

"Contains NO CRT"



DOCUMENT RECEIPT

December 15, 1992

PESTICIDE REGISTRATION ASSOCIATES, INC.

92 DEC 21 AM 7:57

8EHQ-1292-8611

CERTIFIED MAIL P 410 403 790
RETURN RECEIPT REQUESTED



8EHQ-92-8611
INIT 12/21/92

TSCA Document Processing Center (TS-790)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460
Attn: Section 8(e) Coordinator



8893000093

Dear Sir or Madam:

RE: Kasugamycin
8(e) Reports
Tongue Lesions in Dogs
Red Rectal Foci in Rats

The following is submitted by Stewart Pesticide Registration Associates, Inc. in accordance with and fulfillment of the provisions of Section 8(e) of the Toxic Substances Control Act on the basis that the observations discussed below may be considered reportable under the Act.

Kasugamycin (CAS No. 6980-18-3) is a pesticide that is currently manufactured and sold outside the United States and is neither manufactured nor sold in the United States. Technical grade material was imported for research purposes only. The objective of the testing was to obtain future approval from EPA Office of Pesticide Programs.

The two observations noted below occurred in research studies in which kasugamycin was fed at very high doses to the test animals. To our knowledge, no person has been orally exposed to kasugamycin in the United States.

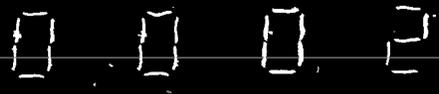
Stewart Pesticide Registration Associates, Inc. has advised the U.S. Environmental Protection Agency Office of Pesticide Programs of both effects.

Tongue Lesions in Dogs

Tongue lesions were first observed on day 35 and day 42 of a 90-day dietary toxicity study in dogs fed diet containing 6000 ppm and 3000 ppm kasugamycin, respectively. Lesions have not been observed in the low dose group (300 ppm) or in the control group.

Suite 603, Crystal Plaza One • 2001 Jefferson Davis Highway • Arlington, Virginia 22202
TELEPHONE: (703) 415-3036 • FAX: (703) 415-3037 • TELEX: 434578 (STEWART LNMO)

18 pgs.



The following documents are attached:

1. November 24, 1992 memo summarizing the telephone conversation between Stewart Pesticide Registration Associates, Inc. and EPA Office of Pesticide Programs, Toxicology Branch.
2. November 25, 1992 memo with a chronology of the observations.
3. December 10, 1992 memo with further observations.

Red Foci Near Rectum in Rats

Red foci near the rectum were observed in the in-life phase of a two-generation reproduction study in rats fed diet containing 6000 ppm kasugamycin. Red foci were first observed during week 10 of treatment and continued to be observed for the duration of the study. Upon necropsy of the F₂ generation, red foci near the rectum were observed in 20 of 25 males and 25 of 25 females fed 6000 ppm kasugamycin in the diet. No red foci were observed at lower doses or controls.

The toxicological significance of this observation is not known at this time.

This observation was discussed with EPA Office of Pesticide Programs during a meeting held December 11, 1992.

Sincerely,



Cynthia Ann Smith
Manager, Regulatory Affairs

Enclosures

November 24, 1992

"Contains NO CBI"

TO: Kasugamycin file
From: Cindy Smith
RE: Kasugamycin
90-Day Dog Study
EPA Guidance

Dr. Charles and I had a conference call today with Beth Doyle (telephone: 703-308-2722), an EPA toxicologist, regarding the kasugamycin 90-day dog study. The conclusions of the conversation are summarized below:

1. If at all possible, it is desirable to complete this study and thereby not require the use of additional dogs.
2. EPA has seen and accepted several toxicology studies for which the high dose was decreased during the study due to toxic effects. In some instances, the effects seen in the high dose animals have been sufficiently severe that exposure of the high dose animals was temporarily discontinued, and later continued at a lower rate. This has not prevented the acceptance of the study.
3. It is important to clearly document in the report the chronology of the observations and explain what was done and why. (Hazleton is doing this, including videotaping the dog's mouths. Still photography was determined not to be practical due to lighting requirements.)
4. In reviewing the study, the main points the reviewer will be looking for are:
 - a. a no observable effect level (NOEL)
 - b. a lowest effect level (LEL), and
 - c. definition of the effects.

