

**A ONE-GENERATION REPRODUCTION  
RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE  
HEXAHYDRATE**

FINAL REPORT

Study Director

Joseph C. Siglin, Ph.D., DABT

Study Completed on

December 28, 2000

Performing Laboratory

Springborn Laboratories, Inc. (SLI)  
Ohio Research Center  
640 North Elizabeth Street  
Spencerville, OH 45887

SLI Study No.

3472.3

Submitted to:

NiPERA, Inc.  
2605 Meridian Parkway  
Suite 200  
Durham, NC 27713


Page 1 of 442

SLI Study No. 3472.3

(2)

COMPLIANCE STATEMENT

This study was conducted in compliance with the Principles of Good Laboratory Practice as described by the OECD [C(97)186/FINAL] and SLI's Standard Operating Procedures.

  
\_\_\_\_\_  
Joseph C. Siglin, Ph.D., DABT  
Study Director  
Springborn Laboratories, Inc.

Date 12/28/00

## QUALITY ASSURANCE STATEMENT

This study was inspected by the Quality Assurance Unit and reports were submitted to management and the Study Director in accordance with SLI's Standard Operating Procedures as follows:

<u>Phase</u>	<u>Date</u>
Dosing	08/04/98
Data Audits	12/22/98, 01/07/99
Draft Report Review	03/24/99
Final Report Review	12/28/00
Reports Submitted to Study Director and Management	08/04/98, 03/25/99, 12/28/00

This study was conducted in compliance with the Principles of Good Laboratory Practice as described by the OECD [C(97)186/FINAL].

  
\_\_\_\_\_  
Deanna M. Talerico, RQAP-GLP  
Supervisor of Nonacute Quality Assurance

Date 12/28/00

*for*   
\_\_\_\_\_  
Anita M. Bosau, RQAP-GLP  
Director of Compliance Assurance

Date 12/28/00

## TABLE OF CONTENTS

COMPLIANCE STATEMENT .....	2
QUALITY ASSURANCE STATEMENT .....	3
TABLE OF CONTENTS .....	4
LIST OF TABLES .....	7
LIST OF APPENDICES .....	9
SUMMARY .....	11
INTRODUCTION .....	12
OBJECTIVE .....	12
MATERIALS AND METHODS .....	12
Experimental Protocol .....	12
Test Article and Vehicle Control Material .....	13
Test Article Receipt, Identification and Storage .....	13
Vehicle Control Material .....	13
Dose Preparation .....	13
Homogeneity, Stability and Concentration Analyses .....	14
Animals and Animal Husbandry .....	14
Animal Receipt, Identification and Housing .....	14
Acclimation .....	14
Diet and Drinking Water .....	15
Environmental Conditions .....	15
Experimental Procedures .....	15
Study Group Design .....	15
Rationale for Dosage Level Selection .....	16
Randomization and Group Assignment .....	16
Treatment .....	16
Breeding .....	16

## TABLE OF CONTENTS

F0 Parameters Evaluated .....	17
F0 Clinical Observations .....	17
F0 Body Weights .....	17
F0 Food and Water Consumption .....	17
F0 Parturition and Lactation .....	18
F0 Euthanasia and Necropsy .....	18
F1 Parameters Evaluated .....	19
F1 Pup Identification .....	19
F1 Standardization of Litter Size .....	19
F1 Litter Data .....	19
Selection of F1 Animals .....	19
Selected F1 Clinical Observations .....	20
Selected F1 Body Weights .....	20
Selected F1 Euthanasia and Necropsy .....	20
STATISTICAL ANALYSES .....	20
MAINTENANCE OF RAW DATA AND RECORDS .....	21
RESULTS .....	21
Analytical Chemistry Evaluations .....	21
F0 Generation .....	21
F0 Survival and Clinical Observations .....	21
F0 Body Weights and Weight Gain .....	22
F0 Food and Water Consumption .....	22
F0 Reproduction Indices, Precoital Intervals and Gestation Lengths .....	22
F0 Gross Necropsy Observations .....	23
F0 Implantation and Post-Implantation Loss Data .....	23
F1 Generation .....	23
F1 Pup Viability .....	23
F1 Pup Observations during Lactation .....	24
F1 Pup Body Weights during Lactation .....	24
F1 Pup Gross Necropsy Observations .....	24
Selected F1 Survival and Clinical Observations .....	24

TABLE OF CONTENTS

Selected F1 Body Weights and Weight Gain .....	25
Selected F1 Gross Necropsy Observations .....	25
DISCUSSION AND CONCLUSION .....	25
REPORT REVIEW .....	26
REFERENCES .....	27

## LIST OF TABLES

1.	Summary of F0 Survival and Clinical Observations . . . . .	28
2.	Summary of F0 Body Weight Data . . . . .	32
3.	Summary of F0 Body Weight Gain Data . . . . .	35
4.	Summary of F0 Gestation Body Weight Data . . . . .	38
5.	Summary of F0 Gestation Body Weight Gain Data . . . . .	39
6.	Summary of F0 Lactation Body Weight Data . . . . .	40
7.	Summary of F0 Lactation Body Weight Gain Data . . . . .	41
8.	Summary of F0 Food Consumption Data (grams/animal/day) . . . . .	42
9.	Summary of F0 Gestation Food Consumption Data (grams/animal/day) . . . . .	44
10.	Summary of F0 Lactation Food Consumption Data (grams/animal/day) . . . . .	45
11.	Summary of F0 Water Consumption Data (grams/animal/day) . . . . .	46
12.	Summary of F0 Gestation Water Consumption Data (grams/animal/day) . . . . .	48
13.	Summary of F0 Lactation Water Consumption Data (grams/animal/day) . . . . .	49
14.	Summary of F0 Copulation, Fertility, Precoital Interval and Gestation Length Data . . . . .	50
15.	Summary of F0 Gross Necropsy Observations . . . . .	51
16.	Summary of F0 Implantation and Post-Implantation Loss Data . . . . .	57

LIST OF TABLES

17.	Summary of F1 Pup Viability .....	58
18.	Summary of F1 Pup Observations during Lactation .....	60
19.	Summary of F1 Pup Weights during Lactation .....	61
20.	Summary of F1 Pup Gross Necropsy Observations .....	62
21.	Summary of F1 Survival and Clinical Observations .....	64
22.	Summary of F1 Body Weight Data .....	66
23.	Summary of F1 Body Weight Gain Data .....	68
24.	Summary of F1 Gross Necropsy Observations .....	70



## LIST OF APPENDICES

A.	A Preliminary Probe Study in Rats .....	72
B.	Protocol, Protocol Amendments and Protocol Deviations/Occurrences .....	100
C.	Certificate of Analysis and Analytical Chemistry Results .....	139
D.	Individual F0 Survival and Clinical Observations .....	147
E.	Individual F0 Body Weight Data .....	171
F.	Individual F0 Body Weight Gain Data .....	184
G.	Individual F0 Gestation Body Weight Data .....	197
H.	Individual F0 Gestation Body Weight Gain Data .....	204
I.	Individual F0 Lactation Body Weight Data .....	211
J.	Individual F0 Lactation Body Weight Gain Data .....	218
K.	Individual F0 Food Consumption Data (grams/animal/day) .....	225
L.	Individual F0 Gestation Food Consumption Data (grams/animal/day) .....	238
M.	Individual F0 Lactation Food Consumption Data (grams/animal/day) .....	245
N.	Individual F0 Water Consumption Data (grams/animal/day) .....	252
O.	Individual F0 Gestation Water Consumption Data (grams/animal/day) .....	264
P.	Individual F0 Lactation Water Consumption Data (grams/animal/day) .....	271

## LIST OF APPENDICES

Q.	Individual F0 Reproductive Performance Data .....	278
R.	Individual F0 Gestation Length Data .....	285
S.	Individual F0 Gross Necropsy Observations .....	288
T.	Individual F0 Implantation and Post-Implantation Loss Data .....	305
U.	Individual F1 Pup Viability .....	312
V.	Individual F1 Pup Observations during Lactation .....	319
W.	Individual F1 Pup Weights during Lactation .....	345
X.	Individual F1 Pup Gross Necropsy Observations .....	376
Y.	Individual F1 Survival and Clinical Observations .....	387
Z.	Individual F1 Body Weight Data .....	392
AA.	Individual F1 Body Weight Gain Data .....	405
BB.	Individual F1 Gross Necropsy Observations .....	418
CC.	SLI Historical Control Data .....	430
DD.	SLI Personnel Responsibilities .....	441

## SUMMARY

This range-finding study was conducted to evaluate the potential effects of nickel sulfate hexahydrate when administered orally to rats over the course of one generation. The study consisted of a vehicle control and five treatment groups, with eight males and eight females in each group. The test article was dissolved in reverse osmosis-deionized (RO-Di) water and administered at dosage levels of 10, 20, 30, 50 and 75 mg/kg/day, by once daily oral gavage, to F0 parental animals and selected F1 offspring. Dosing of the F0 parental animals began two weeks prior to mating. Dosing of the F1 offspring began on postnatal day (PND) 22. For both generations, daily dosing was continued until the day prior to or the day of scheduled euthanasia. All doses were given at a constant volume of 10 mL/kg. Control animals were administered RO-Di water under the same experimental conditions at an equivalent dose volume.

Both F0 parental animals and F1 offspring were closely examined for indications of toxicity. Experimental endpoints for F0 animals included clinical observations, body weights, food and water consumption, mating, parturition, lactation and offspring growth and viability. Experimental endpoints for selected F1 animals included survival, clinical observations and body weights during the F1 dosing phase. All F0 and F1 selected animals were subjected to a gross necropsy examination at the time of death or terminal euthanasia.

Oral administration of the test article had no effect on F0 survival, growth, mating behavior, copulation, fertility, precoital intervals, gestation lengths or gross necropsy findings. The incidence of dead pups on lactation day 0 was significantly increased and mean live litter size was significantly decreased at the 75 mg/kg/day level. Mean post-implantation loss was significantly increased at dosage levels  $\geq 30$  mg/kg/day. Growth of surviving F1 pups during lactation appeared to be unaffected. Administration of the test article to selected F1 animals beginning on postnatal day 22 had no effect on survival or growth of the animals for several weeks following weaning.

In conclusion, based on the results of this one-generation reproduction range-finding study, dosage levels of 1.0, 2.5, 5.0 and 10.0 mg/kg/day were selected for a definitive two-generation reproduction study in rats.

