Preliminary Data Report for TOX210

Investigational Study of the Palatability of Smokeless Tobacco Test Articles Formulated in NTP-2000 Diets for Mice

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Executive Summary

The objective of this study was to evaluate the palatability of diets formulated in NTP-2000 rodent feed with a tobacco blend, an aqueous tobacco extract of the tobacco blend or nicotine hydrogen tartrate as positive control when fed to CD-1 Swiss Webster mice. A tobacco blend and an aqueous extract of the tobacco blend will be tested in an upcoming series of toxicology studies. Also, a positive control, nicotine hydrogen tartrate will be used in some of the planned studies.

Doses for the current study were based upon the nicotine content of the tobacco, tobacco extract and the nicotine tartrate. The tobacco and tobacco extract are complex mixtures of components occurring naturally in the tobacco plant. Nicotine is a significant component of tobacco and is known to be toxic at higher doses. The tobacco blend and aqueous tobacco extract test articles and the positive control were incorporated into the mouse's feed. There is the possibility that incorporation of the test articles and positive control in the feed may alter its palatability to mice. If the feed is less palatable than the control diet, the mice may consume less feed with a resulting decrease in body weight gain. This would also result in lower than anticipated doses during toxicology studies. Therefore, it was necessary to ascertain the palatability of the dosed feed to mice.

Palatability was assessed by comparing the feed intake and body weight of mice fed the standard NTP-2000 diet (control group) to the feed intake and body weight of mice fed NTP-2000 diets formulated to contain different doses of the tobacco blend and different doses of the tobacco extract, as well as different doses of the positive control. The duration of the feeding and data collection period was 14 days. Feed intake and body weight were measured daily during the study. Twice daily mortality and morbidity observations were conducted on all study mice as well as twice weekly standard clinical observations. No additional data were collected.

The control mice demonstrated normal body weights and body weight gains for male mice of the age used in the study. Mice fed feed formulated with the tobacco blend, did not demonstrate a strong dose response. The high dose (40 mg nicotine/kg body weight/day) was consistently below that of the control and other doses and could be used as a dose in additional studies. Unlike the tobacco blend, the tobacco extract produced little or no dose response in respect to body weight gains. Mice exposed to feed containing nicotine hydrogen tartrate at nicotine doses equivalent to those of the tobacco blend and extract demonstrated evidence of decreased body weight gain at 20 and 40 mg nicotine/kg body weight/day with the high dose producing a greater change than that seen with the tobacco blend. Feed consumption among the mice from all treatment groups and the control were too erratic to produce useful data.

No effects were seen during clinical observations. This indicates that at the doses used in this study exposure of mice to the tobacco blend, tobacco extract or nicotine hydrogen tartrate produced no observable nicotinic effects.

Study Objectives

The objective of this study was to evaluate the palatability of diets formulated in NTP-2000 rodent feed with a tobacco blend, an aqueous tobacco extract of the tobacco blend and nicotine hydrogen tartrate as positive control when fed to CD-1 Swiss Webster mice.

Materials and Methods

Study Design: A tobacco blend and an aqueous extract of the tobacco blend will be tested in an upcoming series of toxicology studies. Also, a positive control, nicotine hydrogen tartrate, will be used in some of the planned studies. Doses for this study were based upon the nicotine content of the tobacco, tobacco extract and the nicotine tartrate. The tobacco and tobacco extract are complex mixtures of components occurring naturally in the tobacco plant. Nicotine is a significant component of tobacco and is known to be toxic at higher doses and was used as the tobacco component on which the doses were based.

The tobacco blend and aqueous tobacco extract test articles and the positive control were incorporated into the feed for the mice (NTP-2000 rodent feed manufactured by Zeiglar Brothers, Inc., Gardners, PA). There is the possibility that incorporation of the test articles and positive control in the feed may alter its palatability to the mice. If the feed is less palatable than the control diet, the mice may consume less feed with a resulting decrease in body weight gain. This would also result in lower than anticipated doses during toxicology studies. Therefore, it was necessary to ascertain the palatability of the dosed feed to mice.

Palatability was assessed by comparing the feed intake and body weight gain of mice fed the standard NTP-2000 diet (control group) to the feed intake and body weight gain of mice fed NTP-2000 diets formulated to contain different doses of the tobacco blend and different doses of the tobacco extract as well as different doses of the positive control. The duration of the feeding and data collection period was 14 days. Twice daily mortality and morbidity observations were conducted on all study mice as well as twice weekly standard clinical observations. No additional data were collected.

The doses used for the study were chosen to match a concurrent rat study (TOX209) whose doses were based upon those used in a previous rat study of a tobacco material and the published literature. They are expected to assist in the development of doses to be used in a planned mouse short-term repeated dosing study. No undue toxicity, such as convulsions or death, were expected at these doses.

The experimental groups and the number of mice per group are provided in Table 1.

Table 1: **Treatment Groups and Doses**[1]

Group Number	Treatment Group (mg nicotine/kg body weight/day)	Number of Mice	Mouse ID Numbers
	Control		
1	NTP-2000 feed	5	1-5
	Tobacco Blend		
2	Dose 1 Tobacco in NTP-2000 feed (0.2)	5	6-10
3	Dose 2 Tobacco in NTP-2000 feed (2.0)	5	11-15
4	Dose 3 Tobacco in NTP-2000 feed (4.0)	5	16-20
5	Dose 4 Tobacco in NTP-2000 feed (8.0)	5	21-25
6	Dose 5 Tobacco in NTP-2000 feed (20.0)	5	26-30
7	Dose 6 Tobacco in NTP-2000 feed (40.0)	5	31-35
	Tobacco Extract		
8	Dose 1 Tobacco Extract in NTP-2000 feed (0.2)	5	36-40
9	Dose 2 Tobacco Extract in NTP-2000 feed (2.0)	5	41-45
10	Dose 3 Tobacco Extract in NTP-2000 feed (4.0)	5	46-50
11	Dose 4 Tobacco Extract in NTP-2000 feed (8.0)	5	51-55
12	Dose 5 Tobacco Extract in NTP-2000 feed (20.0)	5	56-60
13	Dose 6 Tobacco Extract in NTP-2000 feed (40.0)	5	61-65
	Positive Control		
14	Dose 1 Nicotine Tartrate in NTP-2000 feed (2.0)	5	66-70
15	Dose 2 Nicotine Tartrate in NTP-2000 feed (8.0)	5	71-75
16	Dose 3 Nicotine Tartrate in NTP-2000 feed (20.0)	5	76-80
17	Dose 4 Nicotine Tartrate in NTP-2000 feed (40.0)	5	81-85
	Sentinels		
	Sentinels (no treatment)	10	86-95

[1] Doses are based upon mg nicotine/kg body weight/day

Test Articles and Positive Control: Two test articles and a positive control were used for the study. Test Article 1 was identified as Tobacco Blend Lot#0T162AF and consisted of a blend of natural tobaccos ground to a powder, which contained no preservatives or other additives. Test Article 1 contained 2.63% nicotine. The Certificate of Analysis (CofA) for Test Article 1 is on file with the Sponsor. Because the tobacco is a complex mixture of natural components, its purity can not be ascertained. Upon arrival at the testing facility, the tobacco blend was stored at 4 ^{O}C for no more than three weeks before use for the last feed formulation. Test Article 1 was mixed to ensure uniformity before aliquots were removed for feed formulation.

Test Article 2 was identified as Tobacco Extract Lot#0T162AE and consisted of an aqueous extract of Test Article 1. Its water content was adjusted to result in 1 ml of Test Article 2 being equivalent to 1 g of Test Article 1. It contained no components not contained in the tobacco blend and the water used for extraction. The water used for extraction of the tobacco blend was analyzed for a series of components and the results are on file with the sponsor. Because the aqueous extract is a complex mixture of materials extracted from the tobacco, its purity can not be ascertained. Upon arrival at the testing facility, Test Article 2 was maintained frozen at approximately -25 ^{O}C for no more than three weeks before use for the last feed formulation. Before each use for feed formulation,

the extract was thawed at room temperature, required aliquots removed and then refrozen. Test Article 2 contained 2.30% nicotine. The CofA for Test Article 2 is on file with the sponsor. Preliminary determination of the density of Test Article 2 revealed a density of 1.203 g/ml.

The positive control used in the study was nicotine hydrogen tartrate (Lot#077K1810). It was obtained from Sigma-Aldrich Co., St. Louis, MO. The CofA for the nicotine salt stated it was 98% pure. Preliminary analysis of the salt at RJRT indicated it was at least 98% pure, if not of higher purity than reported. The nicotine free base is 35.1% of the bulk salt (2.85 g salt contains 1 g of free nicotine). Feed formulation was based upon nicotine and not the bulk salt. The nicotine hydrogen tartrate was stored at room temperature, as recommended by the supplier. After formulation of the first test diet, the nicotine hydrogen tartrate was stored desiccated.

Animals: The protocol and the use of animals for this study were reviewed and approved by the RJRT Institutional Animal Use and Care Committee (IACUC) before arrival of the animals into the facility. Ninety male, juvenile CD-1 Swiss Webster mice (5-7 weeks of age) from Charles River Laboratories (Portage, Maine) were received into the facility on April 09, 2008. An additional 10 male, retired breeder mice were received for use as sentinel animals. These mice were maintained under identical conditions as the study animals, except they were fed Lab Diet, Certified Rodent Diet #5002 feed (PMI Nutrition International), provided as pellets throughout the study.

The mice were housed and cared for in accordance with the Institute of Laboratory Animal Research (ILAR), Commission of Life Sciences, National Research Council document entitled, *Guide for the Care and Use of Laboratory Animals* (1996) in an AAALAC accredited facility.

The mice were housed in a room in the vivarium with controlled lighting (12 hours of darkness, from 6:00 p.m. to 6:00 a.m. +/- 30 minutes). The room temperature was set to maintain 18-26ºC with a relative humidity of 30-70%. Room airflow was greater than 10 room air changes/hour. Seven-day, continuous chart-wheel recordings were kept for room temperature and relative humidity. In addition, room airflow and light cycles were monitored continuously and data recorded every 30 minutes to a computer file via an automated facility data collection system.

Mice were individually housed with no bedding in stainless steel, wire bottomed cages 9 in. (L) x 3.75 in. (W) x 5 in. (H) suspended on stainless steel racks. Mice had *ad libitum* access to NTP-2000 feed during the acclimation period. After acclimation and throughout the dosing period, NTP-2000 feed was provided as a powdered diet formulated with the test articles, positive control or as a control diet with no test article. Data for mice that spilled or contaminated their feed were censored for days when spillage was reported or when the data were unreasonable for the specific animal based upon group means and previous and subsequent feed intake for that specific animal. Water was provided to mice on an *ad libitum* basis through an automatic system. The water source originates from the municipal supply of the City of Winston-Salem, and is subsequently filtered through activated carbon and 5-micron particulate filters prior to delivery to the mice. This water is analyzed semi-

annually. There are no known contaminants expected to be present in the feed or water that would be anticipated to interfere with the outcome of the study.

Mice were quarantined and acclimated to the facility for seven days prior to initiation of the study and fed NTP-2000 feed. On the sixth day of the quarantine/acclimation period, mice were assigned to dose groups according to body weight using the "A" module of the PATH/TOX software (version 4.2.2; Xybion Medical Systems; Cedar Knolls, NJ). Body weights and detailed clinical signs were recorded before allocation. To ensure groups of similar mean body weight, all groups within the PATH/TOX protocol were compared by analysis of variance (ANOVA) and least significant difference criteria, and demonstrated not to be significantly different at a 5 percent, two-sided risk level. Following allocation into groups, mice were uniquely identified with their permanent identification number by tail tattoo and assigned to cages with permanent cage cards attached, which recorded the study number, Study Director's name, species, gender of the animal, group number, pre-allocation animal number, and the animal's permanent identification number.

The Attending Veterinarian performed a health examination of all mice within four days after delivery. Commencement of mouse dosing was dependent upon a favorable review of the health examination, as well as a written statement from the Attending Veterinarian releasing the mice from quarantine.

After allocation to study groups during the acclimation period, it was noted that some animals demonstrated excessive spillage, manipulated the feed and demonstrated other behaviors that could effect the measurement of feed consumption. To further refine the feeding techniques, the start of the study was delayed five days. During this period there was some drift of the animals' body weights resulting in group means being different on the first day of formulated feed administration.

Dosed Diet Formulation: The bulk NTP-2000 unformulated feed was stored at refrigerator temperatures (4ºC) in Lab 95 before being aliquotted to the control group and before it was aliquotted to prepare the formulated feeds.