Attached is a copy of the EPA acceptance criteria for the 90-dog study.

5. Based upon the data available today,
 - a. NOEL = low dose = 300 ppm
 - b. LEL = mid dose = 3000 ppm
 - c. Effects are being defined.
6. Events that would likely cause EPA to reject the study are:
 - a. No NOEL if effects were seen in the low dose group.
 - b. No LEL if the mid dose group animals were not able to complete the 90-day study.

01004

7. **To the extent possible, it will be beneficial to include in the report the mechanism of the effect. Any assessment of the mechanism will first require the results of the histopathological evaluations.**

8. **The possibility that the effect results from a toxic metabolite should be explored. This can be done based upon metabolism data and/or consideration of the complete toxicological data base. If the effect is thought to be due to a toxic metabolite, then metabolite toxicology data would be required to support residue tolerances in crops. (The metabolite would need to be measured in residue chemistry data also.)**

Attachment 2

DATE: November 25, 1992

TO: Jeffery Charles

From: Peter Thornford

CC: Matt Palazzolo
 Elaine Miller

RE: 13-Week Dietary Toxicity Study with Kasugamycin in Dogs

On November 18, 1992 (test day 35) I was informed by the Lead Technician on this study that some of the dogs in Group 4 were developing lesions on their tongues. This included three males and one female. I requested that Dr. Donna Clemons look at these animals on that same day. Because of expected toxicity in this dose group 6000 ppm we had been monitoring the status of these animals closely. The only observation of note previously had been decreased food consumption and decreased body weight gains in the Group 4 females especially.

It was the opinion of Dr. Clemons on November 18th that 3 of 4 Group 4 males had glossitis (inflammation of the tongue) and that one Group 4 female had ulcerative glossitis. The glossitis was characterized by swelling and erythema on the dorsal surface of the tongue. The ulcerative glossitis was characterized by ulcerations with erythema and lifting of the epithelium on the dorsal surface of the tongue with excessive salivation before and during the examination. Dr. Clemons said that the recommended treatment for dogs with glossitis would be switching to soft (canned) food and attempting to remove the source of irritation.

These observations along with a summary of the Week 5 body weights, food consumption and antemortem observations were communicated to you by fax and telephone conversation on November 19th. In these discussions I emphasized that two of the Group 4 females had lost 0.4 kg and that one of these two had a 50% reduction in food consumption during week 5. We discussed the possibility that this might be test material related and that we might have to reduce the high dose level at some point. We confirmed that you would look at the dogs during your visit on the 23rd. I also asked the Lead Technician on this study to observe the dogs closely for any rapid changes in health that would warrant changing their diet to canned dog food.

On November 23rd you observed the dogs and we asked Dr. Clemons to again observe the Group 3 and 4 dogs. The following observations were noted at that time:

<u>Group</u>	<u>Animal No.</u>	<u>Observation</u>
3	H05334 Male	Vesicles-small
3	H05337 Male	Erythema-slight
3	H05352 Female	Erythema, few small vesicles
4	H05338 Male	Erythema, swelling
4	H05342 Male	Erythema, vesicles small

4	H05341 Male	Vesicles, small ulcerations
4	H05347 Male	Erythema, swelling
4	H05354 Female	Ulcers, small
4	H05360 Female	Erythema, small ulcers, swelling
4	H05357 Female	Small Vesicles, erythema
4	H05364 Female	Small vesicles, small ulcers, erythema of oral cavity

These observations were then discussed and compared to the body weight gain data as follows:

<u>Animal No.</u>	<u>Cumulative Body Weight Gain</u>
H05338 Male	+1.4 kg
H05342 Male	+2.1
H05341 Male	+0.3
H05347 Male	+1.0
H05354 Female	-0.6
H05360 Female	+1.1
H05357 Female	+0.1
H05364 Female	+0.0

This was in comparison to an average cumulative body weight gain in control males of 2.0 kg and in females of 1.5 kg. It was our opinion that these findings were test material related.

It was our recommendation that for humane reasons all of the Group 4 animals be removed from the test material diet and be placed on canned (Alpo) dog food for at least one week and that at the end of one week the top dose be reduced from 6000 ppm to 4500 ppm.