## I. INTRODUCTION

This report details the experimental procedures and results of a one-generation reproduction range-finding study in rats with nickel sulfate hexahydrate. The study was authorized by NiPERA, Inc., Durham, North Carolina, and was conducted at Springborn Laboratories, Inc. (SLI), 640 North Elizabeth Street, Spencerville, Ohio. The Sprague-Dawley rat was selected as the experimental model since this species/strain has a proven sensitivity to a variety of agents and provides a suitable animal model for testing chemicals and drugs for human risk assessment. Oral administration of the test article was selected since this is a potential route of human exposure. The protocol was signed by the Study Director on July 9, 1998 (GLP initiation date). The in-life phase of the range-finding study was initiated on August 4, 1998, and concluded on October 30, 1998.

Prior to initiation of the range-finding study, a preliminary probe study was conducted in rats to aid in dosage level selection for the range-finding study. The preliminary probe study was initiated on July 14, 1998, and concluded on July 28, 1998. The experimental methods and results of the preliminary probe study are provided in Appendix A.

## II. OBJECTIVE

This range-finding study was conducted to evaluate the potential effects of nickel sulfate hexahydrate when administered to rats by oral gavage over the course of one generation. Data from this study were used to select dosage levels for a two-generation reproduction study in rats.

## III. MATERIALS AND METHODS

### A. Experimental Protocol

The study protocol, protocol amendments and protocol deviations/occurrences are presented in Appendix B.

## B. Test Article and Vehicle Control Material

### 1. Test Article Receipt, Identification and Storage

The test article was received from Aldrich Chemical Company and identified as follows:

<u>Sponsor's ID</u>	<u>Assigned SLI ID</u>	<u>Physical Description</u>	<u>Receipt Date</u>
Nickel(II) Sulfate Hexahydrate (CAS No. 10101-97-0) Lot No. 08516TQ	S98.001.3472	Blue-green crystalline powder	07/08/98

A one gram retention sample of the test article was taken and stored at SLI. The retention sample and remaining test article were stored at ambient temperature in a tightly closed container. The purity of the test article was 99%. Documentation concerning chemical identification, purity, strength, stability and other required data was the responsibility of the Sponsor. A Certificate of Analysis for the nickel sulfate hexahydrate, as provided by the Aldrich Chemical Company, is included in Appendix C.

### 2. Vehicle Control Material

The vehicle control material used in the preparation of the dosing solutions and for administration to control animals was reverse osmosis-deionized (RO-Di) water from the SLI Pharmacy source.

### 3. Dose Preparation

For each test article dose group, a specified amount of nickel sulfate hexahydrate was weighed into a weigh boat and placed in a volumetric flask. A sufficient quantity of RO-Di water was added to the flask to achieve the desired volume and the mixture was stirred for 15 minutes. Each test article solution was prepared once every 21 days and stored refrigerated (approximately 2 to 8°C) in amber glass containers. During each fresh preparation, RO-Di water was dispensed into daily aliquots for administration to control animals. The physical state of the control and each dosing solution was recorded during each preparation. The vehicle (group 1) was a clear colorless solution; group 2 was a clear, very pale blue-green solution; groups 3 and 4 were clear, pale blue-green solutions; and groups 5 and 6 were clear, light blue-green solutions. Daily aliquots of the dosing solutions were allowed to equilibrate to room temperature prior

to dispensing. The dosing solutions were stirred prior to dispensation and then continuously until dosing was complete.

#### 4. Homogeneity, Stability and Concentration Analyses

Homogeneity of the test article in the vehicle was evaluated by analyzing duplicate 10 mL samples from the top, middle and bottom of the 0.1 and 7.5 mg/mL concentrations. Stability of the test article in the vehicle was assessed by analyzing duplicate 10 mL samples obtained from the middle of the 0.1 and 7.5 mg/mL concentrations following 24 hours of room temperature storage, and following 7, 14, and 21 days of refrigerated storage. In addition, duplicate 10 mL samples were obtained from the vehicle and each test article dosing mixture at the first preparation for verification of test article concentration. The analytical samples were packed in ice and shipped to Lancaster Laboratories, Lancaster, Pennsylvania, for analysis by atomic absorption. The results of the analyses are included in Appendix C.

### C. Animals and Animal Husbandry

Animal housing and care were based on the standards established by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) and the guidelines set forth in the Guide for the Care and Use of Laboratory Animals, NIH Publication No. 96-03, 1996.

#### 1. Animal Receipt, Identification and Housing

Seventy male and seventy female Sprague-Dawley CrI:CD<sup>®</sup>(SD)IGS BR rats were received at SLI on July 9, 1998, from Charles River Laboratories, Inc., St. Constant, Quebec, Canada, for the preliminary probe and range-finding studies. At the time of receipt, each rat was identified with a metal ear tag displaying a unique number. Animals were housed individually (except during cohabitation for mating) in stainless steel cages suspended above cage-board or plastic nesting boxes (F0 females) for parturition and lactation. A cage card displaying the study, group and animal numbers, and sex was affixed to each cage. The cage cards were color-coded based on group number following group assignment.

#### 2. Acclimation

Animals were examined upon receipt and daily thereafter during acclimation for signs of physical or behavioral abnormalities. General

health/mortality checks were performed twice daily, in the morning and afternoon. Individual body weights were recorded on the day following receipt and just prior to randomization on day -1. The animals were acclimated to the laboratory conditions for 25 days prior to randomization.

### 3. Diet and Drinking Water

PMI Certified Rodent Chow<sup>®</sup> #5002 (Purina Mills, Inc.) and municipal tap water were provided to each animal ad libitum. The feed was analyzed by the supplier for nutritional components and environmental contaminants. The lot number and expiration date of each batch of feed used during the study were recorded. The tap water was purified by reverse osmosis and supplied to the animals by an automatic watering system or in water bottles for measurement of water consumption. Water supplying the facility is analyzed on an annual basis for contaminants according to SLI Standard Operating Procedures. The results of the feed and water analyses are maintained at SLI. Within generally accepted limits, there were no contaminants in the diet or drinking water which would interfere with the conduct of the study.

### 4. Environmental Conditions

The environmental controls in the animal room were set to maintain room temperature and relative humidity ranges of 65 to 79°F and 30 to 70%, respectively. Environmental control equipment was monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers were set to maintain a 12-hour light/12-hour dark cycle and the room ventilation was set to produce 10 to 15 air changes per hour. The room temperature and relative humidity were recorded a minimum of once daily.

## D. Experimental Procedures

### 1. Study Group Design

The following table presents the study group design and dosage levels tested:

Group	No. of Animals		Dosage Material	Dosage Level (mg/kg/day)	Dosage Conc. (mg/mL)	Dosage Volume (mL/kg)
	Male	Female				
1	8	8	RO-Di Water	0	0	10
2	8	8	Nickel Sulfate Hexahydrate	10	1.0	10
3	8	8	Nickel Sulfate Hexahydrate	20	2.0	10
4	8	8	Nickel Sulfate Hexahydrate	30	3.0	10
5	8	8	Nickel Sulfate Hexahydrate	50	5.0	10
6	8	8	Nickel Sulfate Hexahydrate	75	7.5	10

## 2. Rationale for Dosage Level Selection

Dosage levels were selected in an attempt to produce graded responses to the test article. Dosage levels were selected based on the results of the preliminary probe study conducted in rats (see Appendix A).

## 3. Randomization and Group Assignment

On day -1, the animals were weighed and examined in detail. Animals determined to be suitable test subjects were randomly assigned to groups using a computer randomization program. The program ranked the animals according on day -1 body weights and randomly assigned the animals to study groups in a stratified block design. Disposition of animals not assigned to the study was documented in the study records. On the day following receipt, the animals were approximately 11 weeks of age with body weights ranging from 269 to 360 grams for males and from 187 to 247 grams for females.

## 4. Treatment

Dosing preparations were administered orally, by gavage, as a single dose daily to F0 parents and selected F1 offspring. Individual doses were adjusted based on the most recent body weight data. Dosing for F0 parental animals was initiated 14 days prior to mating and dosing for F1 offspring was initiated on postnatal day 22. Dosing continued until the day prior to or the day of scheduled euthanasia.

## 5. Breeding

Following 14 days of treatment for the F0 parental animals, each female was cohabited with a single male randomly selected from the same treatment group. Each mating pair was observed daily for evidence of copulation. Evidence of mating was determined by the presence of a copulatory plug in the vagina or a sperm positive vaginal smear. The day



evidence of copulation was confirmed was designated as day 0 of gestation and the female was returned to its cage. If no evidence of copulation was observed after 14 days of mating, the female was separated from the male.

#### E. F0 Parameters Evaluated

##### 1. F0 Clinical Observations

Mortality/general health checks were performed twice daily, in the morning and afternoon. Detailed clinical observations were performed weekly and cage-side observations were performed daily approximately one-half hour to two hours following dosing. During gestation and lactation, detailed clinical observations were performed daily for F0 females. Detailed clinical observations were also performed on the day of scheduled euthanasia.

##### 2. F0 Body Weights

Individual body weights were recorded weekly and on the day of scheduled euthanasia for the males. Individual body weights were recorded weekly for the females until evidence of mating was observed. When positive evidence of mating was detected, the females were weighed on gestation days 0, 7, 14 and 20. Following parturition, the females were weighed on lactation days 1, 4, 7, 10, 14 and 21. Body weights were recorded weekly and on the day of scheduled euthanasia for females with no positive evidence of mating.

##### 3. F0 Food and Water Consumption

Individual food and water consumption were recorded weekly for the males, except during cohabitation. Food and water consumption were not recorded while the animals were paired for breeding. Food and water consumption were recorded weekly for the females until evidence of mating was observed. When positive evidence of mating was detected, food and water consumption were recorded for the females on gestation days 0, 7, 14 and 20. Following parturition, food and water consumption for the females were recorded on lactation days 1, 4, 7 and 10. Food and water consumption were recorded weekly for females with no positive evidence of mating. Both food and water consumption were calculated as grams/animal/day.

#### 4. F0 Parturition and Lactation

On gestation day 18, females with confirmed copulation were transferred to individual plastic boxes containing nesting material. Each female was observed for signs of parturition a minimum of twice daily. The time parturition was first detected and the time parturition was completed were recorded, when possible. Signs of difficult or prolonged delivery were recorded, if observed. The day on which parturition was judged complete was designated as lactation day 0. The females and their offspring remained together until lactation day 21. Abnormal nursing and nesting behaviors were recorded, if observed. The offspring were designated as the F1 generation. Females with no evidence of mating were examined for parturition beginning 19 days following initiation of cohabitation.