Diets were formulated by the addition of the test article to a portion (premix representing approximately 25% of the total feed mix) of the total diet to be formulated. Mixing was done using commercial mixers (*KitchenAid Models #KP26M1XLC and #K45SSWH*). The pre-mix was then added to the bulk diet and mixed to obtain homogeneity. A preliminary test batch of feed formulated with each test article at the high and low dose was produced to refine the formulation techniques required and was not used in the study. Feed formulations were conducted twice during the study. Preparation of formulated feed for the first formulation (Series 1, used during the first week of the study) was based upon extrapolated body weight and feed consumption (30 g body weight, 5 g feed consumed/day) while the data from the first study week were used for these variables for the second formulation (Series 2, used during the second week of the study) (30 g body weight, 6.5 g feed consumed/day). Formulated feeds were stored at room temperature. The control feed was maintained identical to the formulated feed during each feeding period.

Analysis of formulated feed: The preliminary test batch of formulated feed at the high dose and low dose was submitted for analysis of nicotine to determine homogeneity and dose confirmation. Analysis was based upon a previously reported method that involved treating the formulated feed with base followed by solvent extraction and GC-FID quantitation. The initial analysis revealed that this method, as conducted at RJRT for this study, was appropriate only for the high dose used in the trial formulation. The nicotine concentration in the low dose was below the limit of quantitation for the GC-FID method, as conducted at RJRT for this study. Therefore, a new analytical method was rapidly developed at RJRT that allowed quantitation of the nicotine content in the diets at all dose concentrations. This method used GC-MS for quantitation and is not only more sensitive but decreased the sample requirements and analysis time.

Specific subsequent feed formulations at the high dose were assessed for homogeneity and stability and all doses were analyzed for dose confirmation.

Evaluation of Dead or Moribund Animals: Twice daily observations of all mice, once in the morning and once in the afternoon (at least 6 hours apart) were performed to identify dead or moribund mice. Observations were made five days per week, during weekends only one observation per day was performed.

Mice whose condition made it unlikely that they would survive until the next observation period, or appeared to be in pain were to be euthanized and necropsied at the discretion of the Attending Veterinarian or Study Director. Clinical observations were to be recorded shortly before euthanasia.

Any pre-test study mouse, including sentinels, euthanized in a moribund condition during the quarantine/acclimation phase were to have serum collected for serology and necropsied at the discretion of the Attending Veterinarian or Study Director.

Body Weights: Individual non-fasted body weights were determined two days after delivery and again prior to study group allocation (i.e., prior to the initial dosing). Body weights were recorded daily for the duration of the 14-day study. The "A" module of the Xybion PATH/TOX system was used for acquisition of body weight data. Weighing took place at approximately the same time each day. Individual body weights were used to calculate the mean body weight for each experimental group and percent body weight gain. Unscheduled body weight determinations were made at any time, if deemed necessary by the Attending Veterinarian or Study Director. Mouse weights were acquired using Mettler PM2000 balances (Mettler Instrument Corporation, Highstown, NJ). A non-fasted, terminal body weight was obtained from mice euthanized at study completion.

Feed Consumption: On each day of the study, feed was placed into the feed bowl and its weight determined and recorded. The next day, the bowl with uneaten feed was weighed and the feed consumption calculated. Data were entered into the "A" module of the PATH/TOX computer software. Each mouse's feed consumption was used to calculate the mean feed consumption for the group. In cases of excessive spillage or other inconsistencies, feed weight was recorded but not used to determine mean feed consumption for the group. After determination of the feed consumed by a mouse,

additional, fresh feed was placed in a bowl and provided to the mouse after recording the weight in the PATH/TOX software.

Clinical Observations: Except for weekends, daily observations for clinical signs were taken. All positive findings were recorded as unscheduled clinical observations using the "AINPUT" module of the PATH/TOX computer software. Negative findings (normal/no significant findings) were not recorded.

In addition, detailed (scheduled) clinical observations were performed the two days after delivery, when collecting body weights for allocation to study groups and at twice weekly intervals, Monday and Friday, throughout the study. Both positive and negative findings were recorded. The "A" module of the PATH/TOX system was used for acquisition of clinical signs data.

Results and Discussion

Feed Formulation Analysis: During the course of the study three feed formulations were conducted. The first formulation was a trial run to refine the formulation methodology and determine the homogeneity obtained at the high and low doses. The trial run used dosing information for rats to formulate the diet. Even though the rat formulation was used it directly relates to mouse diets because the feed was identical, the test articles were identical and the formulation methodology was identical for rats and mice. Feed from the trial run was not fed to the mice. This was followed by Series 1 formulation for the first week of the study, then Series 2 formulation for the second week of the study. Calculations of feed requirements (feed consumption and body weight) for Series 1 were based upon extrapolation of the growth of the mice. Calculations for Series 2 formulation were based upon data collected during the first week of the study. The formulated feed from certain of these preparations has undergone preliminary analyses for nicotine to determine homogeneity of the test articles and positive control in the diet and for nicotine concentration to confirm that the feed contained the anticipated concentration of nicotine.

Homogeneity data from the trial run are presented in Table 2.

Table 2**: Feed Formulation Trial Run: Homogeneity Data**[1]
(40 mg nicotine/kg body weight/day)

Target Concentration (mg nic/g feed)	Sample Location **Top**	**Middle** (mg nic/g feed)	**Bottom**	Average Concentration (mg nic/g feed)
		Tobacco Blend		
0.50	0.46 ± 0.02 (8%)[2]	0.47 ± 0.01 (6%)	0.45 ± 0.02 (10%)	0.46 ± 0.01 (8% ± 2%)
		Tobacco Extract		
0.50	0.40 ± 0.04 (20%)	0.43 ± 0.06 (14%)	0.39 ± 0.02 (22%)	0.41 ± 0.02 (18% ± 4%)
		Nicotine Tartrate		
0.50	0.42 ± 0.2	0.41 ± 0.01	0.40 ± 0.01	0.41 ± 0.02

	(16%)	(18%)	(20%)	(18% ± 2%)

[1] Analytical method uncertainty for nicotine analysis = ± 5.2%, data represent the mean ± SD of triplicate assays. [2] % difference from target concentration

These data are from the high dose preparation for rats (40 mg nicotine/kg body weight/day) but can equally be used for mice since the methodology for diet formulation is identical for each species with the exception of nicotine concentration. Samples were obtained from the top of the formulated feed mixture as well as the middle and bottom of the mixture. Although the low dose preparation (0.2 mg nicotine/kg body weight/day) was also analyzed for nicotine content, the nicotine concentration was below the limit of quantitation for the GC-FID analysis method, as conducted at RJRT for this study.

Feed formulated with the tobacco blend demonstrated good homogeneity with the samples being within ± 10% of each other. The mean concentration of nicotine in the feed indicated that it was within ± 10% of the anticipated concentration, indicating adequate dose confirmation. Visual inspection of the formulated feed indicated no change in the color of the feed and there were no visible evidence of tobacco particles.

Feed formulated with the aqueous tobacco extract demonstrated adequate homogeneity but was below the anticipated nicotine concentration. The problem appears to occur at the pre-mix stage. The extract is viscous and tends to stick to the blade of the mixer and to some extent the mixing bowl. This would result in a lower than expected concentration. Based upon these data, the mixing methodology was altered to decrease the potential for the extract to contact the blending device by carefully adding the extract to the premix followed by hand mixing to avoid direct contact between the liquid extract and the sides of the bowl.

The nicotine hydrogen tartrate also demonstrated adequate homogeneity in feed but the nicotine concentration was lower than anticipated. Based upon these data, the mixing methodology was modified by placing a small portion of the diet in a mortar and pestle to which the nicotine salt was added. Lumps of the salt were gently broken and mixed with the feed. When there were no longer any visible lumps, the feed was then added to the pre-mix for mechanical mixing. Also, the nicotine salt was stored in a desiccator to minimize moisture absorption.

Homogeneity data for the Series 1 and Series 2 formulations are currently unavailable.

Dose Confirmation Data: Series 1 analytical data were collected during an early stage of development of the GC-MS analytical methodology and may be unreliable and are not presented in this preliminary report. It is anticipated that these samples will be reanalyzed. Dose confirmation data for Series 2 formulations are presented in Tables 3 – 5, respectively. These data are presented as a general comparison not as absolute quantitative data. The nicotine quantitation data are from an analytical method that is currently under development and has not been extensively validated. The data are useful to confirm that the diets contained increasing quantities of nicotine and indicate that there were no major errors in formulation. Additional data may be available in the near future and will be incorporated into the final report for the study. These data in combination with the dose responses seen in the study indicate that the proper formulated feeds were fed to the mice.

Table 3: **Series 2 Dose Confirmation Data Tobacco Blend**

Target Dose (mg of nicotine/kg of bw/day)	**Target Concentration** (g of nicotine/g of feed)	**Analytically Estimated Feed Nicotine Concentration** (mg of nicotine/g of feed)
0.2	0.0009	0.0011
2.0	0.0092	0.009
4.0	0.0185	0.016
8.0	0.0369	0.030
20.0	0.0923	0.090
40.0	0.1846	0.184

Table 4: **Series 2 Dose Confirmation Data Tobacco Extract**

Target Dose (mg of nicotine/kg of bw/day)	**Target Concentration** (g of nicotine/g of feed)	**Analytically Estimated Feed Nicotine Concentration** (mg of nicotine/g of feed)
0.2	0.0009	0.0008
2.0	0.0092	0.004
4.0	0.0185	0.020
8.0	0.0369	0.018
20.0	0.0923	0.062
40.0	0.1846	0.205

Table 5: **Series 2 Dose Confirmation Data Nicotine Tartrate**

Target Dose (mg of nicotine/kg of bw/day)	**Target Concentration** (g of nicotine/g of feed)	**Analytically Estimated Feed Nicotine Concentration** (mg of nicotine/g of feed)
2.0	0.0092	0.008
8.0	0.0369	0.031
20.0	0.0923	-
40.0	0.1846	0.233

These data indicate that the concentrations of nicotine in the formulated feeds were adequate for the purposes of this study.

Stability: Preliminary stability data for nicotine from each test article and the positive control are available for the high dose formulation made during the prestudy trial run. A sample set was allowed to remain at room temperature for 30 days after initial formulation.

The 30-day old samples are compared to the fresh samples in Table 6. These data provide no indication of instability of the nicotine in the 30-day old feed samples.

Table 6: **Prestudy Trial Formulations 30 Day Stability Data**[1]

Dose (mg nic/kg bw/day	Target Concentration (mg nic/g feed)	Analytically Estimated "0" day (mg nic/g feed)	Analytically Estimated 30 Day (mg nic/g feed)	% Difference
		Tobacco Blend		
40	0.50	0.47 ± 0.01	0.44	-6.4
		Tobacco Extract		
40	0.50	0.43 ± 0.06	0.44	+2.3
		Nic. Tartrate		
40	0.50	0.41 ± 0.01	0.42	+2.4

[1] Formulated feed stored at room temperature in the mixing room.

Preliminary stability data are also available for nicotine from low and high dose of each test article and the positive control for the rat Series 2 feed formulations. Because the mouse formulated feed was identical to that of the rat except for the exact nicotine concentrations, these data should also apply for the mouse formulations. These data compare the nicotine content of freshly prepared feed with that of feed maintained in the animal room for one week. There is no indication of a lack of stability of nicotine in these samples. The variability seen in the low dose tobacco blend is believed to be due to the analytical variability and not to a loss of nicotine because no differences were seen with the extract and positive control.

Table 7: **Series 2 Formulations One Week Stability Data**[1]

Dose (mg nic/kg bw/day	Target Concentration (mg nic/g feed)	Analytically Estimated "0" day (mg nic/g feed)	Analytically Estimated One Week (mg nic/g feed)	% Difference
		Tobacco Blend		
0.2	0.002	0.004	0.002	-50
40	0.433	0.36	0.41	+14
		Tobacco Extract		
0.2	0.002	0.001	0.001	0
40	0.433	0.31	0.37	+19
		Nic. Tartrate		
2.0	0.021	0.019	0.019	0
40	0.433	0.036	0.036	0

[1] Formulated feed stored in the animal room for one week.

Body Weight Data: Percent body weight gain data for mice fed the tobacco blend at different doses of nicotine are provided in Figure 1, while absolute body weight gain is presented in Figure 2. The data in Figure 1 are presented in terms of percent body weight gain that normalizes the body weights, which differed slightly at the initiation of the study.

Individual body weights, group mean body weights and their standard deviations as well as additional graphs are presented in the Appendix of this report.