On the morning of November 24th after consultation by you with Hokko, Dick Conn and the EPA we agreed that switching to canned food immediately and dose reduction after at least one week with out test material was the best approach for humane and scientific reasons. These changes were implemented that day by HWI personnel.

In addition, and upon your instruction, HWI took still photographs and a video tape of the lesions from one male and female each from Group 1 and 4. While the quality of the video and potential quality of the photographs are marginal, I feel strongly additional restraint measures or additional attempts to obtain quality pictures would jeopardize the scientific integrity of the study by additionally stressing select dogs in the study.

We have reviewed the environmental records for weeks 4 - 6 for this study and found that the temperature range was 21.4 - 24.0 degrees C and the humidity range was 37.5 - 59.9 %, both of which were well within protocol requirements. Daily food and water checks were done as scheduled per HWI SOP for this same time period and nothing unusual was noted. It is therefore highly unlikely that environmental deviations could have contributed to the observed tongue lesions.

HAZLETON
WISCONSIN

Attachment 3

Facsimile Transmission

Main Fax Number: (608) 241-7227
Toxicology Fax Number: (608) 242-2736

Date: December 10, 1992

To: Richard L. Conn

Company: Stewart Pesticide Registration Associates, Inc.

Facsimile Number: (703) 415-3037

From: Elaine Miller

Number of pages (including cover): 11

To confirm receipt of transmission, call (608) 242-2712, ext. 2593

Comments: Mr. Conn - Attached are the body weights, body weight gains, and food consumption data for HWI 6434-101, "13-Week Dietary Toxicity Study with Kasugamycin in Dogs." In addition, I have attached a copy of this morning's veterinary exam observations for this study.

If you have any questions, do not hesitate to call me at (608) 242-2712, ext. 2593.

cc: P. Thomford, PhD
Study Director

HAZLETON WISCONSIN, INC.
HAZLETON, WISCONSIN 548

13-Week Dietary Toxicity Study
with Nifedipine in Dogs
DRAFT BODY WEIGHTS SUMMARY *DRAFT*

PRINTED: 10-DEC-92
PAGE: 1

STUDY NUMBER: 8434101

NOTE: WEEKS 1-8 ARE
RECORDED IN KG, WEEK
9 IS RECORDED IN G.

ANIMAL NUMBER	INDIVIDUAL BODY WEIGHTS (G)									WEEK 9 UNIT CHANGE WAS	
	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8			
GROUP: DOSE 1 - 0 PPM											
05342	7.2	7.5	7.8	8.2	8.8	9.1	8.8	9.4	9800.0	NECESSARY FOR I.M. CONSUMPTION CALC.	
05340	7.7	8.1	8.2	8.7	9.0	9.7	9.4	10.2	10500.0		
05343	7.1	7.5	8.1	8.4	9.0	9.1	9.9	9.7	9900.0		
05345	7.5	8.1	8.3	8.6	9.2	9.7	10.2	10.2	10300.0		
	4	4	4	4	4	4	4	4	4		
EM	7.4	7.8	8.1	8.5	9.0	9.4	9.6	9.9	10125.0		
S.D.	0.28	0.35	0.22	0.22	0.16	0.35	0.61	0.39	330.41		
GROUP: DOSE 2 - 300 PPM											
05336	6.9	7.2	7.9	7.8	8.3	8.3	9.1	9.0	9500.0		
05339	7.3	8.0	8.6	8.8	9.4	9.9	10.5	10.5	11000.0		
05346	7.7	8.5	8.8	9.1	9.6	10.2	10.6	11.3	11100.0		
05348	7.7	8.6	8.9	9.2	9.8	10.2	11.0	10.8	11200.0		
	4	4	4	4	4	4	4	4	4		
EM	7.4	8.1	8.5	8.7	9.3	9.7	10.3	10.4	10700.0		
S.D.	0.38	0.64	0.65	0.64	0.67	0.91	0.83	0.99	801.16		
GROUP: DOSE 3 - 3000 PPM											
05331	7.5	8.3	8.7	9.2	9.5	9.7	9.2	9.9	10200.0		
05334	7.2	7.7	7.8	7.9	8.1	8.8	9.2	9.0	9500.0		
05335	7.2	7.7	7.9	8.3	8.5	9.0	10.1	9.3	9500.0		
05337	7.1	7.5	7.8	8.3	8.7	8.8	9.2	8.9	8800.0		
	4	4	4	4	4	4	4	4	4		
EM	7.3	7.8	8.1	8.4	8.7	9.1	9.4	9.3	9500.0		
S.D.	0.17	0.38	0.44	0.88	0.39	0.43	0.48	0.48	571.36		
GROUP: DOSE 4 - 6000 PPM											
05338	7.2	7.6	7.7	8.2	8.5	8.6	8.4	8.1	9400.0		
05341	7.2	7.4	7.6	7.7	7.4	7.5	7.2	7.0	8000.0		