#### 5. F0 Euthanasia and Necropsy

All animals were subjected to an abbreviated gross necropsy at the time of death or euthanasia. Females that were found dead during the study were necropsied. The necropsy examination included evaluation of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. Uterine contents were examined and the number of implantation sites and number of corpora lutea on each ovary were recorded. The number of implantation scars was recorded. All abnormalities were recorded and no tissues were retained at necropsy. Pups from dams found dead were euthanized and discarded without necropsy.

Surviving females were euthanized by carbon dioxide (CO<sub>2</sub>) inhalation. Dams that delivered and weaned their offspring were euthanized on lactation day 21. Females that failed to deliver were euthanized 25 days after evidence of mating was first detected (post-breeding day 25). Females with no evidence of mating were euthanized 25 days following conclusion of the mating period (post-breeding period day 25). Females with total litter loss were euthanized and necropsied on the day that no surviving pups remained. The necropsy examination included evaluation of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. Uterine contents were examined and the number of implantation scars was recorded. Uteri with no macroscopic implantations were opened and placed in 10% aqueous ammonium sulfide solution for detection of early embryoletality as described by Salewski [1]. The number of implantation scars was recorded. All abnormalities were recorded and no tissues were retained at necropsy. All males (euthanized moribund and surviving) were euthanized by CO<sub>2</sub> inhalation. Surviving males were euthanized following completion of female

parturition. The necropsy examination included evaluation of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. No tissues were retained at necropsy.

## F. F1 Parameters Evaluated

### 1. F1 Pup Identification

On lactation day 0, each viable pup was identified with a tail tattoo. Nonviable pups were identified with indelible marker on lactation day 0.

### 2. F1 Standardization of Litter Size

Following observations and body weights on lactation day 4, each litter was randomly culled to a maximum of eight pups, four per sex per litter, when possible. The culled pups were euthanized by CO<sub>2</sub> inhalation and discarded without necropsy.

### 3. F1 Litter Data

Pup viability was determined daily throughout lactation. A detailed examination of each pup was performed on lactation days 0, 4, 7, 14 and 21. The sex of each pup was determined on lactation day 0 and verified on lactation days 4, 7, 14 and 21. Individual pup weights were determined on lactation days 1, 4, 7, 14 and 21. Intact (noncannibalized) pups which were found dead during lactation were necropsied. During necropsy, emphasis was placed on the examination of developmental morphology. No tissues were retained at necropsy.

### 4. Selection of F1 Animals

Between postpartum days 6 and 13, eight pups per sex per group were randomly selected for the F1 dosing phase. Each pup was examined externally and the sex was verified prior to selection. Clinical observations recorded prior to selection are maintained in the study records. When possible, one male and one female pup were selected from each litter. Selected animals were identified with metal ear tags displaying unique numbers and transferred to stainless steel cages. The selected F1 weanlings were gang-housed (two or three/sex/group/cage) for three days to allow the animals to become accustomed to the automatic watering system. The F1 rats were then single-housed for the remainder of the growth phase. Mortality/general health checks were performed twice daily,

in the morning and afternoon. Nonselected F1 pups were euthanized by CO<sub>2</sub> inhalation and discarded without necropsy.

#### 5. Selected F1 Clinical Observations

Mortality/general health checks were performed twice daily, in the morning and afternoon. Detailed clinical observations were performed weekly and cage-side observations were performed daily approximately one-half hour to two hours following dosing. Detailed clinical observations were also performed on the day of scheduled euthanasia.

#### 6. Selected F1 Body Weights

Individual body weights were recorded weekly and on the day of scheduled euthanasia.

#### 7. Selected F1 Euthanasia and Necropsy

Following conclusion of F1 dosing, all animals were euthanized by CO<sub>2</sub> inhalation and subjected to an abbreviated gross necropsy at scheduled euthanasia. The necropsy examination included evaluation of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. All abnormalities were recorded and no tissues were retained.

### IV. STATISTICAL ANALYSES

Body weights, body weight gain, food consumption, water consumption, gestation length and mean live litter size were analyzed by One-Way Analysis of Variance (ANOVA) [2]. If significance was observed with ANOVA, control to treatment group comparisons were performed using Dunnett's test [3]. Count data were analyzed using Chi-Square test [4] for copulation and fertility indices, pup sex ratios, the number of live and dead pups per group (on lactation day 0) and pup survival (after lactation day 0). The Mann-Whitney U test was used to compare post-implantation loss [5]. All analyses were two-tailed with a minimum significance level of 5% ( $p < 0.05$ ).

## V. MAINTENANCE OF RAW DATA AND RECORDS

The remaining test article will be properly disposed of following completion of all testing with this compound. All original paper data, magnetically encoded records and the final report will be transferred to the SLI archives and stored for a minimum of ten years. The Sponsor will be consulted prior to final disposition of these items.

## VI. RESULTS

### A. Analytical Chemistry Evaluations

#### Appendix C (Analytical Chemistry Results)

Analytical chemistry analyses demonstrated that the test article was homogeneous and stable in aqueous solution at concentrations of 0.1 and 7.5 mg/mL following room temperature storage for 24 hours, and following refrigerated storage for up to 21 days. With regard to homogeneity in the vehicle, mean analytical concentrations were all within 10% of the respective target concentrations for samples taken from the top, middle and bottom of the 0.1 and 7.5 mg/mL solutions. Similarly, mean analytical concentrations for stability samples from the 0.1 and 7.5 mg/mL solutions were all within 10% of the respective target concentrations after 24 hours of room temperature storage, and after 7, 14 and 21 days of refrigerated storage. Analysis of the first dosing solutions prepared for the study resulted in average test article recoveries ranging from 104.2 to 106.8%. No test article was detected in the vehicle control solution.

### B. F0 Generation

#### 1. F0 Survival and Clinical Observations

Table 1 (Summary Data)  
Appendix D (Individual Data)

One control male (#17035) was euthanized moribund following a gavage error, and one 20 mg/kg/day female (#177) died as a result of an accidental injury sustained during handling. The control male exhibited a perforation of the esophagus at necropsy. The 20 mg/kg/day female was dropped on

the animal room floor after it bit the technician during dosing. Gross necropsy of this female revealed brain hemorrhage, abnormal contents in the thoracic cavity and trachea, and wet matting on the haircoat.

One 10 mg/kg/day female (#229) was euthanized on lactation day 0, and two 75 mg/kg/day females (#213 and #245) were euthanized on lactation days 2 and 1, respectively, due to total litter loss. All other F0 animals survived to scheduled euthanasia. Clinical observations in the F0 animals were generally unremarkable.

## 2. F0 Body Weights and Weight Gain

Tables 2-7 (Summary Data)  
Appendices E-J (Individual Data)

There were no toxicologically meaningful differences in F0 body weights or weight gain during the study. In F0 females, mean body weight and weight gain were comparable among the groups prior to mating and throughout the gestation and lactation phases. In F0 males, mean body weights were comparable among the groups throughout the study, while weight gain was significantly different from controls only during weeks 2-3 in the 50 mg/kg/day group. This difference was not considered toxicologically meaningful since weight gain at the 75 mg/kg/day level remained unaffected.

## 3. F0 Food and Water Consumption

Tables 8-13 (Summary Data)  
Appendices K-P (Individual Data)

There were no toxicologically meaningful differences in F0 food or water consumption during the study. No statistically significant values were detected for either food or water consumption, in either males or females.

## 4. F0 Reproduction Indices, Precoital Intervals and Gestation Lengths

Table 14 (Summary Data)  
Appendices Q and R (Individual Data)  
Appendix CC (SLI Historical Control Data)

There were no statistically significant differences in copulation or fertility indices among the groups. The fertility index was 100% in each group; the

copulation index was 87.5% in the 50 mg/kg/day group and 100% in each of the remaining groups.

No statistically significant differences were observed in group mean precoital intervals or gestation lengths. Mean precoital intervals ranged from 2.1 to 3.5 days; mean gestation lengths ranged from 22.0 to 22.5 days.

#### 5. F0 Gross Necropsy Observations

Table 15 (Summary Data)  
Appendix S (Individual Data)

Gross necropsy findings were generally unremarkable in F0 animals which survived. Those findings which were noted tended to be of low incidence and randomly distributed among the groups.

#### 6. F0 Implantation and Post-Implantation Loss Data

Table 16 (Summary Data)  
Appendix T (Individual Data)  
Appendix CC (SLI Historical Control Data)

Post-implantation loss, calculated as implantation scar count minus live pups on lactation day 0, was significantly increased at the 30, 50 and 75 mg/kg/day levels. Post-implantation loss was also noticeably higher than controls at the 10 and 20 mg/kg/day levels, but was not significantly different from the control group. In addition, the post-implantation loss at the 20 mg/kg/day level ( $1.5 \pm 1.6$ ) remained within the historical range of 0.88 - 2.30 for F0 litters. The post-implantation loss at the 10 mg/kg/day level ( $2.6 \pm 5.4$ ) was primarily attributable to one female with total litter loss.

### C. F1 Generation

#### 1. F1 Pup Viability

Table 17 (Summary Data)  
Appendix U (Individual Data)  
Appendix CC (SLI Historical Control Data)

Mean live litter size on day 0 was significantly decreased at the 75 mg/kg/day level. The incidence of dead pups on day 0 was significantly

increased at the 75 mg/kg/day level. Significant increases in the incidence of dead pups on lactation day 0 were also observed at the 10, 20 and 30 mg/kg/day levels, but not at the 50 mg/kg/day level, suggesting that the former statistical differences were incidental. Pup viability at the 75 mg/kg/day level continued to decline and was significantly lower than controls on lactation day 4 prior to culling. After culling on lactation day 4, pup viability appeared to stabilize at the 75 mg/kg/day level.

## 2. F1 Pup Observations during Lactation

Table 18 (Summary Data)  
Appendix V (Individual Data)

F1 pup observations during lactation were generally unremarkable. Individual findings tended to be randomly distributed among the groups, with no apparent dose-response pattern(s) emerging.

## 3. F1 Pup Body Weights during Lactation

Table 19 (Summary Data)  
Appendix W (Individual Data)  
Appendix CC (SLI Historical Control Data)

There were no statistically significant or toxicologically meaningful differences in F1 pup body weights during lactation.

## 4. F1 Pup Gross Necropsy Observations

Table 20 (Summary Data)  
Appendix X (Individual Data)

In pups which were found dead on lactation day 0, the most notable gross necropsy observations consisted of atelectasis and absence of milk in the stomach, suggesting that these pups were probably stillborn.

## 5. Selected F1 Survival and Clinical Observations

Table 21 (Summary Data)  
Appendix Y (Individual Data)

All animals survived to scheduled euthanasia and no remarkable clinical signs of toxicity were noted during the dosing phase of the selected F1 animals.