Figure 1

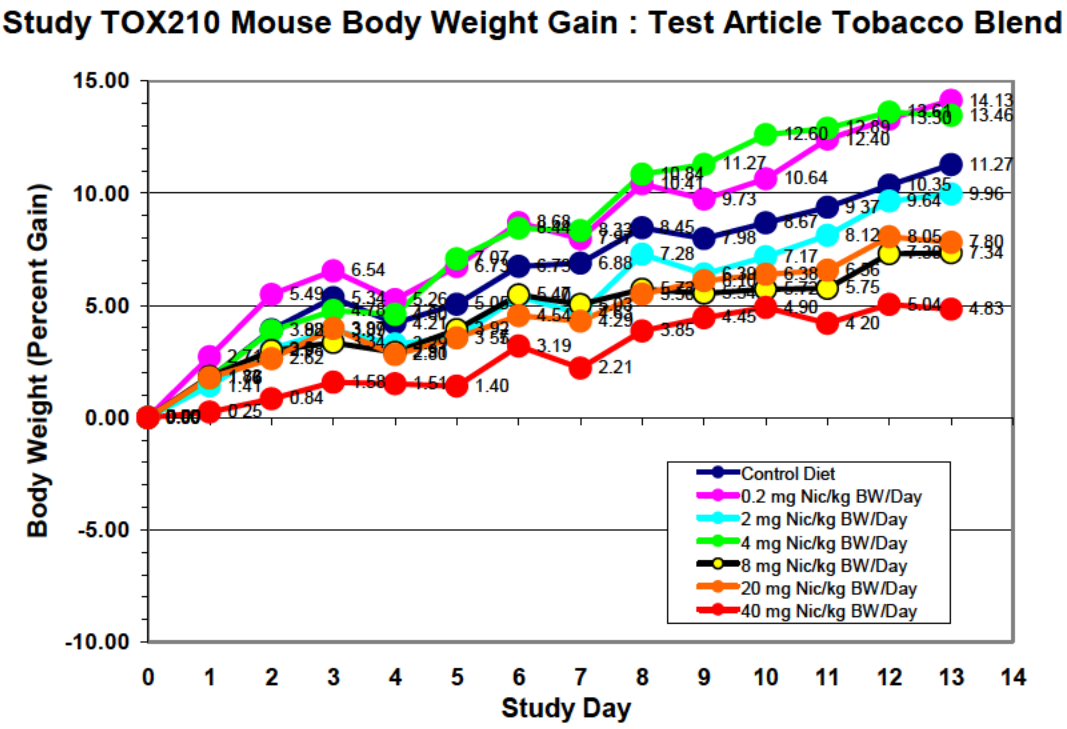
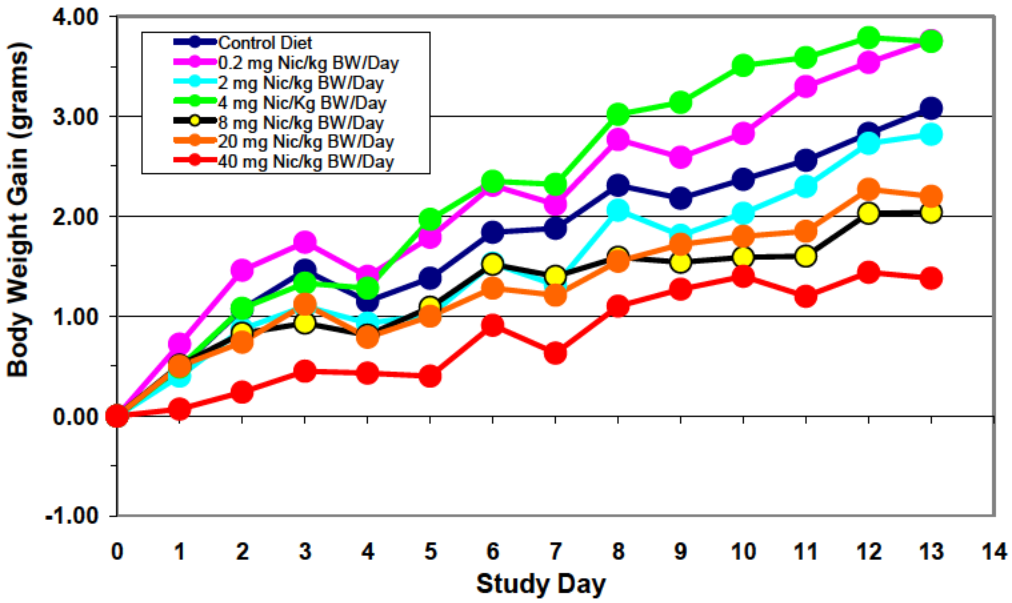


Figure 2

Study TOX210 Mouse Body Weights: Test Article Tobacco Blend
Absolute Gain in Body Weight (grams)



The control demonstrated normal body weight gains for male mice of this age. There is not a strong dose response demonstrated in the data. For two of the nicotine doses, 0.2 and 4 mg nicotine/kg body weight/day, the trend in percent body weight gain actually surpassed that of the control group. The 2 mg nicotine dose trend for body weight gain was slightly below that of the control group, while the 8 and 20 mg nicotine/kg body weight/day were almost identical and their trend in body weight gain was below that of the control. The high dose, 40 mg nicotine/kg body weight/day, was consistently below that of the control and the other doses. The increase in percent body weight gain at the high dose was about one half that of the control, indicating a definitive effect at this dose.

These data indicate that the mice could detect, either at an organoleptic level or a neurophysiological level, the presence of the tobacco blend at the high dose used in this study. These data do not provide evidence for a dose that would produce unwarranted reductions in percent body weight gain but do indicate that a dose of 40 mg nicotine/kg body weight/day could be a potential lower dose for additional studies.

At least two possibilities should be considered in respect to explaining these data. First, at an organoleptic level, the mice may consider diets containing the tobacco to lack palatability and consume them at a lower rate than the control diet. As the dose increased the palatability of the feed became lower resulting in less feed consumption with the resulting decrease in body weight gain. Second, at the neurophysiological level, it is possible that the nicotine in the tobacco blend produced changes in the peripheral or central nervous system that were undetected in this palatability study. These changes could have produced an appetite depression or other effect that may have altered feed intake and body weight gain.

Percent body weight gain data for mice fed the feed formulated with the tobacco extract are presented in Figure 3, while absolute body weight gain data are presented in Figure 4.

Figure 3

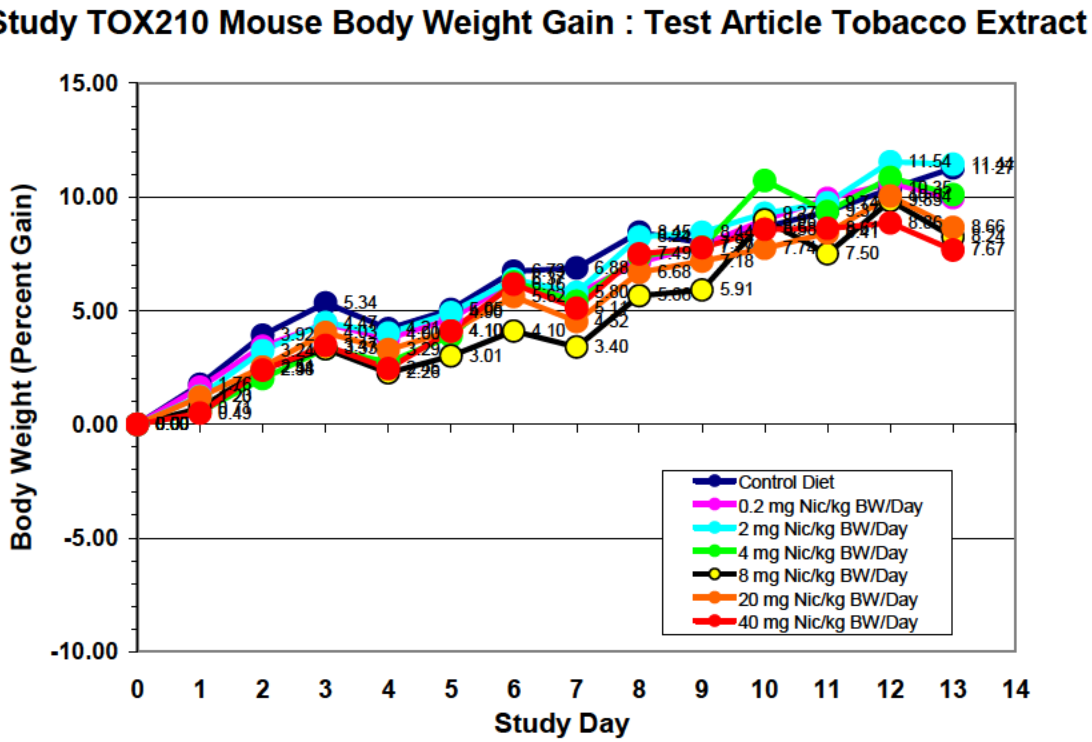
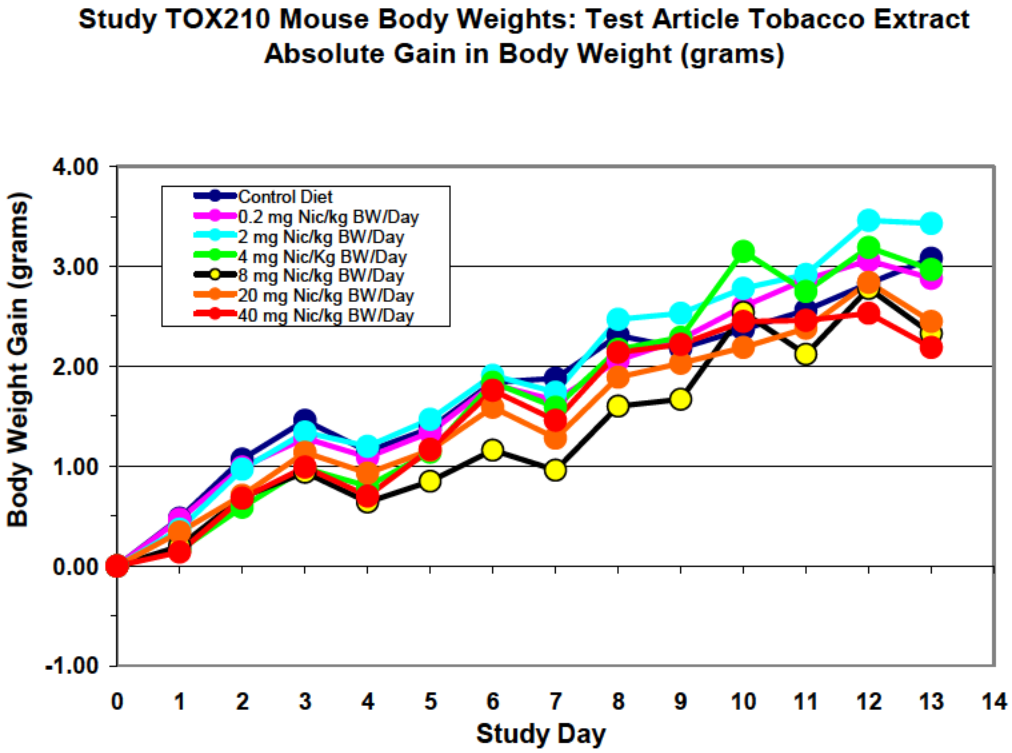


Figure 4



Although there was a trend toward the mice receiving the feed formulated with different doses of the tobacco extract to have slightly reduced body weight gain, there is little evidence of dose related differences. Unlike the tobacco blend there is no dose that shows a definitive trend toward reduced body weight percent gain. The reasons for the different response compared to the tobacco blend are not apparent from the results of this study.

Figure 5 provides the percent body weight gain data for mice fed diets containing the positive control, nicotine hydrogen tartrate, while Figure 6 provides the absolute body weight gains.

