVATIONS

- 1) **Mortality/Morbidity:** Record whether the animal is Alive (AL) or Expired (EX).
- 2) **Moribundity:** Is the animal moribund? Record yes (+) or no (-) for general malaise. Describe under item 12 below General Observations and Comments.
- 3) **Weight:** Record the weight in grams upon selection of the animals, at Zero time, Day 1, Day 7 and Day 14 (or within 24 hours of the post injection dates).
- 4) **Behavior:** Aggressive [animal attacks and bites any object placed in cage] (A), Fearful [irritable, animal jumps when cage is opened and retreats to corner] (B), Malaise [lethargy] (C), or Normal (N).
- 5) **Ocular Effects:** Animal shows Nystagmus [involuntary rapid eye movement and/or rapid rotation of eyes] (E), Ptosis [drooping eye lids] (F) or Lacrimation [tearing or moisture around the eyes] (G), or none of the above, or eyes are Normal (N).
- 6) **Skin and Fur:** Fur shows Piloerection [hairs standing up on the back] (D), or [hair and skin are Normal, smooth and unruffled] (N).
- 7) **Respiratory effects:** dyspnea [difficult or painful breathing] (Y), apnea [temporary suspension of breathing] (Z). Normal (N).
- 8) **Motor Effects:** Animal shows Tremors [shaking, shivering] (H), Fasciculations [Involuntary twitching or contractions of muscles] (I), Clonic Convulsions [Alternating contraction and relaxation of muscles of muscles occurring in rapid succession] (J), Tonic Convulsions [sustained muscle contraction] (K), Ataxia [motor incoordination characterized by staggering or lack of righting reflex] (L), or none of the above, Normal (N).
- 9) **Autonomic Effects:** Excessive Salivation (M) or Normal (N).
- 10) **Reactivity to Handling:** See (4) Behavior above. If motor activity and behavior appear Normal (N).
- 11) **Stereotypic Behavior:** Self Mutilation (P) or Walking Backwards (Q) or Absence of stereotypic behavior (-).
- 12) **General Observations:** Muscular Weakness (R), Micturition [abnormal frequency of urination] (S), Diarrhea [describe feces under comments] (T), Writhing, [pain induced twisting of body movements] (U), Cyanosis [Bluish tint to skin caused by lack of availability of circulating oxygen] (V), Phonation [Vocal noises, may a noxious stimulus] (W), or Absence of any of the above (-).

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**TABLE II
CLINICAL OBSERVATIONS
[Humic Acid 150K (50 mg/kg)]**

Animal No.	Sex	Animal Weights (grams)			Toxicity Summary	Comments
		Initial	7 Days	Final		
12	M	22	28	32	N @ initial; D,F,V @ 4hr thru day 3; N @ day 6 thru 14	Tip of the tail - blue
23	M	20	26	29	N	
17	M	21	28	35	N	
26	M	22	30	35	N	
28	M	19	25	26	N	
63	F	21	23	Not Recorded	N	Tip of the tail - blue
72	F	19	21	23	N @ initial thru 4hr; V @ day 1; F,D,V @ day 2; F,D @ day 3; N @ day 6 thru 14	
68	F	19	22	24	N	
66	F	18	22	24	N	
74	F	18	22	23	N	

**TABLE III
CLINICAL OBSERVATIONS
[Humic Acid 150K (25 mg/kg)]**

Animal No.	Sex	Animal Weights (grams)			Toxicity Summary	Comments
		Initial	7 Days	Final		
20	M	22	30	32	N	
09	M	21	27	32	N	
15	M	20	28	32	N	
33	M	21	29	33	N	
35	M	22	28	30	N	
57	F	18	22	23	N @ initial thru 4hr; D,F,V @ day 1 thru 2; N @ day 6 thru 14	
61	F	20	22	25	N	
46	F	22	25	27	N	
49	F	21	24	27	N	
54	F	19	22	23	N	

Toxicity Key:
 N=Normal AL=Alive EX=Expired M=Moribund (+)=Yes or present (-)=No or none

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**TABLE IV
CLINICAL OBSERVATIONS
[Humic Acid 150K (12.5 mg/kg)]**

Animal No.	Sex	Animal Weights (grams)			Toxicity Summary	Comments
		Initial	7 Days	Final		
30	M	21	29	36	N @ initial thru 4hr; A,D @ day 1; N @ day 2 thru 14	
34	M	19	24	31	N	
24	M	21	28	33	N	
36	M	18	25	26	N	
27	M	21	28	33	N	
41	F	19	22	23	N	
67	F	22	25	26	N	
58	F	19	22	24	N	
62	F	19	22	24	N	
38	F	21	23	24	D @ initial thru 4hr; N @ day 1 thru 14	

**TABLE V
CLINICAL OBSERVATIONS
[Zero Dose]**

Animal No.	Sex	Animal Weights (grams)			Toxicity Summary	Comments
		Initial	7 Days	Final		
37	M	21	28	32	N	
22	M	23	30	34	N	
18	M	19	28	27	N	
26	M	20	27	33	N	
29	M	21	30	34	N	
62	F	22	24	27	N	
51	F	22	24	25	N	
75	F	20	22	23	N	
73	F	20	24	25	N	
43	F	20	23	25	N	

Toxicity Key:
 N=Normal AL=Alive EX=Expired M=Moribund (+)=Yes or present (-)=No or none