## 6. Selected F1 Body Weights and Weight Gain

Tables 22 and 23 (Summary Data)  
Appendices Z and AA (Individual Data)

No statistically significant differences in body weights or weight gain were noted during the post-weaning growth phase of the selected F1 animals.

## 7. Selected F1 Gross Necropsy Observations

Table 24 (Summary Data)  
Appendix BB (Individual Data)

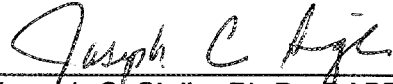
Gross necropsy findings in selected F1 animals were generally unremarkable. Those findings which were noted tended to be of low incidence and randomly dispersed among the groups.

# VII. DISCUSSION AND CONCLUSION

This study evaluated the effects of the test article, nickel sulfate hexahydrate, when administered orally to rats over the course of one generation for the primary purpose of selecting dosage levels for a definitive two-generation reproduction toxicity study in rats.

Oral administration of the test article had no effect on F0 survival, growth, mating behavior, copulation, fertility, precoital intervals, gestation lengths or gross necropsy findings. The incidence of dead pups on lactation day 0 was significantly increased and mean live litter size was significantly decreased at the 75 mg/kg/day level. Mean post-implantation loss was significantly increased at dosage levels  $\geq 30$  mg/kg/day. Growth of surviving F1 pups during lactation appeared to be unaffected. Administration of the test article to selected F1 animals beginning on postnatal day 22 had no effect on survival or growth of the animals for several weeks following weaning.

In conclusion, based on the results of this one-generation reproduction range-finding study, dosage levels of 1.0, 2.5, 5.0 and 10.0 mg/kg/day were selected for a definitive two-generation reproduction study in rats.

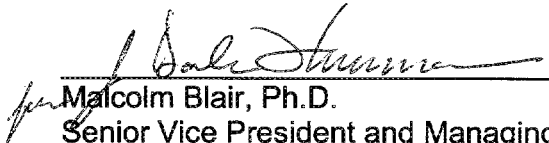


Joseph C. Siglin, Ph.D., DABT  
Study Director

Date

12/28/00

VIII. REPORT REVIEW



Malcolm Blair, Ph.D.  
Senior Vice President and Managing  
Director

Date

12.28.00

## IX. REFERENCES

1. Salewski, E., Farbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte, Naunyn-Schm. Archiv. Fur Exper. Pathologic und Pharm., 247:367, 1964.
2. Snedecor, G. W., and Cochran, W. G., Statistical Methods, Sixth Edition, Iowa State University Press, Ames, Iowa, pp. 258-268, 1967.
3. Dunnett, C. W., J. Am. Sta. Assn., 50:1096-1121, 1955.
4. Siegel, S., Nonparametric Statistics, McGraw Hill Book Company, New York, NY, pp. 104-111, 1956.
5. Gad, Shayne, C., Common Statistical Procedures Used at the Chemical Hygiene Fellowship, Carnegie-Mellon Institute of Research, pp. 43-44, May 1978.

TABLE 1  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

	M A L E					
	1	2	3	4	5	6
GROUP: LEVEL (MG/KG/DAY):	0	10	20	30	50	75
NORMAL	49/ 8	48/ 8	61/ 8	52/ 8	61/ 8	62/ 8
-NO CLINICAL SIGNS						
DEAD	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-UNSCHEДУLED EUTHANASIA - MORIBUND						
-SCHEDULED EUTHANASIA	7/ 7	8/ 8	8/ 8	8/ 8	8/ 8	8/ 8
ACTIVITY						
-LABORED BREATHING	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-SALIVATION	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
EXCRETA/EMESIS						
-FEW FECES	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
BODY						
-SCAB(S) - LEFT PINNA	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
-SCAB(S) - LEFT FORELIMB	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-SCAB(S) - RIGHT FORELIMB	0/ 0	1/ 1	0/ 0	1/ 1	0/ 0	0/ 0
-SWELLING - RIGHT LATERAL THORACIC	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-SWELLING - LEFT HINDLIMB DIGIT(S)	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
-HAIRLOSS	4/ 1	12/ 2	2/ 1	6/ 2	0/ 0	0/ 0
-ENLARGEMENT - TAIL	0/ 0	0/ 0	0/ 0	4/ 1	0/ 0	0/ 0
-PURPLE DISCOLORATION - LEFT HINDLIMB DIGIT(S)	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1	0/ 0
-URINE STAIN	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-FECAL STAIN	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
EYES						
-DARK MATERIAL AROUND EYE(S)	3/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 1  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

	M A L E					
	1	2	3	4	5	6
GROUP: LEVEL (MG/KG/DAY):	0	10	20	30	50	75
NOSE/MOUTH						
-REDDISH NASAL DISCHARGE	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-DARK MATERIAL AROUND NOSE	3/ 3	3/ 3	0/ 0	3/ 3	0/ 0	0/ 0
-SCAB(S) - AROUND MOUTH	2/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-MALALIGNMENT	4/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-INCISOR(S) TRIMMED	2/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-INCISOR(S) - BROKEN	2/ 1	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
POST-DOSE OBSERVATIONS						
-ACTIVITY DECREASED	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 1  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

		----- F E M A L E -----					
GROUP:		1	2	3	4	5	6
LEVEL (MG/KG/DAY):		0	10	20	30	50	75
-----							
NORMAL							
- NO CLINICAL SIGNS		291/ 8	299/ 8	199/ 5	321/ 8	283/ 8	317/ 8
DEAD							
- FOUND DEAD		0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
- SCHEDULED EUTHANASIA		8/ 8	8/ 8 a	7/ 7	8/ 8 b	8/ 8 c	8/ 8 d
ACTIVITY							
- INCREASED SENSITIVITY TO TOUCH		0/ 0	0/ 0	13/ 1	0/ 0	0/ 0	0/ 0
EXCRETA/EMESIS							
- FEW FECES		0/ 0	0/ 0	0/ 0	1/ 1	0/ 0	1/ 1
- SOFT STOOLS		0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
- DIARRHEA		0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
BODY							
- HAIRLOSS		82/ 3	47/ 2	141/ 3	30/ 1	46/ 1	15/ 2
- SCAB(S) - FACIAL AREA		0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	6/ 1
- SCAB(S) - LEFT FORELIMB		2/ 1	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
- SCAB(S) - RIGHT FORELIMB		4/ 1	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
- SWELLING - ABDOMINAL MAMMARY(IES)		0/ 0	0/ 0	0/ 0	2/ 1	0/ 0	0/ 0
- SKIN PALE IN COLOR - ALL EXTREMITIES		0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	3/ 2
- COOL TO THE TOUCH		0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

- a INCLUDES FEMALE #229 THAT WAS EUTHANIZED ON LACTATION DAY 0 AFTER TOTAL LITTER LOSS.
- b INCLUDES FEMALE #204 THAT WAS EUTHANIZED ON GESTATION DAY 25 (POST-BREEDING DAY 25 - FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED).
- c INCLUDES FEMALE #227 THAT WAS EUTHANIZED ON STUDY DAY 54 (POST-BREEDING PERIOD DAY 25 - NO EVIDENCE OF MATING, FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER COMPLETION OF THE MATING PERIOD).
- d INCLUDES FEMALE #213 THAT WAS EUTHANIZED ON LACTATION DAY 2 AND FEMALE #245 THAT WAS EUTHANIZED ON LACTATION DAY 1 AFTER TOTAL LITTER LOSS.

TABLE 1  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

----- F E M A L E -----

	GROUP: LEVEL (MG/KG/DAY):					
	1 0	2 10	3 20	4 30	5 50	6 75
<b>BODY</b>						
-HUNCHED POSTURE	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-DEHYDRATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-DARK MATERIAL - FORELIMB(S)	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-URINE STAIN	2/ 2	0/ 0	0/ 0	0/ 0	2/ 2	2/ 2
-FECAL STAIN	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1
-REDDISH VAGINAL DISCHARGE	1/ 1	1/ 1	0/ 0	1/ 1	0/ 0	0/ 0
<b>EYES</b>						
-DARK MATERIAL AROUND EYE(S)	0/ 0	0/ 0	2/ 1	0/ 0	0/ 0	0/ 0
-EYE(S) PALE IN COLOR	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	3/ 2
<b>NOSE/MOUTH</b>						
-DARK MATERIAL AROUND NOSE	4/ 2	2/ 2	3/ 2	2/ 1	1/ 1	1/ 1
-DARK MATERIAL AROUND MOUTH	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1
-SCAB(S) - AROUND MOUTH	0/ 0	3/ 1	0/ 0	2/ 1	11/ 1	0/ 0
-MALALIGNMENT	0/ 0	0/ 0	11/ 1	0/ 0	0/ 0	0/ 0
-INCISOR(S) - BROKEN	0/ 0	10/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-SWELLING - UPPER LIP	0/ 0	2/ 1	0/ 0	0/ 0	0/ 0	0/ 0
-SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
<b>POST-DOSE OBSERVATIONS</b>						
-SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-CONVULSIONS	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
<b>PARTURITION OBSERVATIONS</b>						
-REDDISH VAGINAL DISCHARGE	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
-SKIN PALE IN COLOR - ALL EXTREMITIES	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1
-EYE(S) PALE IN COLOR	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	2/ 1

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 2  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 BODY WEIGHT DATA (GRAMS)

PAGE 1

GROUP: LEVEL (MG/KG/DAY):	M A L E											
	1 0	2 10	3 20	4 30	5 50	6 75						
WEEK 1	MEAN 472	MEAN 468	MEAN 467	MEAN 465	MEAN 468	MEAN 469						
	S. D. 32.2	S. D. 21.6	S. D. 29.0	S. D. 22.6	S. D. 15.2	S. D. 30.5						
	N 8	N 8	N 8	N 8	N 8	N 8						
2	MEAN 488	MEAN 475	MEAN 479	MEAN 477	MEAN 479	MEAN 477						
	S. D. 33.5	S. D. 19.7	S. D. 33.6	S. D. 23.6	S. D. 19.6	S. D. 31.2						
	N 8	N 8	N 8	N 8	N 8	N 8						
3	MEAN 510	MEAN 493	MEAN 498	MEAN 493	MEAN 488	MEAN 497						
	S. D. 37.6	S. D. 25.9	S. D. 29.9	S. D. 26.6	S. D. 22.4	S. D. 35.3						
	N 8	N 8	N 8	N 8	N 8	N 8						
4	MEAN 519	MEAN 503	MEAN 507	MEAN 498	MEAN 498	MEAN 502						
	S. D. 36.8	S. D. 27.3	S. D. 29.9	S. D. 18.9	S. D. 20.7	S. D. 33.4						
	N 8	N 8	N 8	N 8	N 8	N 8						
5	MEAN 537	MEAN 516	MEAN 525	MEAN 513	MEAN 511	MEAN 513						
	S. D. 36.3	S. D. 27.5	S. D. 30.2	S. D. 27.4	S. D. 20.9	S. D. 35.5						
	N 8	N 8	N 8	N 8	N 8	N 8						
6	MEAN 548	MEAN 532	MEAN 540	MEAN 526	MEAN 521	MEAN 525						
	S. D. 39.1	S. D. 28.3	S. D. 33.6	S. D. 32.9	S. D. 19.1	S. D. 39.5						
	N 7	N 8	N 8	N 8	N 8	N 8						

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 2  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 BODY WEIGHT DATA (GRAMS)

		M A L E					
GROUP:	1	2	3	4	5	6	
LEVEL (MG/KG/DAY):	0	10	20	30	50	75	
WEEK 7							
MEAN	548	525	536	528	514	515	
S. D.	46.3	38.9	39.3	40.2	22.3	48.1	
N	7	8	8	8	8	8	
FBW							
MEAN	563	532	548	543	531	539	
S. D.	44.0	43.9	41.3	43.7	24.0	53.0	
N	7	8	8	8	8	8	

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL  
 NOTE: FBW = FINAL BODY WEIGHT.