Figure 5

Study TOX210 Mouse Body Weight Gain : Test Article Nicotine Tartrate

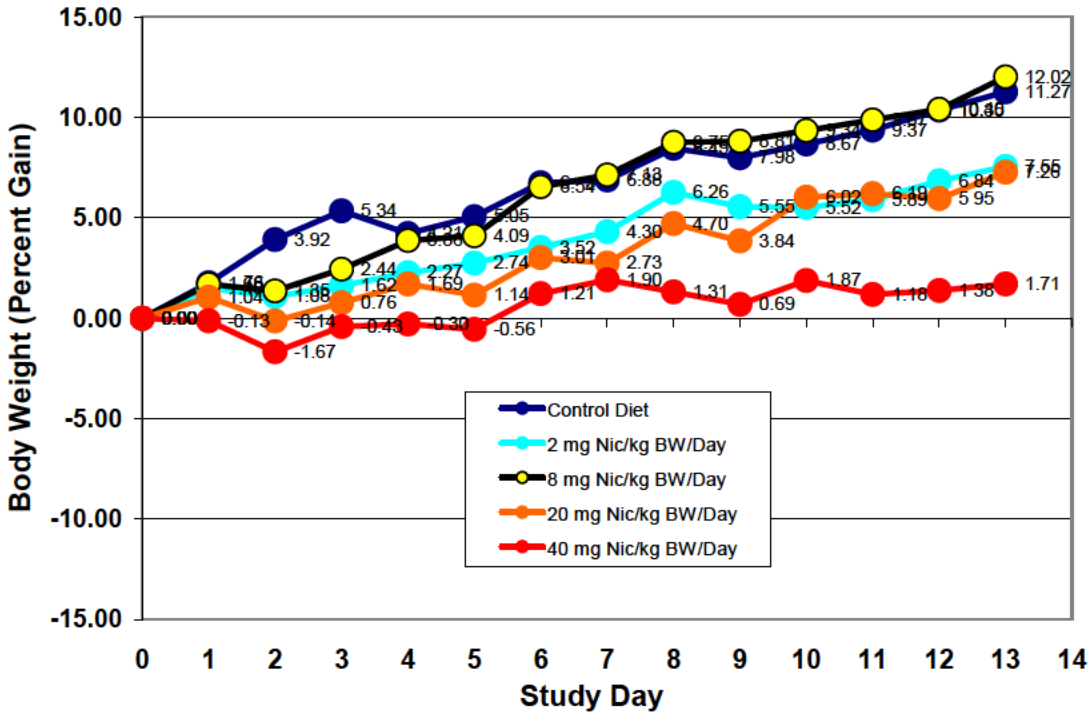
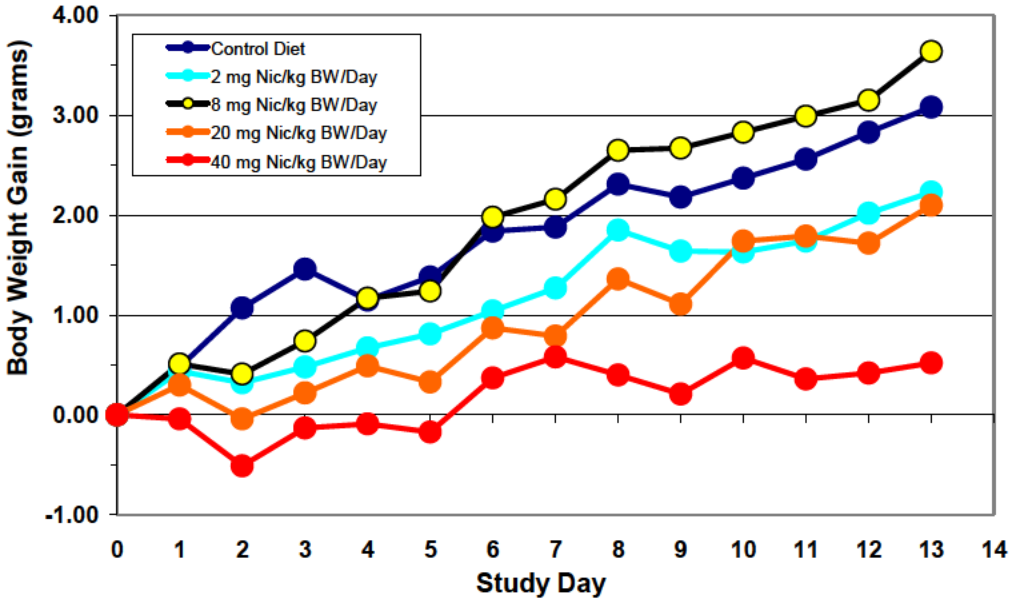


Figure 6

Study TOX210 Mouse Body Weights: Test Article Nicotine Tartrate Absolute Gain in Body Weight (grams)



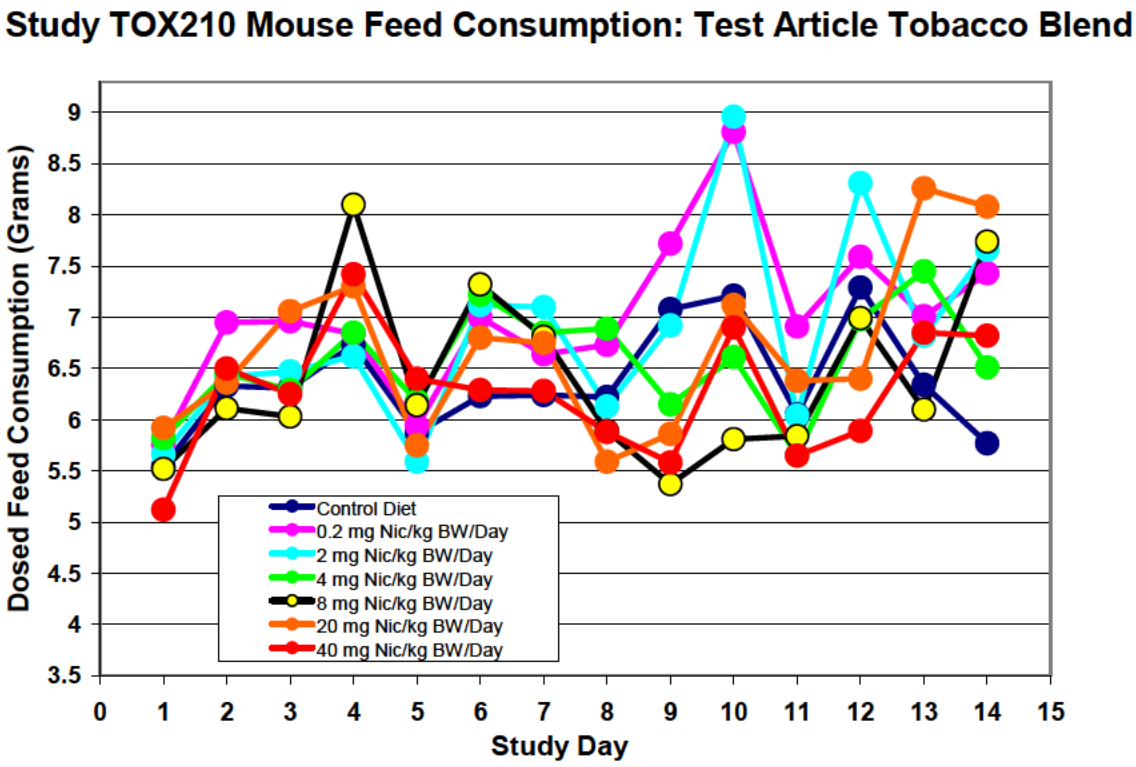
Mice fed feed containing nicotine tartrate demonstrated a definitive dose response in percent body weight gain at the 20 and 40 mg nicotine/kg body weight/day doses. At the high dose there was no increase in percent body weight gain until day six of the study and from day six to study termination there was little change in percent body weight gain, while the control demonstrated a normal increase in percent body weight gain. At 20 mg nicotine/kg body weight, there was a lag of 2-3 days before body weight gain began to increase. At this dose, body weight gain continued to increase throughout the remainder of the study at a rate similar to the control but remained quantitatively below that of the control. The 2 mg nicotine/kg body weight/day dose followed a trend similar to the 20 mg nicotine dose but remained quantitatively below that of the control. At 8 mg nicotine/kg body weight/day, there was a depression in body weight on days 2 and 3 compared to the control while on day 4 body weight was equivalent to the control. During the second week of the study, this dose group's mean body weight was similar, if not slightly higher, than that of the control group. Nicotine hydrogen tartrate produced a somewhat greater effect at 40 mg nicotine/kg body weight that did the tobacco blend. The overall trends in the data follow those seen with the tobacco blend as opposed to the tobacco extract. Whether or not this is due to a lack of palatability of the feed or to a physiological effect of nicotine can not be ascertained from this study.

Based upon these nicotine hydrogen tartrate data, doses substantially higher than 40 mg nicotine/kg body weigh/day for long durations may result in unwarranted decreases in body weight in mice fed diets formulated with this nicotine salt.

Because the nicotine tartrate dosed group contained no tobacco, these data may indicate that the decreased percent body weight gains seen in this study in the various treatment groups may be associated with their nicotine content more than with the presence of other tobacco components.

Feed Consumption: Feed consumption data for mice fed feed containing the tobacco blend are shown in Figure 7.

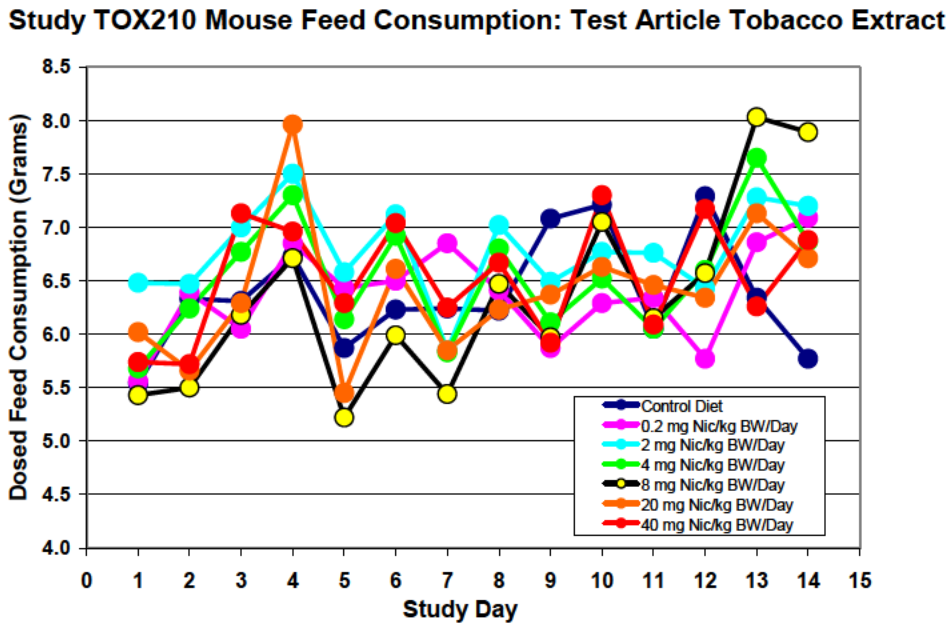
Figure 7



Data for feed consumption for the mice in this study appears highly erratic, even for the control group. No dose related trends can be ascertained.

Feed consumption data for mice fed feed containing the tobacco extract are shown in Figure 8.

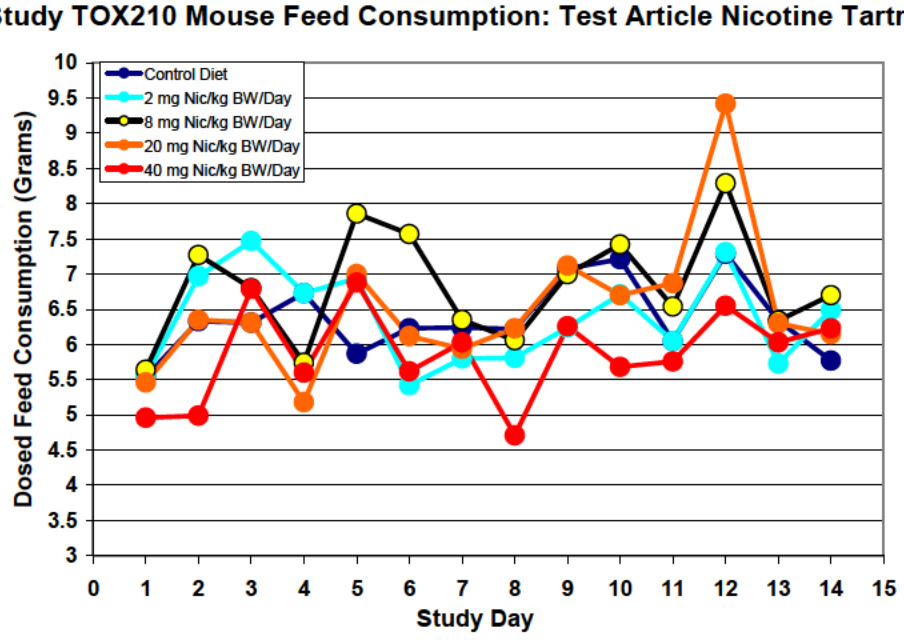
Figure 8



As seen with the tobacco blend, the feed consumption data for the tobacco extract appears erratic and no dose trends are obvious.

Feed consumption data for the mice fed feed containing nicotine hydrogen tartrate are shown in Figure 9.