POOR COPY

13-Week Dietary Toxicity Study
with Kanamycin in Dogs
"DRAFT" BODY WEIGHTS SUMMARY "DRAFT"

STUDY NUMBER: 6434101

NOTE: WKS 1-8 in kg.
WKS 9 in g.

INDIVIDUAL BODY WEIGHTS (G)

WEEK NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	WEEK 9
-------------	--------	--------	--------	--------	--------	--------	--------	--------	--------

GROUP: MALE 4 - 6000 PPM

165342	7.8	8.6	8.8	9.2	9.4	9.9	9.7	9.2	14500.0
165347	7.2	7.6	7.6	7.8	8.1	8.2	8.0	7.3	8500.0
N	4	4	4	4	4	4	4	4	4
SEM	7.4	7.8	7.9	8.2	8.4	8.6	9.3	8.0	9700.6
S.D.	0.30	0.34	0.39	0.68	0.83	1.01	1.04	0.95	1078.49

After 1
week
at 4500ppm

GROUP: FEMALE 1 - 0 PPM

165351	6.1	6.5	6.9	7.2	7.4	7.5	7.8	8.5	8100.0
165356	6.3	7.1	7.4	7.7	8.3	8.4	8.5	8.9	9400.0
165368	7.6	7.9	8.2	8.7	9.1	9.2	9.2	9.1	9400.0
165379	4.8	5.1	5.3	5.6	5.9	6.0	6.2	6.3	6300.0
N	4	4	4	4	4	4	4	4	4
SEM	6.3	6.4	6.9	7.3	7.7	7.8	7.9	8.2	8350.6
S.D.	1.16	1.08	1.22	1.29	1.37	1.37	1.28	1.29	1377.28

GROUP: FEMALE 2 - 300 PPM

165370	6.1	6.5	6.7	7.2	7.6	7.7	7.8	8.4	8000.0
165380	6.6	7.0	7.4	7.9	8.1	8.6	8.8	9.0	9400.0
165381	6.1	6.8	6.6	7.5	7.9	8.4	8.5	9.0	9300.0
165384	6.0	6.8	6.8	7.2	7.4	7.8	8.1	8.0	8300.0
N	4	4	4	4	4	4	4	4	4
SEM	6.2	6.7	6.9	7.5	7.8	8.1	8.3	8.6	8925.0
S.D.	0.27	0.24	0.36	0.33	0.33	0.44	0.44	0.49	492.45

GROUP: FEMALE 3 - 3000 PPM

165382	6.1	6.2	6.2	6.5	6.9	7.0	7.1	7.6	7700.0
165383	6.1	6.7	6.9	7.8	7.8	8.0	7.9	8.4	8400.0
165388	6.6	6.8	6.9	7.2	7.3	7.7	7.6	7.7	8000.0
165389	6.4	6.7	6.9	7.3	7.4	7.8	7.8	7.9	7900.0

13-Week Dietary Toxicity Study
with Kasugamycin in Dogs
DRAFT PUPPY HEIGHTS SUMMARY *DRAFT*

STUDY NUMBER: 6434101

NOTE: WKS 1-8 in Kg.
Wks 9 in g.