TABLE 2  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 BODY WEIGHT DATA (GRAMS)

		F E M A L E					
GROUP:	LEVEL (MG/KG/DAY):	1	2	3	4	5	6
WEEK		0	10	20	30	50	75
1	MEAN	275	274	276	275	275	273
	S. D.	14.1	15.3	8.5	16.6	16.3	11.9
	N	8	8	8	8	8	8
2	MEAN	277	274	279	279	274	277
	S. D.	13.3	12.0	15.9	15.7	17.4	16.9
	N	8	8	8	8	8	8
3	MEAN	282	277	287	281	278	282
	S. D.	14.8	17.7	13.1	17.6	18.3	15.8
	N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 3  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO BODY WEIGHT GAIN DATA (GRAMS)

		M A L E					
GROUP:	1	2	3	4	5	6	
LEVEL (MG/KG/DAY):	0	10	20	30	50	75	
WEEK 1 TO 2							
MEAN	16	7	12	12	11	8	
S. D.	11.2	6.8	13.6	3.3	6.2	11.7	
N	8	8	8	8	8	8	
2 TO 3							
MEAN	22	18	18	16	9**	20	
S. D.	6.0	9.8	5.1	4.3	9.2	6.6	
N	8	8	8	8	8	8	
3 TO 4							
MEAN	9	11	10	5	10	6	
S. D.	4.9	3.8	7.0	11.9	10.5	9.7	
N	8	8	8	8	8	8	
4 TO 5							
MEAN	18	13	17	15	13	11	
S. D.	9.1	3.8	6.3	11.6	4.1	8.9	
N	8	8	8	8	8	8	
5 TO 6							
MEAN	15	15	16	12	10	11	
S. D.	4.0	5.6	6.1	8.1	4.5	12.4	
N	7	8	8	8	8	8	
6 TO 7							
MEAN	0	-7	-4	2	-8	-10	
S. D.	7.9	12.2	9.9	10.4	12.2	15.6	
N	7	8	8	8	8	8	

----- SIGNIFICANTLY DIFFERENT FROM CONTROL: \*\* = P<0.01 -----

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 3  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO BODY WEIGHT GAIN DATA (GRAMS)

		M A L E					
GROUP:	1	2	3	4	5	6	
LEVEL (MG/KG/DAY):	0	10	20	30	50	75	
WEEK 7 TO 8							
MEAN	14	7	12	15	17	24	
S. D.	9.4	13.3	7.6	6.8	7.0	8.9	
N	7	8	8	8	8	8	

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 3  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO BODY WEIGHT GAIN DATA (GRAMS)

----- F E M A L E -----

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
WEEK 1 TO 2						
MEAN	3	0	3	4	-2	4
S. D.	8.2	8.1	8.4	6.6	5.0	7.0
N	8	8	8	8	8	8
WEEK 2 TO 3						
MEAN	5	4	8	3	5	5
S. D.	3.8	7.5	4.3	5.6	5.4	5.1
N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 4  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 GESTATION BODY WEIGHT DATA (GRAMS)

DAY	GROUP: LEVEL (MG/KG/DAY):	1		2		3		4		5		6	
		0	8	10	8	20	8	30	8	50	75		
DAY 0	MEAN	284		274		283		284		274		280	
	S. D.	16.5		22.7		13.6		18.8		22.6		18.9	
	N	8	8	8	8	8	8	8	8	7	8	8	8
DAY 7	MEAN	310		308		313		315		310		312	
	S. D.	18.9		13.7		9.6		19.2		17.8		23.2	
	N	8	8	8	8	8	8	8	8	7	8	8	8
DAY 14	MEAN	335		333		336		335		334		331	
	S. D.	20.7		17.0		8.7		15.3		25.7		29.7	
	N	8	8	8	8	8	8	8	8	7	8	8	8
DAY 20	MEAN	416		402		404		409		397		403	
	S. D.	25.2		24.5		14.6		27.9		21.5		34.2	
	N	8	8	8	8	8	8	8	8	7	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 5  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 0- 7 MEAN	26	34	30	31	36	32
S. D.	8.6	12.3	5.8	5.2	8.6	14.2
N	8	8	8	8	7	8
DAY 7- 14 MEAN	25	25	24	21	24	19
S. D.	4.1	6.2	6.1	8.5	9.7	14.5
N	8	8	8	8	7	8
DAY 14- 20 MEAN	81	68	68	74	63	71
S. D.	13.9	14.8	11.7	23.5	6.7	18.8
N	8	8	8	8	7	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 6  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F0 LACTATION BODY WEIGHT DATA (GRAMS)

DAY	GROUP: LEVEL (MG/KG/DAY):	1		2		3		4		5		6	
		0	8	10	7	20	8	30	7	50	7	75	8
DAY 1	MEAN	302		306		295		308		300		296	
	S.D.	20.7		15.2		22.5		18.0		19.4		28.1	
	N	8		7		8		7		7		8	
DAY 4	MEAN	318		318		314		320		309		308	
	S.D.	14.4		17.9		14.4		19.7		21.3		20.1	
	N	8		7		8		7		7		6	
DAY 7	MEAN	325		322		320		322		318		317	
	S.D.	11.4		18.3		12.1		17.0		23.0		16.1	
	N	8		7		8		7		7		6	
DAY 10	MEAN	335		333		328		334		327		327	
	S.D.	12.8		22.0		9.6		15.4		12.7		17.9	
	N	8		7		7		7		7		6	
DAY 14	MEAN	347		342		345		354		344		340	
	S.D.	14.4		23.2		10.4		22.7		20.2		21.5	
	N	8		7		7		7		7		6	
DAY 21	MEAN	345		331		340		347		333		330	
	S.D.	20.4		14.8		12.1		14.5		18.6		22.7	
	N	8		7		7		7		7		6	

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL



TABLE 7  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 1- 4 MEAN	16	12	20	12	9	11
S.D.	13.7	11.8	12.0	13.9	13.1	12.0
N	8	7	8	7	7	6
DAY 4- 7 MEAN	7	4	6	2	9	9
S.D.	8.5	9.6	11.1	8.5	10.6	6.2
N	8	7	8	7	7	6
DAY 7- 10 MEAN	11	11	11	12	9	10
S.D.	8.6	7.6	4.5	7.6	12.7	5.1
N	8	7	7	7	7	6
DAY 10- 14 MEAN	11	9	17	20	17	13
S.D.	12.9	8.5	6.8	13.7	9.6	5.5
N	8	7	7	7	7	6
DAY 14- 21 MEAN	-2	-12	-5	-8	-10	-10
S.D.	12.1	9.5	11.6	13.2	18.8	11.3
N	8	7	7	7	7	6

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 8  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1

		M A L E									
GROUP:		1	2	3	4	5	6				
LEVEL (MG/KG/DAY):		0	10	20	30	50	75				
WEEK	1 TO 2	25	23	24	24	24	24				
	MEAN	2.3	2.5	2.3	2.3	1.3	2.3				
	S. D.	8	8	8	8	8	8				
	N										
2 TO 3	MEAN	26	24	25	24	25	26				
	S. D.	2.9	2.3	0.9	2.3	1.3	2.6				
	N	8	8	8	8	8	8				
4 TO 5	MEAN	28	26	29	28	28	29				
	S. D.	2.0	1.7	2.0	2.9	1.7	2.8				
	N	7	8	8	8	7	8				
5 TO 6	MEAN	30	28	30	28	28	28				
	S. D.	2.3	1.8	1.9	3.3	1.0	5.0				
	N	7	8	8	8	8	8				
6 TO 7	MEAN	27	26	27	27	26	28				
	S. D.	3.2	2.6	1.8	3.1	1.8	4.3				
	N	7	8	8	8	8	8				
7 TO 8	MEAN	27	25	28	28	28	30				
	S. D.	3.6	4.0	1.8	3.4	1.9	3.6				
	N	7	8	8	8	8	8				

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL  
 NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).

TABLE 8  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

----- F E M A L E -----

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
WEEK 1 TO 2	17	16	17	17	17	17
MEAN	1.6	1.5	1.3	1.1	1.4	2.0
S. D.						
N	8	8	8	8	8	8
2 TO 3	17	18	18	17	17	17
MEAN	1.6	2.7	1.1	1.4	1.6	1.3
S. D.						
N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 9  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 0- 7 MEAN	22	23	23	23	24	23
S. D.	2.4	2.1	1.2	2.0	2.3	4.1
N	8	8	8	8	7	8
DAY 7- 14 MEAN	22	24	23	24	24	24
S. D.	2.6	1.9	2.0	2.9	3.7	5.8
N	8	8	8	8	7	8
DAY 14- 20 MEAN	24	24	23	25	23	24
S. D.	2.1	1.3	2.7	1.4	1.3	3.2
N	8	8	8	8	7	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 10  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 1- 4 MEAN	36	59	33	33	36	32
S. D.	5.0	60.2	5.8	8.1	10.6	7.4
N	8	7	8	7	7	6
DAY 4- 7 MEAN	41	42	43	40	43	46
S. D.	4.2	5.0	8.2	6.4	8.1	7.7
N	8	7	8	7	7	6
DAY 7- 10 MEAN	52	52	51	51	53	51
S. D.	5.4	4.8	6.1	6.8	4.4	6.4
N	8	7	7	7	7	6

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 11  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1

		M A L E							
GROUP:		1	2	3	4	5	6		
LEVEL (MG/KG/DAY):		0	10	20	30	50	75		
WEEK	1 TO 2	35 6.5 8	32 4.5 8	37 7.9 8	34 6.1 8	44 18.2 8	43 17.8 8		
	2 TO 3	38 9.6 8	33 4.5 8	38 9.1 8	33 5.0 8	45 18.8 8	38 5.3 7		
	4 TO 5	36 5.4 7	34 4.8 8	39 7.5 8	35 7.4 8	45 12.4 6	50 29.8 8		
	5 TO 6	43 14.2 7	35 5.0 8	39 6.9 8	34 6.7 8	47 22.8 8	36 6.4 7		
	6 TO 7	39 11.9 7	33 4.4 8	37 8.2 8	34 6.7 8	48 24.5 8	47 22.2 8		
	7 TO 8	38 12.7 7	29 6.9 8	35 6.1 8	34 6.6 8	48 28.3 7	48 25.7 8		

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL  
 NOTE: WATER CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).