Figure 9



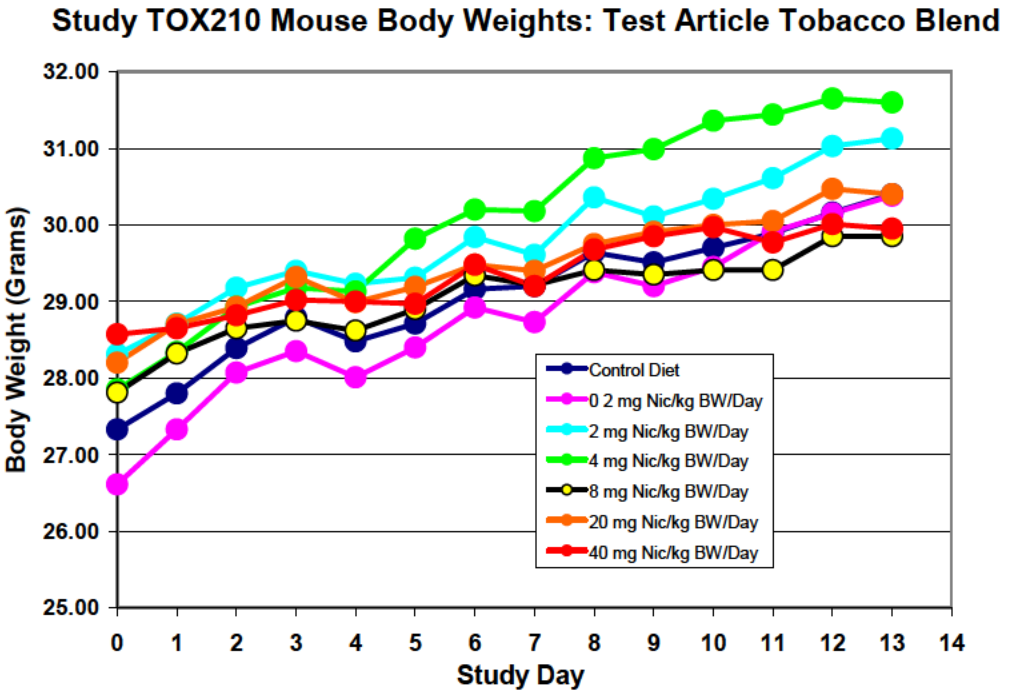
As seen with the tobacco blend and the tobacco extract, the data for feed consumption for the mice dosed with nicotine hydrogen tartrate are too erratic to discern dose related effects.

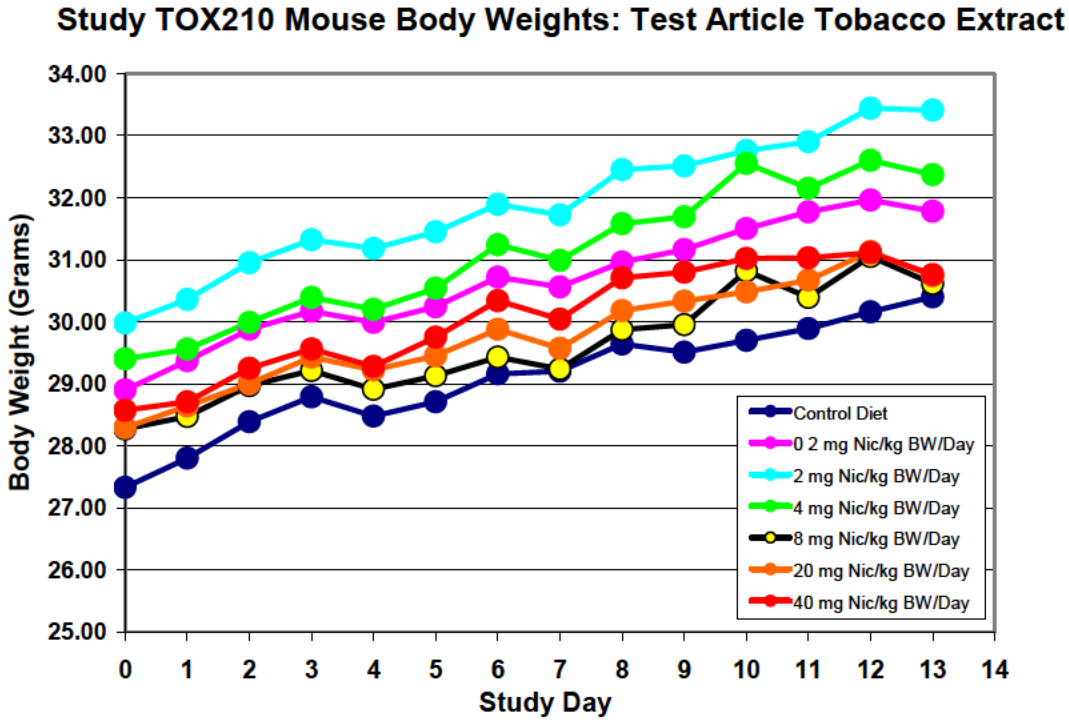
Clinical Observations: There were no clinical observations indicating altered behavior or any other evidence of nicotine toxicity during the study. This indicates that the doses used in the study were below those that may elicit nicotinic effects in the animals detectable by clinical observations.

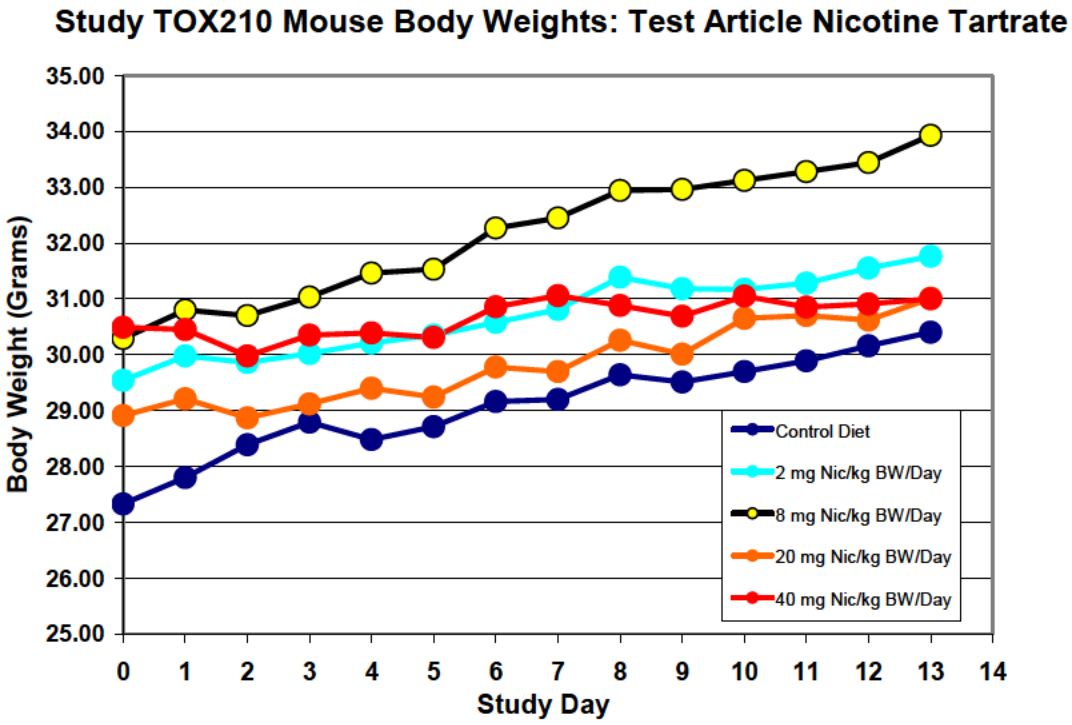
Serology: Serological screening provided no indication of disease in the sentinel mice.

Appendix

Additional Graphs of Data






Study TOX210 Mouse Body Weights: Test Article Nicotine Tartrate
Body Weight (Grams)
35.00
34.00
33.00
32.00
31.00
30.00
29.00
28.00
27.00
26.00
25.00
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Study Day
Control Diet
2 mg Nic/kg BW/Day
8 mg Nic/kg BW/Day
20 mg Nic/kg BW/Day
40 mg Nic/kg BW/Day

Comments Concerning Path/Tox Data Outputs

Data associated with the use of mice on study were acquired with the aid of the Path/Tox (Xybion Medical Systems, Cedar Knolls, NJ) software version 4.2.2 resident on a VAX operating system under the Path/Tox protocols referred to as TOX210A and TOX210B.

The Xybion data collection protocols TOX210A and TOX210B were used for body weights and feed consumption of mice used on this study. Body weight data and feed consumption data were input into the Xybion Path/Tox collection protocols under "A" module, "AINPUT'.

Because of the limitations in the Path/Tox system, two protocols were created to accommodate all 17 dosed groups. TOX210A contains Dose Groups 1-13. TOX210B contains the four Nicotine Tartrate Positive Control Groups .

Xybion Group Number	*Treatment Group (Doses based on Nicotine) (mg/kg body weight/day)*	*Number of Mice*	*Mouse ID Numbers*
	Xybion Protocol TOX210A Control		
1	NTP-2000 feed	5	1-5
	Xybion Protocol TOX210A Tobacco Blend		
2	Dose 1 Tobacco in NTP-2000 feed (0.2)	5	6-10
3	Dose 2 Tobacco in NTP-2000 feed (2.0)	5	11-15
4	Dose 3 Tobacco in NTP-2000 feed (4.0)	5	16-20
5	Dose 4 Tobacco in NTP-2000 feed (8.0)	5	21-25
6	Dose 5 Tobacco in NTP-2000 feed (20.0)	5	26-30
7	Dose 6 Tobacco in NTP-2000 feed (40.0)	5	31-35
	Xybion Protocol TOX210A Tobacco Extract		
8	Dose 1 Tobacco Extract in NTP-2000 feed (0.2)	5	36-40
9	Dose 2 Tobacco Extract in NTP-2000 feed (2.0)	5	41-45
10	Dose 3 Tobacco Extract in NTP-2000 feed (4.0)	5	46-50
11	Dose 4 Tobacco Extract in NTP-2000 feed (8.0)	5	51-55
12	Dose 5 Tobacco Extract in NTP-2000 feed (20.0)	5	56-60
13	Dose 6 Tobacco Extract in NTP-2000 feed (40.0)	5	61-65
	Xybion Protocol TOX210B Nicotine Tartrate		
1	Dose 1 Nicotine Tartrate in NTP-2000 feed (2.0)	5	66-70
2	Dose 2 Nicotine Tartrate in NTP-2000 feed (8.0)	5	71-75
3	Dose 3 Nicotine Tartrate in NTP-2000 feed (20.0)	5	76-80
4	Dose 4 Nicotine Tartrate in NTP-2000 feed (40.0)	5	81-85
	Sentinels		
	Sentinels (no treatment)	10	86-95

Because the start of the exposure phase was delayed five days for both TOX210A and TOX210B studies, Exposure Phase Day 6 of the Xybion data output is study Day 0 when the dosed feed was first administered to the mice (April 21, 2008). Day 1 (Exposure Phase Day 7 of the Xybion data output) represents data collected after a full 24-hr exposure either to the control feed, or the tobacco blend, or tobacco extract or nicotine tartrate formulated feed.