IMPROVED BODY HEIGHTS (G)

WEEK	WEEK	WEEK	WEEK	WEEK	WEEK	WEEK	WEEK	WEEK	WEEK
NUMBER	1	2	3	4	5	6	7	8	9
GROUP: FEMALE 3 - 3000 PPM									
A	4	4	4	4	4	4	4	4	4
MEAN	6.2	6.6	6.7	7.1	7.4	7.6	7.6	7.9	8250.0
S.E.	0.42	0.27	0.35	0.43	0.37	0.43	0.36	0.36	387.31
GROUP: FEMALE 4 - 6000 PPM									
MS354	6.2	5.6	5.3	5.7	6.0	5.6	5.5	5.2	6200.0
MS357	5.3	5.4	5.6	6.0	6.0	5.6	5.6	5.4	6400.0
MS360	6.4	6.0	7.2	7.3	7.3	7.5	7.6	7.0	8100.0
MS364	6.6	6.8	6.6	5.4	6.5	6.6	6.3	6.4	7600.0
A	4	4	4	4	4	4	4	4	4
MEAN	6.2	6.1	6.2	6.4	6.4	6.3	6.2	6.0	7075.0
S.E.	0.40	0.75	0.92	0.70	0.61	0.91	1.02	0.85	921.51

- after 1
week at
4500 ppm
diet.

13-Week Dietary Toxicity Study
with Kasparocin in Dogs
DRAFT BODY WEIGHT GAINS *DRAFT*

STUDY NUMBER: 6434101

WEEK NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8		
GROUP: DOSE 1 - 0 PPM										
105332	0.3	0.6	1.0	1.6	1.9	1.6	2.2	-7772-0	2.6	
105340	0.4	0.5	1.0	1.3	2.0	1.7	2.5	10492-3	2.8	
105343	0.4	1.0	1.3	1.9	2.0	2.0	2.6	-8092-8	2.8	
105345	0.6	0.8	1.1	1.7	2.2	2.7	2.7	10592-5	2.8	
SEM	0.4	0.7	1.1	1.6	2.0	2.2	2.5	10112-6	2.8	
S.D.	0.13	0.22	0.19	0.25	0.13	0.64	0.22	-330-09	0.12	

GROUP: DOSE 2 - 300 PPM										
105326	0.3	0.6	0.9	1.4	1.4	2.2	2.1	1092-1	2.6	
105329	0.7	1.3	1.3	2.1	2.6	3.2	3.2	10992-7	3.7	
105346	0.8	1.1	1.4	1.9	2.3	2.9	3.6	11092-3	3.4	
105349	0.9	1.2	1.3	2.1	2.3	3.3	3.1	11102-3	2.5	
SEM	0.7	1.0	1.3	1.9	2.3	2.9	3.0	10692-6	2.3	
S.D.	0.26	0.31	0.29	0.33	0.37	0.39	0.64	-802-28	0.48	

GROUP: DOSE 3 - 3000 PPM										
105331	0.8	1.2	1.7	2.0	2.2	1.7	2.4	10192-0	2.7	
105334	0.5	0.6	0.7	0.9	1.6	2.0	1.8	1092-0	2.3	
105335	0.3	0.7	1.1	1.3	1.8	2.9	2.1	1092-9	2.3	
105337	0.4	0.7	1.2	1.6	1.7	2.1	1.8	1092-9	1.7	
SEM	0.5	0.8	1.2	1.5	1.8	2.2	2.0	1092-0	2.3	
S.D.	0.17	0.27	0.41	0.47	0.26	0.31	0.29	-674-41	0.41	

GROUP: DOSE 4 - 6000 PPM										
105338	0.4	0.5	1.0	1.3	1.4	1.2	0.9	-5992-0	2.2	
105341	0.2	0.4	0.5	0.2	0.3	0.0	-2	7992-0	2.0	
105342	0.0	1.0	1.4	1.6	2.1	1.9	1.4	10992-3	2.7	
105347	0.4	0.4	0.6	0.9	1.0	0.8	0.3	-9992-8	1.3	

NOTE: Cumulative BW gains
hand-calculated because
of g-kg software limitations.

HAZLETON WISCONSIN, INC.
HAZLETON, WISCONSIN USA

13-Week Dietary Toxicity Study
with Kanaganylin in Dogs
GRF1 BODY WEIGHT GAINS *GRF1*