TABLE 11  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

----- F E M A L E -----

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
WEEK 1 TO 2	27	26	28	29	28	29
MEAN	5.7	6.2	4.5	4.5	7.5	6.1
S. D.						
N	8	7	8	8	7	8
2 TO 3	26	26	29	26	28	32
MEAN	5.8	6.9	4.4	5.2	7.7	13.2
S. D.						
N	8	7	8	8	7	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 0- 7 MEAN	36	40	41	48	42	49
S. D.	6.7	9.9	6.9	9.4	4.7	20.3
N	8	7	8	8	6	8
DAY 7- 14 MEAN	41	42	44	48	45	53
S. D.	10.1	10.1	8.6	11.0	7.0	23.3
N	8	6	8	7	5	8
DAY 14- 20 MEAN	49	54	50	62	55	54
S. D.	7.3	14.3	10.2	14.9	8.0	12.8
N	8	7	8	7	7	6

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL



GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 1- 4 MEAN	55	59	57	52	57	60
S. D.	9.2	7.6	10.3	13.4	15.5	13.5
N	8	6	8	7	7	6
DAY 4- 7 MEAN	56	64	63	60	66	71
S. D.	5.1	7.0	9.0	10.2	12.6	18.0
N	8	7	8	7	7	6
DAY 7- 10 MEAN	67	78	73	81	81	84
S. D.	7.9	9.3	9.8	13.4	7.7	20.6
N	8	7	7	7	7	6

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 14  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO COPULATION, FERTILITY, PRECOITAL INTERVAL  
 AND GESTATION LENGTH DATA

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
COPULATION INDEX						
NO. OF ANIMALS PAIRED	8/8	8/8	8/8	8/8	7/8	8/8
PERCENT	100.0	100.0	100.0	100.0	87.5	100.0
FERTILITY INDEX						
NO. OF ANIMALS PAIRED	8/8	8/8	8/8	8/8	7/7	8/8
PERCENT	100.0	100.0	100.0	100.0	100.0	100.0
PRECOITAL INTERVAL (DAYS)						
MEAN	3.5	2.8	2.1	3.4	2.9	2.6
S. D.	1.9	0.9	1.1	1.6	0.9	0.9
N	8	8	8	8	7	8
GESTATION LENGTH (DAYS)						
MEAN	22.0	22.5	22.1	22.1	22.4	22.5
S. D.	0.0	0.8	0.4	0.4	0.5	0.5
N	8	8	8	7	7	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL  
 NOTE: COPULATION INDEX = NO. OF ANIMALS PAIRED WITH SUCCESSFUL COPULATION / NO. OF MATED ANIMALS X 100.  
 FERTILITY INDEX = NO. OF GRAVID FEMALES / NO. OF ANIMALS PAIRED WITH SUCCESSFUL COPULATION X 100.

TABLE 15  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO GROSS NECROPSY OBSERVATIONS

	FOUND DEAD OR EUTHANIZED MORIBUND													
	M A L E					F E M A L E								
GROUP: LEVEL (MG/KG/DAY):	1	2	3	4	5	6	75	1	2	3	4	5	6	75
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8	8	8
NUMBER OF ANIMALS FOUND DEAD OR EUTHANIZED MORIBUND	1	0	0	0	0	0	0	0	0	0	1	0	0	0
EXTERNAL APPEARANCE														
-HAIRCOAT - DARK MATERIAL	1	0	0	0	0	0	0	0	0	0	0	0	0	0
-HAIRCOAT - WET MATTING	1	0	0	0	0	0	0	0	0	0	1	0	0	0
BRAIN														
-HEMORRHAGE	0	0	0	0	0	0	0	0	0	1	0	0	0	0
ESOPHAGUS														
-PERFORATION	1	0	0	0	0	0	0	0	0	0	0	0	0	0
LUNGS														
-MOTTLED	0	0	0	0	0	0	0	0	0	1	0	0	0	0
OVARIES														
-CORPORA LUTEA - REGRESSING	0	0	0	0	0	0	0	0	0	1	0	0	0	0
TRACHEA														
-CONTENT ABNORMAL	0	0	0	0	0	0	0	0	0	1	0	0	0	0
UTERINE HORNS														
-IMPLANTATION SCARS PRESENT	0	0	0	0	0	0	0	0	0	1	0	0	0	0
THORACIC CAVITY														
-CONTENT ABNORMAL	0	0	0	0	0	0	0	0	0	1	0	0	0	0
-FLUID CONTENTS	1	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 15  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO GROSS NECROPSY OBSERVATIONS

GROUP: LEVEL (MG/KG/DAY) :	M A L E					F E M A L E								
	1	2	3	4	5	6	75	1	2	3	4	5	6	75
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8	8	8
NUMBER OF ANIMALS FOUND DEAD OR EUTHANIZED MORIBUND	1	0	0	0	0	0	0	0	0	0	1	0	0	0
SUBCUTANEOUS TISSUE -HEMORRHAGIC AREA - EDEMA	0	0	0	0	0	0	0	0	0	0	1	0	0	0
	1	0	0	0	0	0	0	0	0	0	0	0	0	0

SCHEDULED EUTHANASIA

GROUP: LEVEL (MG/KG/DAY):	M A L E					F E M A L E								
	1	2	3	4	5	6	75	1	2	3	4	5	6	75
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8	8	8
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	7	8	8	8	8	8	8	8	8	8	a	7	8	b
NO REMARKABLE FINDINGS	6	5	7	4	3	3	3	0	0	0	0	0	0	0
EXTERNAL APPEARANCE	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-HAIRCOAT - DARK MATERIAL	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-HAIRCOAT - WET MATTING	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-HAIRCOAT - HAIRLOSS	0	1	0	0	0	0	0	0	1	3	1	1	0	0
-TAIL - ENLARGEMENT	0	0	0	1	0	0	0	0	0	0	0	0	0	0
ABDOMINAL CAVITY	0	0	0	0	0	1	1	0	0	0	0	0	0	1
-ADHESION	0	0	0	0	0	0	0	0	0	0	0	0	0	0
KIDNEYS	0	0	1	0	2	1	1	0	0	0	0	0	0	0
-DILATED PELVIS	0	0	0	0	1	0	0	0	0	0	0	0	0	0
-ENLARGED	0	0	0	0	1	0	0	0	0	0	0	0	0	0
-CALCULI	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-CYST(S)	0	1	0	0	0	0	0	0	0	0	0	0	0	0
-TAN AREA(S)	0	0	0	0	0	0	0	0	0	0	0	0	0	1

a INCLUDES FEMALE #229 THAT WAS EUTHANIZED ON LACTATION DAY 0 AFTER TOTAL LITTER LOSS.  
 b INCLUDES FEMALE #204 THAT WAS EUTHANIZED ON GESTATION DAY 25 (POST-BREEDING DAY 25 - FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED).  
 c INCLUDES FEMALE #227 THAT WAS EUTHANIZED ON STUDY DAY 54 (POST-BREEDING PERIOD DAY 25 - NO EVIDENCE OF MATING, FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER COMPLETION OF THE MATING PERIOD).  
 d INCLUDES FEMALE #213 THAT WAS EUTHANIZED ON LACTATION DAY 2 AND FEMALE #245 THAT WAS EUTHANIZED ON LACTATION DAY 1 AFTER TOTAL LITTER LOSS.

	SCHEDULED EUTHANASIA															
	M A L E					F E M A L E										
GROUP:	1	2	3	4	5	6	1	2	3	4	5	6				
LEVEL (MG/KG/DAY):	0	10	20	30	50	75	0	10	20	30	50	75				
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8				
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	7	8	8	8	8	8	8	8	a	7	8	b	8	c	8	d
LIVER																
- PALE	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1
- ACCENTUATED LOBULAR MARKINGS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
- TAN AREA(S)	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
LUNGS																
- PALE	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
- MOTTLED	0	0	0	0	0	0	0	1	1	1	0	1	1	0	0	1
- DARK RED FOCI	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0	0
- FOCI	0	0	0	1	1	0	3	0	2	0	0	2	0	0	0	2
- NODULE(S)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
ORAL CAVITY																
- INCISOR(S) - BROKEN	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SKIN																
- SCABBING	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0

a INCLUDES FEMALE #229 THAT WAS EUTHANIZED ON LACTATION DAY 0 AFTER TOTAL LITTER LOSS.  
 b INCLUDES FEMALE #204 THAT WAS EUTHANIZED ON GESTATION DAY 25 (POST-BREEDING DAY 25 - FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED).  
 c INCLUDES FEMALE #227 THAT WAS EUTHANIZED ON STUDY DAY 54 (POST-BREEDING PERIOD DAY 25 - NO EVIDENCE OF MATING, FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER COMPLETION OF THE MATING PERIOD).  
 d INCLUDES FEMALE #213 THAT WAS EUTHANIZED ON LACTATION DAY 2 AND FEMALE #245 THAT WAS EUTHANIZED ON LACTATION DAY 1 AFTER TOTAL LITTER LOSS.