Animal	Group		Day of Phase 6	7	8	9	10	11	12	13	14	15	16	17	18
			Male Animals												
1	1		30.41	30.65	31.36	32.00	31.68	31.71	31.86	31.98	32.52	32.44	32.69	33.05	33.33
2			28.83	29.47	30.23	30.52	30.12	30.55	31.30	31.17	32.05	31.85	32.27	32.41	33.20
3			29.52	30.19	30.61	31.17	31.06	31.24	32.15	32.42	32.70	32.89	33.47	33.11	33.51
4			25.75	26.46	26.97	27.49	27.33	27.69	28.07	28.32	28.46	28.25	28.06	28.52	28.41
5			22.12	22.24	22.79	22.76	22.20	22.36	22.44	22.12	22.45	22.11	22.00	22.34	22.35
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	27.33	27.80	28.39	28.79	28.48	28.71	29.16	29.20	29.64	29.51	29.70	29.89	30.16
		Sdevs	3.40	3.51	3.55	3.78	3.88	3.88	4.10	4.27	4.37	4.52	4.79	4.63	4.86
6	2		29.34	30.71	31.59	31.90	31.38	32.20	32.32	32.08	32.90	32.72	32.90	33.64	34.01
7			26.14	26.61	27.19	27.63	27.29	27.78	28.60	28.34	29.29	29.07	29.50	29.89	30.02
8			23.21	23.81	24.55	24.93	24.64	24.53	25.20	25.09	25.83	25.61	25.79	26.24	26.50
9			26.64	27.17	27.85	28.02	27.86	28.32	28.74	28.75	28.99	28.72	29.09	29.01	29.37
10			27.73	28.36	29.18	29.29	28.87	29.17	29.73	29.39	29.91	29.89	29.95	30.76	30.85
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	26.61	27.33	28.07	28.35	28.01	28.40	28.92	28.73	29.38	29.20	29.45	29.91	30.15
		Sdevs	2.26	2.52	2.59	2.54	2.45	2.76	2.56	2.50	2.52	2.55	2.53	2.69	2.71
11	3		33.30	33.94	34.32	34.97	34.99	35.14	35.56	35.24	36.11	35.87	36.41	36.69	37.59
12			26.55	26.65	27.16	27.02	27.35	27.30	28.22	28.27	29.15	28.91	28.91	29.38	29.53
13			28.86	29.03	29.78	30.36	29.44	29.52	30.47	30.00	30.45	30.14	30.69	30.65	31.02
14			28.56	29.13	29.71	29.61	29.26	29.13	29.36	29.19	29.57	29.42	29.55	29.84	30.02
15			24.26	24.80	24.91	25.05	25.13	25.48	25.58	25.36	26.54	26.22	26.14	26.49	27.01
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.31	28.71	29.18	29.40	29.23	29.31	29.84	29.61	30.36	30.11	30.34	30.61	31.03
		Sdevs	3.35	3.43	3.51	3.76	3.66	3.63	3.68	3.60	3.53	3.54	3.78	3.74	3.95
16	4		25.66	26.13	27.02	27.34	27.50	28.66	28.69	28.63	29.47	29.62	29.38	29.54	29.42
17			30.00	30.83	31.42	32.01	31.80	32.28	32.99	33.23	33.96	34.19	34.88	34.85	35.20
18			29.85	30.42	31.02	31.53	31.42	32.02	32.38	32.44	33.60	33.76	34.41	34.26	34.58
19			27.74	28.09	28.49	28.45	28.26	29.10	29.49	29.74	30.08	30.13	30.63	30.62	30.87
20			26.01	26.23	26.69	26.58	26.69	27.04	27.44	26.84	27.25	27.26	27.50	27.95	28.16
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	27.85	28.34	28.93	29.18	29.13	29.82	30.20	30.18	30.87	30.99	31.36	31.44	31.65
		Sdevs	2.05	2.23	2.20	2.46	2.33	2.26	2.39	2.65	2.86	2.93	3.20	3.00	3.12
21	5		27.97	28.31	28.69	28.70	28.63	28.88	29.10	29.22	29.73	29.31	29.21	29.12	29.60
22			30.10	30.61	31.09	30.93	30.79	31.12	31.81	31.78	31.47	31.68	31.77	31.80	32.11
23			28.03	28.20	28.15	28.68	28.56	29.15	29.41	29.19	29.24	29.44	29.52	29.44	30.09
24			26.08	26.76	27.08	27.04	26.99	27.37	27.72	27.37	27.79	28.09	28.04	28.08	28.88

Note: Data for Exposure phase

Animal	Group		Day of Phase 6	7	8	9	10	11	12	13	14	15	16	17	18
			Male Animals												
25	5		26.89	27.74	28.22	28.38	28.14	27.99	28.65	28.51	28.81	28.24	28.49	28.61	28.56
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	27.81	28.32	28.65	28.75	28.62	28.90	29.34	29.21	29.41	29.35	29.41	29.41	29.85
		Sdevs	1.51	1.42	1.49	1.40	1.38	1.43	1.52	1.62	1.36	1.44	1.44	1.43	1.40
26	6		32.03	32.81	32.84	33.49	33.41	33.65	34.03	33.82	34.06	34.34	34.54	34.77	35.20
27			27.12	27.44	27.50	27.91	27.71	28.23	28.77	28.73	29.20	29.30	29.43	29.68	30.12
28			24.87	25.17	25.34	25.60	25.28	25.40	25.46	25.35	25.80	25.92	26.05	26.10	26.32
29			28.76	29.22	29.94	30.19	29.64	30.06	30.08	30.24	30.78	30.87	31.07	31.01	31.33
30			28.20	28.86	29.04	29.41	28.91	28.63	29.06	28.87	28.90	29.13	28.89	28.69	29.36
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.20	28.70	28.93	29.32	28.99	29.19	29.48	29.40	29.75	29.91	30.00	30.05	30.47
		Sdevs	2.61	2.79	2.80	2.91	2.97	3.01	3.08	3.06	3.01	3.06	3.12	3.19	3.23
31	7		29.30	29.70	29.91	30.14	29.80	29.70	30.09	29.90	30.16	30.26	30.09	29.95	30.56
32			29.07	28.94	28.83	28.90	29.30	28.97	30.08	29.88	30.34	30.86	30.84	30.36	30.76
33			28.47	28.23	28.93	29.20	29.48	29.49	29.98	29.85	30.18	30.57	30.90	30.91	30.93
34			31.03	31.06	30.82	31.27	30.79	31.24	31.25	30.61	31.61	31.49	31.72	31.40	31.43
35			24.99	25.30	25.59	25.59	25.63	25.47	26.02	25.77	26.09	26.05	26.30	26.23	26.39
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.57	28.65	28.82	29.02	29.00	28.97	29.48	29.20	29.68	29.85	29.97	29.77	30.01
		Sdevs	2.22	2.14	1.98	2.13	1.97	2.13	2.01	1.94	2.09	2.17	2.13	2.05	2.05
36	8		24.01	24.47	24.90	25.06	24.72	24.92	25.69	25.42	25.75	25.62	26.16	26.15	26.32
37			30.93	31.29	32.22	32.34	32.83	33.45	33.51	33.06	33.80	33.81	34.27	34.35	34.51
38			29.34	29.68	30.22	30.40	29.97	30.00	30.50	30.54	30.56	31.01	31.33	31.40	31.94
39			31.70	32.33	32.66	33.23	32.63	32.93	33.62	33.52	34.05	34.31	34.56	35.14	34.97
40			28.51	29.06	29.42	29.84	29.79	29.90	30.29	30.26	30.64	31.07	31.17	31.80	32.06
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.90	29.37	29.88	30.17	29.99	30.24	30.72	30.56	30.96	31.16	31.50	31.77	31.96
		Sdevs	3.01	3.03	3.10	3.18	3.27	3.39	3.23	3.22	3.35	3.45	3.38	3.53	3.44
41	9		28.19	28.93	29.29	29.86	29.70	29.81	30.24	29.81	30.65	30.83	30.97	31.06	31.44
42			28.31	28.86	29.21	29.65	29.90	30.28	30.35	30.41	30.71	30.36	30.99	30.69	31.69
43			33.90	34.08	35.08	35.22	35.51	35.87	36.08	36.08	36.82	36.79	37.28	37.36	37.63
44			32.64	32.80	33.35	33.83	33.77	33.57	34.81	35.12	35.88	35.45	35.24	35.90	36.10
45			26.87	27.11	27.83	28.04	27.03	27.73	27.96	27.19	28.19	29.13	29.34	29.51	30.36
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	29.98	30.36	30.95	31.32	31.18	31.45	31.89	31.72	32.45	32.51	32.76	32.90	33.44
		Sdevs	3.09	2.94	3.10	3.05	3.41	3.24	3.41	3.76	3.72	3.38	3.34	3.49	3.21

Note: Data for Exposure phase

Animal	Group		Day of Phase 6	7	8	9	10	11	12	13	14	15	16	17	18
			Male Animals												
46	10		26.17	26.67	27.19	27.32	27.04	27.78	28.69	27.91	29.28	29.03	29.16	29.40	29.70
47			30.29	30.27	30.70	30.97	30.61	30.73	31.59	30.97	31.17	31.32	34.58	30.85	31.06
48			30.78	31.40	31.59	32.08	32.16	32.42	33.17	33.46	34.10	34.34	34.52	35.22	35.48
49			28.27	28.23	28.45	28.95	28.82	29.18	29.66	29.57	29.76	29.75	29.79	30.24	30.64
50			31.50	31.22	32.01	32.61	32.36	32.59	33.10	33.05	33.57	34.02	34.69	35.03	36.10
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	29.40	29.56	29.99	30.39	30.20	30.54	31.24	30.99	31.58	31.69	32.55	32.15	32.60
		Sdevs	2.17	2.05	2.08	2.21	2.27	2.08	2.02	2.34	2.18	2.42	2.81	2.77	2.97
51	11		31.46	31.61	32.36	32.90	32.28	32.65	33.05	32.72	33.31	33.38	33.68	33.88	34.42
52			27.06	27.18	27.67	28.03	27.79	27.60	27.87	27.68	27.98	28.16	28.49	28.60	29.01
53			27.85	28.18	28.47	28.52	28.24	28.59	28.64	28.84	29.42	29.31	29.99	27.17	27.75
54			25.70	25.73	26.07	26.60	26.40	26.56	27.11	26.41	27.36	27.46	30.01	30.26	30.84
55			29.30	29.65	30.27	30.00	29.86	30.23	30.50	30.54	31.30	31.42	31.91	32.05	33.24
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.27	28.47	28.97	29.21	28.91	29.13	29.43	29.24	29.87	29.95	30.82	30.39	31.05
		Sdevs	2.21	2.26	2.43	2.39	2.25	2.39	2.38	2.47	2.45	2.44	2.01	2.67	2.80
56	12		32.54	33.01	33.40	33.55	33.58	33.53	33.69	33.17	33.10	33.06	33.58	33.59	33.89
57			26.90	27.65	28.04	28.56	28.28	28.88	28.94	28.81	28.98	29.08	29.07	28.81	29.31
58			30.30	30.35	30.87	30.96	30.78	31.34	31.89	31.97	32.57	32.84	33.01	33.95	34.16
59			23.42	23.69	24.14	24.46	24.38	24.37	24.76	23.86	24.99	25.34	25.25	25.30	26.04
60			28.30	28.48	28.55	29.62	29.09	29.15	30.13	30.06	31.28	31.31	31.49	31.71	32.27
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.29	28.64	29.00	29.43	29.22	29.45	29.88	29.57	30.18	30.33	30.48	30.67	31.13
		Sdevs	3.46	3.45	3.45	3.35	3.38	3.41	3.38	3.61	3.31	3.21	3.40	3.63	3.44
61	13		28.45	28.79	28.92	29.19	28.90	29.25	30.27	29.87	30.37	30.40	30.28	30.32	30.21
62			26.17	26.19	27.03	27.28	27.29	27.60	28.29	28.24	28.57	28.75	29.23	29.24	29.35
63			26.97	27.38	27.48	27.65	27.37	27.92	28.74	27.97	29.31	29.42	29.78	29.74	30.05
64			28.93	28.27	29.04	29.35	29.16	29.59	29.83	29.66	29.66	29.78	30.06	30.06	29.93
65			32.35	32.93	33.79	34.33	33.66	34.37	34.56	34.44	35.65	35.64	35.75	35.79	36.00
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.57	28.71	29.25	29.56	29.28	29.75	30.34	30.04	30.71	30.80	31.02	31.03	31.11
		Sdevs	2.38	2.56	2.68	2.82	2.60	2.72	2.49	2.60	2.84	2.77	2.67	2.69	2.75

Note: Data for Exposure phase

Animal	Group	Day of Phase 19
		Male Animals
1	1	33.76
2		33.40
3		33.84
4		28.54
5		22.47
	(n)	5
	Means	30.40
	Sdevs	4.96
6	2	34.04
7		30.14
8		26.79
9		29.66
10		31.25
	(n)	5
	Means	30.38
	Sdevs	2.63
11	3	37.81
12		29.66
13		31.12
14		30.29
15		26.76
	(n)	5
	Means	31.13
	Sdevs	4.08
16	4	29.40
17		35.21
18		34.26
19		31.26
20		27.88
	(n)	5
	Means	31.60
	Sdevs	3.12
21	5	29.78
22		32.09
23		30.22
24		28.86

Note: Data for Exposure phase

Animal	Group		Day of Phase 19
			Male Animals
25	5		28.32
		(n)	5
		Means	29.85
		Sdevs	1.46
26	6		34.71
27			30.13
28			26.23
29			31.37
30			29.56
		(n)	5
		Means	30.40
		Sdevs	3.07
31	7		30.45
32			30.51
33			30.76
34			31.76
35			26.28
		(n)	5
		Means	29.95
		Sdevs	2.12
36	8		25.88
37			34.46
38			31.54
39			35.05
40			31.97
		(n)	5
		Means	31.78
		Sdevs	3.63
41	9		31.34
42			31.11
43			37.66
44			36.29
45			30.64
		(n)	5
		Means	33.41
		Sdevs	3.30