PRINTED: 10-DEC-92
PAGE: 2

STUDY NUMBER: 6434101

WEEK NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	
GROUP: FEMALE 1 - 6000 PPM									
MEAN	0.5	0.6	0.9	1.0	1.2	1.0	0.6	0.002.7	1.8
S.D.	0.25	0.29	0.41	0.61	0.75	0.7	0.70	0.001.22	0.86
GROUP: FEMALE 1 - 0 PPM									
05351	0.4	0.8	1.1	1.5	1.4	1.7	2.4	0.003.9	2.0
05356	0.6	0.9	1.2	1.8	1.9	2.0	2.4	0.003.4	2.4
05358	0.1	0.6	1.1	1.5	1.6	1.6	1.5	0.002.4	1.8
05359	0.3	0.5	0.8	1.1	1.2	1.4	1.5	0.005.2	1.7
MEAN	0.3	0.7	1.0	1.4	1.5	1.7	1.9	0.003.0	2.1
S.D.	0.29	0.16	0.17	0.30	0.30	0.25	0.52	0.001.11	0.55
GROUP: FEMALE 2 - 300 PPM									
05349	0.4	0.6	1.1	1.5	1.6	1.7	2.3	0.005.9	2.4
05350	0.4	0.8	1.3	1.5	2.0	2.2	2.4	0.002.4	2.8
05361	0.7	0.5	1.4	1.8	2.3	2.4	2.9	0.007.9	3.2
05366	0.5	0.8	1.2	1.4	1.8	2.1	2.0	0.004.0	2.5
MEAN	0.5	0.7	1.2	1.5	1.9	2.1	2.4	0.008.0	2.7
S.D.	0.14	0.15	0.13	0.17	0.30	0.29	0.37	0.002.24	0.36
GROUP: FEMALE 3 - 3000 PPM									
05352	0.6	0.6	0.9	1.3	1.4	1.5	2.0	0.004.4	2.1
05353	0.6	0.8	1.4	1.7	1.9	1.9	2.3	0.003.9	2.5
05362	0.2	0.3	0.6	0.7	1.1	1.0	1.1	0.003.4	1.4
05365	0.3	0.5	0.9	1.0	1.4	1.4	1.5	0.002.6	1.5
MEAN	0.4	0.5	0.9	1.2	1.4	1.4	1.7	0.003.0	1.9
S.D.	0.21	0.21	0.33	0.43	0.33	0.33	0.53	0.002.19	0.52

MILITON RESEARCH, INC.
MILITON, WISCONSIN USA

13-Week Dietary Toxicity Study
with Ranaprycic in Dogs
DRAFT BODY HEIGHT GAINS *DRAFT*

PRINTED: 10-DEC-92
PAGE: 3

STUDY NUMBER 6434107

WEEK NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	
GROUP: FEMALE 4 - 6000 PPD									
Y05304	-0.6	-0.7	-0.3	-0.2	-0.6	-0.7	-1.0	-0.8	0
Y05357	-0.1	0.1	0.3	0.3	0.1	-0.1	-0.1	-0.5	0.9
Y05360	0.4	0.8	0.9	0.9	1.1	1.2	0.6	0.6	1.7
Y05364	0.2	0.8	-0.2	-0.1	0.9	-0.3	-0.2	-0.4	1.0
MEAN	0	0.1	0.2	0.3	0.2	0.0	-0.2	-0.8	0.9
S.D.	0.43	0.61	0.64	0.52	0.70	0.82	0.66	0.10	0.70

HAZLETON RESEARCH, INC.
 HAZLETON, PENNSYLVANIA USA

PRINTED: 10-28-82
 PAGE: 1

12-Week Electrocardiography Study
 with Minoxidil in Dogs
 SUBJECT: FOOD CONSUMPTION STUDY REPORT

STUDY NUMBER: 6434101

FOOD CONSUMPTION BY INTERVAL (G)

ANIMAL NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	WEEK 9
GROUP: DOSE 1 - 0 PPM									
105332	2440	1991	2237	2513	2423	2325	2193	2499	
105340	2259	2069	2224	2250	2474	2240	2360	2439	
105343	2483	2314	2272	2383	2260	2119	1984	1928	
105345	2741	2400	2445	2743	2479	2297	2501	2462	
MEAN	2461	2218	2294	2432	2411	2245	2275	2317	0
S.D.	282.7	220.5	182.6	224.6	98.8	97.5	266.2	262.7	
GROUP: DOSE 2 - 300 PPM									
105336	2000	1896	1810	1896	1818	1998	1924	2061	
105339	2542	2522	2522	2587	2386	2134	2351	2497	
105346	2883	2738	2699	2963	3023	2856	3214	3042	
105348	2653	2494	2453	2649	2629	2578	2686	2640	
MEAN	2591	2499	2372	2529	2464	2392	2551	2560	0
S.D.	345.9	361.7	388.5	451.4	504.4	396.5	541.6	405.0	
GROUP: DOSE 3 - 3000 PPM									
105331	2487	2374	2358	2292	2057	2291	2160	2540	
105334	2817	2886	2886	2764	2818	2846	2109	2663	
105335	1936	2035	1921	1971	1996	2225	1955	2043	
105337	2106	2269	2291	2784	2200	1534	2273	2314	
MEAN	2141	2175	2194	2453	2193	2024	2125	2365	0
S.D.	238.8	174.3	289.7	393.5	233.1	342.8	132.4	242.3	
GROUP: DOSE 4 - 6000 PPM									
105330	1972	2048	2245	2238	1872	1545	NOT TAKEN	2664	
105341	1493	1833	1764	1150	1269	939	NOT TAKEN	2714	