	SCHEDULED EUTHANASIA											
	M A L E					F E M A L E						
GROUP:	1	2	3	4	5	6	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75	0	10	20	30	50	75
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	7	8	8	8	8	8	8	8	8	8	8	8
SMALL INTESTINE												
- CONTENT ABNORMAL	0	0	0	0	0	0	0	1	0	1	1	0
- REDDENED MUCOSA	0	0	0	0	0	0	0	0	0	1	0	0
STOMACH												
- CONTENT ABNORMAL	0	0	0	0	0	0	0	1	0	0	0	1
- REDDENED	0	1	0	1	0	0	0	0	0	0	0	0
TESTES												
- DISCOLORED	0	0	0	0	0	1	0	0	0	0	0	0
- SMALL	0	0	0	0	0	1	0	0	0	0	0	0
THYMUS												
- FOCI	0	0	0	0	0	2	0	0	0	0	0	0
THYROID												
- PALE	0	0	0	0	0	0	0	1	0	0	0	2

a INCLUDES FEMALE #229 THAT WAS EUTHANIZED ON LACTATION DAY 0 AFTER TOTAL LITTER LOSS.  
 b INCLUDES FEMALE #204 THAT WAS EUTHANIZED ON GESTATION DAY 25 (POST-BREEDING DAY 25 - FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED).  
 c INCLUDES FEMALE #227 THAT WAS EUTHANIZED ON STUDY DAY 54 (POST-BREEDING PERIOD DAY 25 - NO EVIDENCE OF MATING, FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER COMPLETION OF THE MATING PERIOD).  
 d INCLUDES FEMALE #213 THAT WAS EUTHANIZED ON LACTATION DAY 2 AND FEMALE #245 THAT WAS EUTHANIZED ON LACTATION DAY 1 AFTER TOTAL LITTER LOSS.

SLI STUDY NO. : 3472.3  
 CLIENT: NIPERA, INC.

TABLE 15  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO GROSS NECROPSY OBSERVATIONS

PAGE 6

	SCHEDULED EUTHANASIA															
	M A L E					F E M A L E										
GROUP:	1	2	3	4	5	6	1	2	3	4	5	6				
LEVEL (MG/KG/DAY):	0	10	20	30	50	75	0	10	20	30	50	75				
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8				
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	7	8	8	8	8	8	8	8	a	7	8	b	8	c	8	d
URETERS																
- DISTENDED	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
- CALCULI	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
URINARY BLADDER																
- CONTENT ABNORMAL	0	0	0	1	3	0	0	0	0	0	0	0	0	0	0	0
- DISTENDED	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
- CALCULI	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
- THICKENED	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
UTERINE HORNS																
- IMPLANTATION SCARS PRESENT	0	0	0	0	0	0	0	8	8	7	7	7	8			
- NONGRAVID -- AMMONIUM SULFIDE NEGATIVE	0	0	0	0	0	0	0	0	0	0	0	1	0			
- RETAINED FETUS(ES) - PRESENT	0	0	0	0	0	0	0	0	0	0	1	0	0			
- RESORPTION(S) PRESENT	0	0	0	0	0	0	0	0	0	0	1	0	0			

a INCLUDES FEMALE #229 THAT WAS EUTHANIZED ON LACTATION DAY 0 AFTER TOTAL LITTER LOSS.  
 b INCLUDES FEMALE #204 THAT WAS EUTHANIZED ON GESTATION DAY 25 (POST-BREEDING DAY 25 - FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED).  
 c INCLUDES FEMALE #227 THAT WAS EUTHANIZED ON STUDY DAY 54 (POST-BREEDING PERIOD DAY 25 - NO EVIDENCE OF MATING, FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER COMPLETION OF THE MATING PERIOD).  
 d INCLUDES FEMALE #213 THAT WAS EUTHANIZED ON LACTATION DAY 2 AND FEMALE #245 THAT WAS EUTHANIZED ON LACTATION DAY 1 AFTER TOTAL LITTER LOSS.



TABLE 16  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
<b>IMPLANTATION SCAR COUNT</b>						
MEAN	16.4	15.1	14.8	15.4	15.4	14.8
S. D.	1.7	3.9	2.6	1.7	1.6	3.2
N	8	8	8	7	7	8
<b>NUMBER OF LIVE PUPS (DAY 0)</b>						
MEAN	16.0	12.5 a	13.3	13.1	12.7	10.0 a
S. D.	1.3	6.2	2.8	2.0	2.3	4.5
N	8	8	8	7	7	8
<b>POST-IMPLANTATION LOSS</b>						
MEAN	0.4	2.6	1.5	2.3*	2.7**	4.8**
S. D.	0.7	5.4	1.6	2.0	2.0	2.3
N	8	8	8	7	7	8

SIGNIFICANTLY DIFFERENT FROM CONTROL (MANN-WHITNEY U TEST): \* = P<0.05; \*\* = P<0.01  
 NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.  
 a INCLUDES ONE FEMALE WITH TOTAL LITTER LOSS ON LACTATION DAY 0.

TABLE 17  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 PUP VIABILITY

GROUP: LEVEL (MG/KG/DAY):	LACTATION DAY 0					
	1	2	3	4	5	6
0	10	10	20	30	50	75
NO. DEAD	1	12**	10**	10**	4	23**
NO. LIVE	128	100	106	92	89	80
NO. LITTERS WITH LIVE OFFSPRING	8	7	8	7	7	7
MEAN LIVE LITTER SIZE a	16.0	14.3	13.3	13.1	12.7	11.4**
SEX RATIO (MALE: FEMALE)	65: 63	46: 54	49: 57	45: 47	34: 55	48: 32

SIGNIFICANTLY DIFFERENT FROM CONTROL: \*\* = P<0. 01  
 NOTE: NO. DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.  
 a INCLUDES ONLY FEMALES WITH LIVE PUPS ON LACTATION DAY 0.

GROUP: LEVEL	(MG/KG/DAY)	DURING LACTATION					
		1 0	2 10	3 20	4 30	5 50	6 75
DAY 1	NO. ALIVE/NO. PUPS PERCENT	126/128 98.4	100/100 100.0	105/106 99.1	92/92 100.0	88/89 98.9	76/80 95.0
DAY 4 BEFORE SELECTION	NO. ALIVE/NO. PUPS PERCENT	126/128 98.4	100/100 100.0	103/106 97.2	91/92 98.9	88/89 98.9	71/80 88.8**
DAY 4 AFTER SELECTION	NO. ALIVE/NO. PUPS PERCENT	64/64 100.0	54/54 100.0	63/63 100.0	56/56 100.0	56/56 100.0	48/48 100.0
DAY 7	NO. ALIVE/NO. PUPS PERCENT	63/64 98.4	54/54 100.0	63/63 100.0	56/56 100.0	56/56 100.0	48/48 100.0
DAY 14	NO. ALIVE/NO. PUPS PERCENT	62/64 96.9	54/54 100.0	55/63 87.3	56/56 100.0	56/56 100.0	48/48 100.0
DAY 21	NO. ALIVE/NO. PUPS PERCENT	62/64 96.9	54/54 100.0	55/63 87.3	56/56 100.0	56/56 100.0	48/48 100.0

-----  
 SIGNIFICANTLY DIFFERENT FROM CONTROL: \*\* = P<0.01  
 -----

TABLE 18  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 PUP OBSERVATIONS DURING LACTATION (OCCURRENCE/ANIMALS AFFECTED)

	GROUP:						332/ 88	278/ 71
	1	2	3	4	5	6		
	LEVEL (MG/KG/DAY):							
	0	10	20	30	50	75		
NORMAL	404/124	354/100	354/104	337/ 91	332/ 88	278/ 71		
-NO REMARKABLE OBSERVATIONS								
DEAD								
-CANNIBALIZED	1/ 1	10/ 10	0/ 0	0/ 0	0/ 0	4/ 4		
-FOUND DEAD	2/ 2	2/ 2	11/ 11	10/ 10	4/ 4	28/ 28		
-MISSING - PRESUMED CANNIBALIZED	2/ 2	0/ 0	2/ 2	1/ 1	1/ 1	0/ 0		
-CULLED ON SCHEDULED DAY	62/ 62	46/ 46	40/ 40	35/ 35	32/ 32	23/ 23		
ACTIVITY								
-GASPING	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	2/ 2		
BODY								
-APPARENT UMBILICAL HERNIA	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1		
-BENT TAIL	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0		
-CONSTRICTED AREA(S)	7/ 3	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0		
-HAIRLOSS	8/ 8	0/ 0	16/ 8	0/ 0	0/ 0	0/ 0		
-LACERATION(S)	0/ 0	1/ 1	2/ 2	1/ 1	2/ 1	1/ 1		
-PUP COOL TO THE TOUCH	3/ 3	0/ 0	2/ 2	0/ 0	0/ 0	10/ 10		
-PUP PALE IN COLOR	1/ 1	0/ 0	1/ 1	0/ 0	1/ 1	1/ 1		
-PUP PURPLE IN COLOR	1/ 1	0/ 0	1/ 1	1/ 1	0/ 0	0/ 0		
-PUP SMALL IN SIZE	1/ 1	0/ 0	2/ 2	0/ 0	0/ 0	1/ 1		
-SCAB(S)	7/ 5	3/ 3	1/ 1	1/ 1	9/ 5	1/ 1		
-SUBCUTANEOUS HEMORRHAGE(S)	13/ 13	5/ 5	6/ 5	10/ 10	3/ 3	3/ 3		
-TAIL TIP ABSENT	3/ 2	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0		

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 19  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 PUP WEIGHTS DURING LACTATION (GRAMS)

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
DAY 1	MEAN 6.6 S. D. 0.39 N 8	7.2 1.23 7	6.4 0.71 8	7.0 0.48 7	7.2 0.33 7	6.6 0.82 7
DAY 4 BEFORE SELECTION	MEAN 9.2 S. D. 8	10.4 7	9.4 8	9.8 7	10.2 7	10.1 6
DAY 4 AFTER SELECTION	MEAN 9.2 S. D. 8	10.4 7	9.3 8	9.9 7	10.2 7	10.1 6
DAY 7	MEAN 15.3 S. D. 1.01 N 8	17.1 2.41 7	15.2 1.56 8	15.6 1.96 7	15.7 1.68 7	16.0 1.73 6
DAY 14	MEAN 31.9 S. D. 1.49 N 8	33.7 3.26 7	31.2 3.24 7	31.5 2.23 7	31.2 3.12 7	31.4 2.82 6
DAY 21	MEAN 51.5 S. D. 1.91 N 8	55.1 5.96 7	50.8 4.71 7	51.0 4.58 7	50.2 6.67 7	49.8 5.39 6

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 20  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 PUP GROSS NECROPSY OBSERVATIONS