Note: Data for Exposure phase

Animal	Group		Day of Phase 19
			Male Animals
46	10		29.86
47			30.80
48			35.05
49			30.42
50			35.74
		(n)	5
		Means	32.37
		Sdevs	2.79
51	11		33.91
52			28.36
53			27.85
54			30.22
55			32.69
		(n)	5
		Means	30.61
		Sdevs	2.65
56	12		33.73
57			28.75
58			34.05
59			25.57
60			31.61
		(n)	5
		Means	30.74
		Sdevs	3.58
61	13		29.39
62			28.96
63			29.93
64			29.25
65			36.27
		(n)	5
		Means	30.76
		Sdevs	3.10

Note: Data for Exposure phase

Animal	Group		Day of Phase 6	7	8	9	10	11	12	13	14	15	16	17	18
			Male Animals												
66	1		30.63	30.70	30.44	30.75	31.01	31.11	31.02	31.50	31.87	31.26	31.58	31.75	32.43
67			28.17	28.68	28.60	28.65	28.81	29.10	29.23	29.25	29.57	29.41	29.71	29.62	29.98
68			29.68	29.96	29.58	29.68	29.70	29.54	29.68	29.98	31.18	30.61	30.02	30.58	30.49
69			31.92	32.29	32.43	32.76	33.15	33.18	33.76	34.00	34.50	35.02	34.79	34.76	34.98
70			27.29	28.25	28.23	28.26	28.37	28.81	29.22	29.32	29.82	29.59	29.73	29.69	29.89
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	29.54	29.98	29.86	30.02	30.21	30.35	30.58	30.81	31.39	31.18	31.17	31.28	31.55
		Sdevs	1.86	1.62	1.68	1.81	1.93	1.81	1.92	2.00	1.98	2.28	2.17	2.13	2.17
71	2		32.34	32.69	32.16	32.73	33.31	33.55	34.14	34.46	34.79	35.02	34.91	35.23	36.36
72			29.98	30.87	30.72	31.19	31.40	31.44	32.70	32.75	33.42	33.66	33.89	34.57	34.08
73			30.11	30.65	30.42	30.26	30.70	30.76	31.50	31.48	31.89	31.50	31.73	31.90	31.96
74			29.54	29.82	29.60	29.99	30.26	30.12	30.68	30.89	31.55	31.78	31.87	31.53	31.75
75			29.48	29.96	30.58	30.98	31.63	31.77	32.34	32.68	33.06	32.85	33.21	33.15	33.03
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	30.29	30.80	30.70	31.03	31.46	31.53	32.27	32.45	32.94	32.96	33.12	33.28	33.44
		Sdevs	1.18	1.15	0.93	1.07	1.17	1.30	1.30	1.37	1.29	1.44	1.35	1.62	1.88
76	3		29.35	29.45	29.42	29.86	30.29	30.35	30.89	30.94	31.10	30.78	31.36	31.56	31.21
77			29.09	29.69	29.18	29.53	29.61	29.44	29.83	30.09	30.49	30.54	31.10	30.82	30.82
78			30.10	30.02	29.85	30.02	30.25	29.82	30.47	30.62	31.36	31.43	31.93	32.07	32.23
79			27.14	27.49	27.11	27.24	27.32	27.32	28.10	27.86	28.76	28.05	28.72	28.84	28.90
80			28.86	29.38	28.79	28.97	29.54	29.25	29.60	29.00	29.61	29.27	30.14	30.20	29.96
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	28.91	29.21	28.87	29.12	29.40	29.24	29.78	29.70	30.26	30.01	30.65	30.70	30.62
		Sdevs	1.09	0.99	1.06	1.13	1.21	1.15	1.07	1.27	1.08	1.35	1.26	1.26	1.26
81	4		30.04	30.22	29.81	30.02	29.96	29.89	30.47	30.43	30.68	30.56	31.63	30.93	31.68
82			29.18	28.93	28.16	28.36	28.66	28.65	29.33	29.68	29.23	29.01	29.26	28.81	28.87
83			30.15	29.51	29.45	30.53	30.08	30.24	30.26	30.10	30.33	30.36	30.69	30.54	31.26
84			30.97	31.44	30.79	31.02	31.34	31.13	31.90	32.13	31.79	31.39	31.43	31.40	30.76
85			32.09	32.14	31.69	31.84	31.93	31.66	32.33	32.97	32.39	32.15	32.26	32.55	31.97
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	30.49	30.45	29.98	30.35	30.39	30.31	30.86	31.06	30.88	30.69	31.05	30.85	30.91
		Sdevs	1.10	1.33	1.34	1.30	1.28	1.17	1.23	1.42	1.24	1.18	1.15	1.37	1.23

Note: Data for Exposure phase

Animal	Group		Day of Phase 19
			Male Animals
66	1		32.33
67			30.19
68			30.57
69			35.52
70			30.21
		(n)	5
		Means	31.76
		Sdevs	2.28
71	2		36.18
72			35.14
73			32.23
74			32.32
75			33.77
		(n)	5
		Means	33.93
		Sdevs	1.73
76	3		32.08
77			31.10
78			32.59
79			29.26
80			30.01
		(n)	5
		Means	31.01
		Sdevs	1.39
81	4		31.74
82			29.00
83			30.92
84			31.04
85			32.31
		(n)	5
		Means	31.00
		Sdevs	1.25

Note: Data for Exposure phase

Animal	Group		Day of Phase 7	8	9	10	11	12	13	14	15	16	17	18	19
			Male Animals												
1	1		4.85	5.94	6.48	6.99	5.87	5.96	6.45	5.68	6.93	6.33	6.30	6.55	6.24
2			6.35	7.20	7.17	7.17	7.12	7.36	7.31	7.20	7.56	7.30	6.91	7.30	7.34
3			5.38	5.94	6.53	6.57	6.20	6.47	6.22	6.93	7.72	6.98	5.86	6.82	5.66
4			6.47	7.34	6.98	7.68	5.88	6.17	6.21	6.09	6.40		5.93	7.17	6.38
5			4.66	5.22	4.41	5.23	4.28	5.21	4.99	5.22	6.81	8.21	5.25	8.62	6.06
		(n)	5	5	5	5	5	5	5	5	5	4	5	5	5
		Means	5.54	6.33	6.31	6.73	5.87	6.23	6.24	6.22	7.08	7.21	6.05	7.29	6.34
		Sdevs	0.84	0.91	1.10	0.93	1.02	0.78	0.83	0.83	0.55	0.78	0.61	0.80	0.62
6	2		6.28	5.95	7.34	7.58	7.32	6.93	6.73	7.85	7.67	11.78	7.68	8.53	7.15
7			4.49	6.70	7.59	6.21	7.58	7.31	6.04	6.16	7.47	8.88	6.43	6.44	5.96
8			6.29		7.51	7.74	4.99	7.43	7.18	8.68	8.28		7.41		9.18
9			5.96	7.62	6.04	6.22	5.19	6.45	7.89	5.53	8.45	8.33	6.66	8.14	6.97
10				7.54	6.34	6.45	4.62	6.86	5.36	5.44	6.73	6.25	6.39	7.23	5.79
		(n)	4	4	5	5	5	5	5	5	5	4	5	4	5
		Means	5.76	6.95	6.96	6.84	5.94	7.00	6.64	6.73	7.72	8.81	6.91	7.59	7.01
		Sdevs	0.86	0.79	0.72	0.76	1.40	0.39	0.98	1.46	0.69	2.28	0.59	0.94	1.35
11	3		6.40	7.64	7.28	7.39	5.75	8.13	6.59	6.93	7.17	9.78	7.44	10.47	8.53
12				6.49	6.92	8.35	6.03	6.78	6.05	6.05	6.94	8.63	5.68	7.50	6.62
13			5.63	6.67	7.28	5.80	5.42	7.55	6.39	6.37	7.09	7.45	5.78	7.78	6.31
14			5.37	6.31	5.86	5.69	5.51	7.28	8.73	5.26	7.02	9.97	5.57	7.17	7.10
15			5.25	5.00	4.99	5.89	5.25	5.88	7.75	6.02	6.36		5.75	8.62	5.53
		(n)	4	5	5	5	5	5	5	5	5	4	5	5	5
		Means	5.66	6.42	6.47	6.62	5.59	7.12	7.10	6.13	6.92	8.96	6.04	8.31	6.82
		Sdevs	0.52	0.95	1.01	1.19	0.30	0.85	1.11	0.61	0.32	1.17	0.78	1.32	1.11
16	4		5.74	6.15	6.04	7.62	6.86	8.10	7.68	7.58	5.91	5.45	4.52	6.33	6.98
17			6.33	6.65	6.81	6.88	6.50	7.12	6.57	6.95	6.48	6.36	5.90	6.49	6.59
18			5.71	7.42	7.75	7.78	6.45	6.59	6.55	7.40	6.81	8.91	6.71	7.12	9.83
19			5.97	6.30	5.36	6.32	5.88	6.64	6.12	6.16	6.23	6.19	5.46	5.80	6.87
20			5.36	5.73	5.51	5.65	5.21	7.67	7.34	6.35	5.32	6.14		9.16	6.98
		(n)	5	5	5	5	5	5	5	5	5	5	4	5	5
		Means	5.82	6.45	6.29	6.85	6.18	7.22	6.85	6.89	6.15	6.61	5.65	6.98	7.45
		Sdevs	0.36	0.63	0.99	0.89	0.65	0.66	0.64	0.63	0.57	1.33	0.91	1.31	1.34
21	5		5.29	5.78	6.85	9.12	7.44	7.73	7.41	5.70	4.93	5.61	4.63	6.83	6.06
22			5.39	6.54	6.69	8.49	5.90	6.67	7.30	5.19	5.59	5.64	5.50	6.26	5.94
23			5.14	5.30	4.88	8.22	6.52	7.91	5.81	5.34	5.51	5.70	7.47	7.80	6.79
24			5.85	6.64	6.04	8.34	5.04	6.43	5.66	7.09	5.18	6.68	6.09	8.45	11.57

Note: Data for Exposure phase

Animal	Group		Day of Phase 7	8	9	10	11	12	13	14	15	16	17	18	19
			Male Animals												
25	5		5.93	6.27	5.71	6.34	5.82	7.86	7.86	6.14	5.64	5.42	5.53	5.61	5.60
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	5.52	6.11	6.03	8.10	6.14	7.32	6.81	5.89	5.37	5.81	5.84	6.99	7.19
		Sdevs	0.35	0.56	0.80	1.04	0.90	0.71	1.00	0.76	0.30	0.50	1.05	1.15	2.49
26	6		7.14	6.96	8.18	9.28	5.82	6.19	6.08	5.38	5.71	6.17	5.77	6.49	6.96
27			5.37	5.83	6.65	6.71	6.62	6.52	7.60	6.17	5.66	6.20	6.98	6.23	7.81
28			5.17	5.50	6.73	6.63	4.64	6.89	5.55	5.55	4.91	9.77	7.39	5.90	
29			6.12	6.52	6.90	7.38	6.46	5.52	8.22	5.84	6.14	6.94	6.89	6.14	9.95
30			5.78	7.01	6.83	6.50	5.23	8.87	6.31	4.99	6.87	6.54	4.89	7.23	8.32
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	4
		Means	5.92	6.36	7.06	7.30	5.75	6.80	6.75	5.59	5.86	7.12	6.38	6.40	8.26
		Sdevs	0.78	0.68	0.63	1.16	0.83	1.26	1.11	0.45	0.72	1.51	1.03	0.51	1.26
31	7		5.56	6.15	5.63	6.16	4.62	5.51	5.35	5.15	5.06	5.08	4.84	5.37	5.00
32			5.12	5.87	5.59	6.94	5.81	6.31	5.87	6.63	6.02	6.82	5.65	5.91	6.43
33			5.11	7.24	6.08	6.97	6.85	7.07	5.96	5.79	5.59	6.08	5.40	5.64	7.07
34			4.44	6.63	6.03	9.70	8.87	6.36	8.81	6.44	5.91	7.15	5.55	6.71	7.95
35			5.36	6.60	7.91	7.33	5.87	6.22	5.40	5.38	5.33	9.37	6.80	5.83	7.81
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	5.12	6.50	6.25	7.42	6.40	6.29	6.28	5.88	5.58	6.90	5.65	5.89	6.85
		Sdevs	0.42	0.52	0.96	1.34	1.59	0.55	1.44	0.65	0.40	1.59	0.72	0.50	1.20
36	8		4.95	5.79	5.86	5.94	8.08	6.29	8.27	5.15	4.97	5.62	6.06	4.77	6.09
37			5.99	7.09	6.07	7.95	5.71	6.43	6.80	6.02	6.23	6.65	6.95	6.50	7.40
38			6.06	6.78	7.11	6.84	5.01	6.53	6.70	7.74	5.75		5.52	5.31	7.00
39			5.65	6.25	5.59	6.48	7.57	6.25	5.65	6.91	6.07	6.20	6.11	5.84	
40			5.15	6.05	5.62	7.04	5.80	6.99	6.85	6.21	6.32	6.68	7.07	6.42	6.94
		(n)	5	5	5	5	5	5	5	5	5	4	5	5	4
		Means	5.56	6.39	6.05	6.85	6.43	6.50	6.85	6.41	5.87	6.29	6.34	5.77	6.86
		Sdevs	0.50	0.53	0.62	0.74	1.32	0.30	0.93	0.97	0.55	0.50	0.65	0.74	0.55
41	9		5.73	5.82	8.75	5.80	5.19	6.24	5.72	7.45	6.15		7.85	6.78	7.77
42			8.42	6.82	6.22	8.85	6.85	8.36	6.01	7.43	5.57	6.81	5.02	5.75	6.75
43			6.82	7.42	6.96	8.61	6.65	7.04	6.21	6.72	6.41	6.74	6.05	6.53	7.09
44			6.00	6.29	6.32	7.31	5.90	7.00	6.93	6.82	6.59	6.24	6.06	6.65	7.50
45			5.42	6.00	6.73	6.92	8.31	6.96	4.39	6.67	7.73	7.28	8.81		
		(n)	5	5	5	5	5	5	5	5	5	4	5	4	4
		Means	6.48	6.47	7.00	7.50	6.58	7.12	5.85	7.02	6.49	6.77	6.76	6.43	7.28
		Sdevs	1.20	0.65	1.03	1.26	1.17	0.77	0.93	0.39	0.79	0.43	1.53	0.46	0.45