HAZLETON WISCONSIN, INC.
HAZLETON, WISCONSIN USA

PRINTED: 10-DEC-92
PAGE: 2

13-Week History Toxicity Study
with Kasugamycin in Dogs
DRAFT FOOD CONSUMPTION SUMMARY *DRAFT*

STUDY NUMBER: 6434701

FOOD CONSUMPTION BY INTERVAL (G)

ANIMAL NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	WEEK 9
---------------	--------	--------	--------	--------	--------	--------	--------	--------	--------

GROUP: MALE 4 - 6000 PPM

W03342	2400	2313	2409	2372	2265	1737	NOT TAKEN	3090	
W03347	1750	1702	2164	2102	2103	1320	NOT TAKEN	2641	
MEAN	2075	2007	2286	2237	2184	1528	0	2866	0
S.D.	423.0	333.1	300.3	362.4	436.2	302.1		219.0	

GROUP: FEMALE 1 - 0 PPM

F03331	1005	1921	2009	1901	1902	1009	1919	1560	
F03306	2203	2152	2115	2150	2100	2107	2190	2303	
F03300	2097	2321	2196	2233	2300	2043	2040	2233	
F03339	1701	1906	1809	2022	1703	1034	1070	1014	
MEAN	1901	2075	2047	2059	2041	1900	2009	1979	0
S.D.	240.3	190.9	141.4	196.1	216.0	159.3	146.5	349.2	

NOTE: AT
REDUCED LEVEL
OF 4500 ppm

GROUP: FEMALE 2 - 300 PPM

F03319	1006	1701	1020	1009	1740	1771	1009	1605	
F03330	1075	1996	2076	2290	2563	2021	2630	2692	
F03301	2162	1993	2291	2203	2642	2560	2497	2601	
F03306	2006	1000	2203	1947	2106	1940	1991	2000	
MEAN	1990	1907	2200	2002	2203	2173	2257	2251	0
S.D.	147.0	100.7	273.0	242.4	413.0	377.5	373.5	470.6	

GROUP: FEMALE 3 - 3000 PPM

F03302	1461	1373	1040	2150	1775	1099	1977	1735	
F03303	2032	1967	2100	2100	2027	2000	1997	1917	
F03302	1690	1990	1024	1700	1017	1539	1677	1033	
F03300	2073	1900	1961	2100	1740	1991	2004	1903	

AZLETON RESEARCH, INC.
 MILWAUKEE, WISCONSIN USA

13-Week Dietary Toxicity Study
 with Naloxonyl in Dogs
 DRAFT FOOD CONSUMPTION SUMMARY *DRAFT*

PRINTED: 10-DEC-92
 PAGE: 3

STUDY NUMBER: 6434101

FOOD CONSUMPTION BY INTERVAL (G)

WEEK NUMBER	WEEK 1	WEEK 2	WEEK 3	WEEK 4	WEEK 5	WEEK 6	WEEK 7	WEEK 8	WEEK 9
----------------	-----------	-----------	-----------	-----------	-----------	-----------	-----------	-----------	-----------

GROUP: FEMALE 3 - 3000 PPM

I	4	4	4	4	4	4	4	4	0
MEAN	1815	1725	1956	2061	1942	1869	1914	1867	
S.D.	290.5	292.7	172.7	202.2	126.8	233.3	198.6	107.1	

GROUP: FEMALE 4 - 6000 PPM

05334	922	1344	1152	1229	1024	618	NOT TAKEN	2267
05337	1208	1336	1508	1439	626	545	NOT TAKEN	2113
05340	1692	1782	1666	1762	1591	1242	NOT TAKEN	2541
05344	1694	1143	1449	1368	1255	988	NOT TAKEN	2361

I	4	4	4	4	4	4	0	4	0
MEAN	1399	1401	1443	1449	1124	848		2321	
S.D.	371.0	270.0	214.9	225.8	405.5	326.4		179.3	

↑
 NOTE:
 AT REDUCED
 LEVEL OF
 4500 ppm

STUDY NUMBER: 6434-101Page 7 of

NOTATIONS

12-10-92 Examination of oral cavities of all dogs on study 6434-101

Findings: Group 1: ♂ - no lesions

♀ - no lesions

Group 2: ♂ - no lesions

♀ - no lesions

Group 3:

H05331 ♂ - small foci of erythema on center of tongue.

H05335 ♂ - large (2cm x 3cm) area of erythema on center of tongue.

H05334 ♂ - small, multifocal erythematous foci on tongue

H05337 ♂ - small, multifocal erythematous foci on tongue.

H05352 ♀ - slight erythema of dorsal tongue surface.

H05362 ♀ - no lesions

H05353 ♀ - no lesions.

H05365 ♀ - slight erythema of dorsal tongue surface.

Group 4:

H05338 ♂ - small area of erythema on center of tongue

H05340 ♂ - large (3cm x 3cm) area of erythema on dorsal tongue.

H05341 ♂ - central erythema flanked by tan plaques on dorsal tongue.

H05347 ♂ - large areas of erythema, cuprused vesicles on tongue.

H05354 ♀ - slight erythema; single healing ulceration in center of tongue.

H05360 ♀ - large (2cm x 3cm) erythematous area on center of tongue.

H05357 ♀ - no lesions.

H05364 ♀ - 1cm x 2cm area of erythema on center of tongue.

Comment: Overall, the condition of the dogs has improved in the last week. No new lesions have been noted and existing lesions have healed or remained static. (Denny) (Denny) 12-10-92

ORGAN AND KEYWORD(S) OR PHRASE	--- NUMBER OF ANIMALS AFFECTED ---							
	SEX: -----MALE-----				-----FEMALE-----			
	GROUP: -1-	-2-	-3-	-4-	-1-	-2-	-3-	-4-
	NUMBER:	25	25	25	25	25	25	25
		-2-	-2-	-2-	-2-	-2-	-2-	-2-
NERVE, OTHER (NO)	NUMBER EXAMINED:	25	25	25	25	25	25	25
	NOT REMARKABLE:	25	25	24	25	25	25	25
LARGE		0	0	1	0	0	0	0
RECTUM (RE)	NUMBER EXAMINED:	25	25	25	25	25	25	25
	NOT REMARKABLE:	25	25	25	5	25	25	0
RED FOCUS(I)/AREA(S)		0	0	0	20	0	0	25
LIGHT FOCUS(I)/AREA(S)		0	0	0	1	0	0	0
SKIN (SK)	NUMBER EXAMINED:	25	25	25	25	25	25	25
	NOT REMARKABLE:	25	25	25	25	24	25	25
ALOPECIA-FOCAL		0	0	0	0	1	0	0
KIDNEYS (KD)	NUMBER EXAMINED:	25	25	25	25	25	25	25
	NOT REMARKABLE:	23	24	22	24	25	24	25
LARGE PELVIS(ES)		2	0	3	1	0	0	1
LARGE		0	0	0	0	0	0	1
SEMIFLATTENED BIVEXIAL-PELVIS		0	0	1	0	0	0	1
BOTTLED		0	1	0	0	0	0	0
PERICARDIAL LN (ML)	NUMBER EXAMINED:	25	25	25	25	25	25	25
	NOT REMARKABLE:	24	24	25	25	25	25	25
DIFFUSELY RED		1	1	0	0	0	0	0
HEART (HT)	NUMBER EXAMINED:	25	25	25	25	25	25	25
	NOT REMARKABLE:	24	24	25	25	25	25	25
RED FOCUS(I)/AREA(S)		1	0	0	0	0	0	0
LARGE		1	1	0	0	0	0	0