Note: Data for Exposure phase

Animal	Group		Day of Phase 7	8	9	10	11	12	13	14	15	16	17	18	19
			Male Animals												
46	10		6.14	6.55	6.51	7.56		8.35	6.16	8.30	5.90	6.84	7.37	6.17	7.19
47			5.38	5.83	6.17	8.20	6.90	7.07	5.17	6.14	5.74	5.68	5.17	6.68	8.62
48			5.93	6.40	6.35	6.89	6.08	6.62	6.30	6.96	6.42	6.38	6.06	5.85	6.81
49			4.93	5.44	5.22	6.36	5.62	5.98	5.33	5.88	5.50	6.28	5.15	6.48	6.94
50			6.03	6.98	9.60	7.47	5.97	6.60	6.21	6.73	6.99	7.43	6.49	7.82	8.67
		(n)	5	5	5	5	4	5	5	5	5	5	5	5	5
		Means	5.68	6.24	6.77	7.30	6.14	6.92	5.83	6.80	6.11	6.52	6.05	6.60	7.65
		Sdevs	0.51	0.61	1.66	0.70	0.54	0.89	0.54	0.94	0.60	0.65	0.94	0.75	0.92
51	11		5.01	5.36	5.46	5.79	4.73	5.16	5.23	6.10	5.40	5.72	5.07	5.56	5.94
52			5.37	5.12	5.68	6.32	4.57	5.38	5.49	5.99	5.73	6.55	7.03	5.91	8.89
53			6.05	5.98	6.98	7.50	6.68	6.89		6.73	6.43	8.41	5.54	6.44	9.93
54			4.81	5.15	6.79	7.43	4.43	6.59	4.94	6.45	6.04	7.85	6.89	8.00	8.83
55			5.89	5.87	5.98	6.53	5.71	5.93	6.09	7.06	6.27	6.72	6.20	6.92	6.56
		(n)	5	5	5	5	5	5	4	5	5	5	5	5	5
		Means	5.43	5.50	6.18	6.71	5.22	5.99	5.44	6.47	5.97	7.05	6.15	6.57	8.03
		Sdevs	0.54	0.40	0.67	0.74	0.96	0.75	0.49	0.44	0.42	1.07	0.85	0.95	1.70
56	12		6.27	6.41	5.81	7.63	5.67	7.56	5.40	5.61	5.30	6.86	5.39	6.03	6.59
57			6.38	6.02	6.81	7.76	6.83	5.55	7.37	5.66	6.09	6.91	5.63	4.94	6.12
58			5.65	5.54	6.28	8.58	5.87	5.75	6.15	6.37	6.57	6.23	6.01	6.22	6.63
59			6.17	5.29	6.33	8.48	4.83	6.89	4.56	6.45	6.79	6.67	8.01	7.85	7.71
60			5.62	5.05	6.23	7.33	4.05	7.28	5.79	7.06	7.09	6.48	7.26	6.66	8.59
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	6.02	5.66	6.29	7.96	5.45	6.61	5.85	6.23	6.37	6.63	6.46	6.34	7.13
		Sdevs	0.36	0.55	0.36	0.55	1.06	0.91	1.03	0.61	0.70	0.28	1.13	1.06	1.00
61	13		6.03	5.88	7.39	6.60	5.96	7.67	5.94	6.54	5.57	5.44	5.32	5.79	5.34
62			5.86	5.78	7.37	7.36	6.67	7.00	6.32	6.43	5.97	7.00	7.10	7.97	7.31
63			5.00	4.73	6.68	6.70	6.85	7.28	6.69	6.90	6.39	8.77	5.82	6.69	6.14
64			5.30	5.71	7.08	7.29	5.95	6.45	6.51	6.17	5.70		5.81	9.50	
65			6.50	6.49		6.85	6.04	6.82	5.79	7.33	5.99	7.98	6.42	5.92	
		(n)	5	5	4	5	5	5	5	5	5	4	5	5	3
		Means	5.74	5.72	7.13	6.96	6.29	7.04	6.25	6.67	5.92	7.30	6.09	7.17	6.26
		Sdevs	0.60	0.63	0.33	0.35	0.43	0.46	0.38	0.45	0.32	1.43	0.68	1.56	0.99

Note: Data for Exposure phase

Animal	Group		Day of Phase 20
			Male Animals
1	1		6.17
2			5.93
3			6.22
4			4.93
5			5.62
		(n)	5
		Means	5.77
		Sdevs	0.53
6	2		5.20
7			6.60
8			9.41
9			6.17
10			9.79
		(n)	5
		Means	7.43
		Sdevs	2.05
11	3		8.98
12			7.85
13			5.87
14			7.83
15			7.76
		(n)	5
		Means	7.66
		Sdevs	1.12
16	4		5.99
17			6.19
18			6.65
19			6.31
20			7.41
		(n)	5
		Means	6.51
		Sdevs	0.56
21	5		7.70
22			6.13
23			7.54
24			8.05

Note: Data for Exposure phase

Animal	Group		Day of Phase 20
			Male Animals
25	5		9.26
		(n)	5
		Means	7.74
		Sdevs	1.12
26	6		5.99
27			8.19
29			10.17
30			7.96
		(n)	4
		Means	8.08
		Sdevs	1.71
31	7		6.13
32			6.33
33			6.64
34			7.19
35			7.79
		(n)	5
		Means	6.82
		Sdevs	0.68
36	8		6.45
37			8.57
38			6.79
39			7.49
40			6.15
		(n)	5
		Means	7.09
		Sdevs	0.97
41	9		6.56
42			5.99
43			5.99
44			7.54
45			9.94
		(n)	5
		Means	7.20
		Sdevs	1.66

Note: Data for Exposure phase

Animal	Group		Day of Phase 20
			Male Animals
46	10		8.58
47			6.15
48			6.18
49			6.90
50			6.52
		(n)	5
		Means	6.87
		Sdevs	1.01
51	11		6.05
52			5.73
53			10.25
54			11.02
55			6.39
		(n)	5
		Means	7.89
		Sdevs	2.53
56	12		6.65
57			6.59
58			7.39
59			5.28
60			7.64
		(n)	5
		Means	6.71
		Sdevs	0.92
61	13		5.58
62			6.07
63			7.36
64			8.49
		(n)	4
		Means	6.88
		Sdevs	1.31

Note: Data for Exposure phase

Animal	Group		Day of Phase 7	8	9	10	11	12	13	14	15	16	17	18	19
			Male Animals												
66	1		5.49	6.06	6.73	4.84	6.38	5.77	5.27	5.42	5.61	5.63	6.57	7.34	5.49
67			5.44	7.01	8.89	7.02		6.50	5.44	5.41	7.19	7.72	6.01		5.52
68			5.55		7.71	9.71	6.90	6.46	5.93	6.59	5.97	7.48	6.18	7.13	5.73
69			6.25	7.49	8.05	6.28	7.54	6.18	6.92	6.03	6.82	5.54	5.28	7.04	5.53
70			5.02	7.31	5.97	5.79	6.95	2.17	5.45	5.60	5.60	7.19	6.19	7.74	6.36
		(n)	5	4	5	5	4	5	5	5	5	5	5	4	5
		Means	5.55	6.97	7.47	6.73	6.94	5.42	5.80	5.81	6.24	6.71	6.05	7.31	5.73
		Sdevs	0.44	0.64	1.14	1.85	0.47	1.84	0.67	0.50	0.73	1.05	0.47	0.31	0.37
71	2		5.94	6.30	6.36	5.85	7.30	6.85	6.11	6.29	7.53	7.35	6.17	8.91	6.05
72			5.81	9.08	7.45	6.02	10.24	9.90	6.09	7.25	8.06	9.15	8.26	9.93	6.68
73			5.26	6.58	5.48	4.95	6.90	6.84	6.36	4.99	5.75	7.06	6.57	8.26	5.44
74			5.88	7.03	6.43	5.07	6.60	7.50	6.25	5.91	6.82	6.34	5.79	6.66	7.08
75			5.29	7.38	8.30	6.82	8.27	6.74	6.92	5.88	6.85	7.19	5.90	7.69	6.43
		(n)	5	5	5	5	5	5	5	5	5	5	5	5	5
		Means	5.64	7.27	6.80	5.74	7.86	7.57	6.35	6.06	7.00	7.42	6.54	8.29	6.34
		Sdevs	0.33	1.09	1.09	0.76	1.47	1.34	0.34	0.82	0.87	1.04	1.01	1.23	0.63
76	3		6.63	6.14	6.77	5.85	7.32	5.95	5.12		6.51	6.19	7.80	9.47	9.02
77			5.94	6.90	6.47	4.76	3.81	6.46	6.63	2.81	9.56	7.10	7.33		5.46
78			5.08	7.45	6.26		7.53	6.06	6.11	12.44	6.84	6.87	7.29	8.71	7.11
79			4.56	5.11	6.67	5.36	8.40	7.07	6.49	5.31	6.99	7.36	6.02	10.07	5.78
80			5.10	6.13	5.40	4.75	7.92	5.07	5.35	4.34	5.70	5.99	5.92		4.14
		(n)	5	5	5	4	5	5	5	4	5	5	5	3	5
		Means	5.46	6.35	6.31	5.18	7.00	6.12	5.94	6.23	7.12	6.70	6.87	9.42	6.30
		Sdevs	0.82	0.89	0.55	0.53	1.83	0.73	0.68	4.27	1.45	0.59	0.85	0.68	1.85
81	4		4.85	5.59	6.74	5.22	6.20	3.15	5.35	4.98	6.59	6.57	5.28	6.91	6.66
82			4.57	0.00		6.02	7.04	7.42	7.16	5.02	7.28	5.69	6.61	7.36	6.81
83			4.28	6.52	7.13	6.37	7.47	5.40	5.95	4.41	6.39	5.87	5.27	6.91	4.45
84			5.53	5.99	5.61	4.74	5.54	5.55	5.47	3.83	5.22	4.38	4.26	4.84	5.83
85			5.56	6.85	7.67	5.63	8.13	6.56	6.22	5.32	5.83	5.91	7.37	6.72	6.38
		(n)	5	5	4	5	5	5	5	5	5	5	5	5	5
		Means	4.96	4.99	6.79	5.60	6.88	5.62	6.03	4.71	6.26	5.68	5.76	6.55	6.03
		Sdevs	0.57	2.83	0.87	0.64	1.02	1.60	0.72	0.59	0.78	0.80	1.23	0.98	0.96

Note: Data for Exposure phase

Animal	Group		Day of Phase 20
			Male Animals
66	1		5.34
67			7.29
68			7.60
69			5.61
70			6.59
		(n)	5
		Means	6.49
		Sdevs	1.00
71	2		6.15
72			6.83
73			6.85
74			6.94
75			6.74
		(n)	5
		Means	6.70
		Sdevs	0.32
76	3		5.57
77			6.92
78			7.69
79			5.63
80			4.96
		(n)	5
		Means	6.15
		Sdevs	1.12
81	4		7.68
82			7.00
83			5.85
84			4.71
85			5.91
		(n)	5
		Means	6.23
		Sdevs	1.15

Note: Data for Exposure phase