	FOUND DEAD						FEMALE					
	1	2	3	4	5	6	1	2	3	4	5	6
GROUP:	0	10	20	30	50	75	0	10	20	30	50	75
LEVEL (MG/KG/DAY):	1	1	6	6	2	17	1	1	5	4	2	11
NUMBER OF ANIMALS FOUND DEAD	0	0	0	0	0	1	0	0	1	0	0	0
NO REMARKABLE FINDINGS	1	0	0	0	0	0	0	0	0	0	0	0
EXTERNAL APPEARANCE	1	0	0	0	0	0	0	0	0	0	0	0
-TAIL - CONSTRICTION	0	0	0	0	0	0	0	0	0	0	0	0
EYES	0	0	0	0	0	0	0	0	0	0	0	0
-ANOPHTHALMIA	1	0	0	0	0	0	0	0	0	0	0	0
-MICROPHthalmia	0	0	0	0	0	0	0	0	0	0	0	0
HEAD	0	0	0	0	0	0	0	0	0	0	0	0
-EXENCEPHALY	0	0	0	0	0	0	0	0	0	0	0	0
-RHINOCEPHALY	0	0	0	0	0	0	0	0	0	0	0	0
HEART	0	0	0	0	0	0	0	0	0	0	0	0
-TRANSPOSITION OF GREAT VESSELS	0	0	0	0	0	0	0	0	0	0	0	0
KIDNEYS	0	0	0	0	0	0	0	0	0	0	0	0
-RENAL PAPILLA(E) INCOMPLETELY DEVELOPED	1	0	0	0	0	3	0	0	0	0	0	0
-RENAL PAPILLA(E) NOT DEVELOPED	0	0	0	0	0	0	0	0	0	0	0	0
LIVER	0	0	0	0	0	1	0	0	0	0	0	0
-PALE	0	0	0	0	0	0	0	0	0	0	0	0
LUNGS	0	0	5	6	0	8	1	0	3	2	1	9
-ATELECTASIS	0	0	0	0	0	0	0	0	0	0	0	0

TABLE 20  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 PUP GROSS NECROPSY OBSERVATIONS

	FOUND DEAD					
	M A L E			F E M A L E		
GROUP: LEVEL (MG/KG/DAY):	1	2	3	4	5	6
NUMBER OF ANIMALS FOUND DEAD	1	1	6	6	2	17
MULTIPLE ANOMALIES	0	0	0	0	1	0
-SHORTENED TORSO	0	0	0	0	0	0
SKIN	0	0	0	0	0	0
-SUBCUTANEOUS EDEMA	0	0	0	0	0	0
STOMACH	0	1	5	6	1	14
-MILK NOT PRESENT	0	0	0	0	0	0
TRACHEA	0	0	0	0	0	0
-CONTENT ABNORMAL	1	0	0	1	1	3
URETERS	0	0	0	0	0	0
-DISTENDED	0	0	0	0	0	0

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 21  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

	M A L E					
	1	2	3	4	5	6
GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
NORMAL						
-NO CLINICAL SIGNS	35/ 8	39/ 8	37/ 8	39/ 8	38/ 8	40/ 8
DEAD						
-SCHEDULED EUTHANASIA	8/ 8	8/ 8	8/ 8	8/ 8	8/ 8	8/ 8
EXCRETA/EMESIS						
-SOFT STOOLS	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
BODY						
-SCAB(S) - TAIL	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
EYES						
-CORNEAL OPACITY - RIGHT EYE	4/ 1	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
-MALPOSITIONED PUPIL - RIGHT EYE	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0
POST-DOSE OBSERVATIONS						
-SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	3/ 3

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 21  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

		F E M A L E					
GROUP:		1	2	3	4	5	6
LEVEL (MG/KG/DAY):		0	10	20	30	50	75
-----							
NORMAL							
-NO CLINICAL SIGNS		39/ 8	39/ 8	35/ 8	40/ 8	40/ 8	40/ 8
DEAD							
-SCHEDULED EUTHANASIA		8/ 8	8/ 8	8/ 8	8/ 8	8/ 8	8/ 8
BODY							
-SCAB(S) - TAIL		0/ 0	0/ 0	2/ 1	0/ 0	0/ 0	0/ 0
POST-DOSE OBSERVATIONS							
-SALIVATION		0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	2/ 1
-----							

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

TABLE 22  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 BODY WEIGHT DATA (GRAMS)

		M A L E					
GROUP:	LEVEL (MG/KG/DAY):	1	2	3	4	5	6
WEEK		0	10	20	30	50	75
1	MEAN	55	62	54	57	53	54
	S. D.	3.8	5.0	4.3	5.5	13.7	7.0
	N	7	8	8	8	8	8
2	MEAN	80	91	89	82	79	81
	S. D.	12.1	6.9	9.8	13.6	16.2	8.2
	N	8	8	8	8	8	8
3	MEAN	133	149	146	141	134	134
	S. D.	19.0	11.3	14.8	19.0	23.6	14.4
	N	8	8	8	8	8	8
4	MEAN	194	215	208	204	196	192
	S. D.	26.1	11.6	21.4	20.4	30.5	26.0
	N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 22  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 BODY WEIGHT DATA (GRAMS)

		F E M A L E					
GROUP:	LEVEL (MG/KG/DAY):	1	2	3	4	5	6
WEEK		0	10	20	30	50	75
1	MEAN	53	60	52	52	53	51
	S. D.	4.3	6.8	4.9	4.7	6.3	7.9
	N	7	8	8	8	8	8
2	MEAN	75	84	82	72	76	74
	S. D.	10.4	7.0	9.7	12.3	8.8	10.0
	N	8	8	8	8	8	8
3	MEAN	118	129	125	117	119	116
	S. D.	13.4	7.3	10.4	15.7	13.2	16.7
	N	8	8	8	8	8	8
4	MEAN	154	167	160	151	155	151
	S. D.	11.9	11.5	9.7	12.7	14.8	25.3
	N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 23  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 BODY WEIGHT GAIN DATA (GRAMS)

		M A L E					
GROUP:	LEVEL (MG/KG/DAY):	1	2	3	4	5	6
WEEK	1 TO 2	0	10	20	30	50	75
	MEAN	29	29	35	26	26	27
	S. D.	5.3	10.0	7.1	11.1	8.8	5.8
	N	7	8	8	8	8	8
	2 TO 3						
	MEAN	53	58	57	59	56	53
	S. D.	8.2	4.9	5.3	5.7	7.5	7.8
	N	8	8	8	8	8	8
	3 TO 4						
	MEAN	61	66	62	63	61	58
	S. D.	7.9	5.0	8.9	5.7	7.3	13.3
	N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

TABLE 23  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 BODY WEIGHT GAIN DATA (GRAMS)

----- F E M A L E -----

GROUP:	1	2	3	4	5	6
LEVEL (MG/KG/DAY):	0	10	20	30	50	75
WEEK 1 TO 2						
MEAN	25	24	30	20	23	22
S. D.	5.4	9.4	7.3	10.9	7.5	5.9
N	7	8	8	8	8	8
WEEK 2 TO 3						
MEAN	43	45	43	45	43	43
S. D.	4.0	1.8	5.7	4.3	7.1	7.9
N	8	8	8	8	8	8
WEEK 3 TO 4						
MEAN	37	38	35	34	36	35
S. D.	3.7	6.5	4.0	6.4	6.0	10.2
N	8	8	8	8	8	8

NONE SIGNIFICANTLY DIFFERENT FROM CONTROL

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

TABLE 24  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 SUMMARY OF F1 GROSS NECROPSY OBSERVATIONS

PAGE 1

SCHEDULED EUTHANASIA

GROUP: LEVEL (MG/KG/DAY):	M A L E					F E M A L E								
	1	2	3	4	5	6	75	1	2	3	4	5	6	75
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8	8	8
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	8	8	8	8	8	8	8	8	8	8	8	8	8	8
NO REMARKABLE FINDINGS	5	6	5	5	4	7	7	4	7	5	5	5	5	5
EXTERNAL APPEARANCE														
-TAIL BENT	0	1	0	1	0	0	0	2	0	0	1	1	1	0
-HAIRCOAT - WET MATTING	0	0	0	0	0	0	0	0	0	0	0	0	1	0
EYES														
-OPACITY	1	0	0	0	0	0	0	0	0	0	0	0	0	0
HEART														
- APPARENT CONSTRICTION	0	0	0	0	0	0	0	0	0	1	0	0	0	0
KIDNEYS														
- DILATED PELVIS	0	0	1	1	0	1	1	0	1	1	2	0	1	0
- PITTED	1	1	0	0	0	0	0	0	0	0	0	0	0	0
LUNGS														
- MOTTLED	1	0	1	0	0	0	0	0	0	0	0	0	0	1
- NODULE(S)	0	0	0	1	2	0	0	0	0	0	0	0	0	0
- DARK RED	0	0	0	0	0	0	0	1	0	1	0	0	0	0
MEDIASTINAL LYMPH NODE														
- REDDENED	0	0	0	0	0	0	0	1	0	0	0	0	0	0
SKIN														
- SCABBING	0	0	0	0	1	0	0	0	0	0	0	0	0	0

SCHEDULED EUTHANASIA

GROUP: LEVEL (MG/KG/DAY) :	M A L E					F E M A L E						
	1	2	3	4	5	6	1	2	3	4	5	6
	0	10	20	30	50	75	0	10	20	30	50	75
NUMBER OF ANIMALS IN DOSE GROUP	8	8	8	8	8	8	8	8	8	8	8	8
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	8	8	8	8	8	8	8	8	8	8	8	8
SPLEEN -GRAY AREA(S)	0	1	1	2	1	0	1	0	0	0	1	0
TRACHEA -CONTENT ABNORMAL	1	0	0	0	0	0	0	0	0	0	0	0
VAGINA -CONTENT ABNORMAL	0	0	0	0	0	0	2	0	0	0	0	1

SLI Study No. 3472.3

APPENDIX A

A Preliminary Probe Study in Rats



SLI Study No. 3472.3

## I. INTRODUCTION

This report details the experimental procedures and results of a preliminary probe study in rats with nickel sulfate hexahydrate. This preliminary study was performed to select dosage levels for the one-generation range-finding reproduction study. The procedures for animal husbandry and methods of test article preparation were similar to those described for the range-finding study animals.

## II. MATERIALS AND METHODS

The animals were acclimated to the laboratory conditions for five days prior to randomization (day -1). Animals were examined upon receipt and daily thereafter during acclimation for signs of physical or behavioral abnormalities. On the day following receipt, the rats were approximately 11 weeks of age with body weights ranging from 333 to 356 grams for males and 224 to 244 grams for females. Animals determined to be suitable test subjects were assigned to groups using a computer randomization program. The program ranked the animals according to day -1 body weights and randomly assigned the rats to study groups in a stratified block design. The study group design and dosage levels tested in the preliminary probe study were as follows:

Group	No. of Animals		Dosage Material	Dosage Level (mg/kg/day)	Dosage Conc. (mg/mL)	Dosage Volume (mL/kg)
	Male	Female				
1	2	2	RO-Di Water	0	0	10
2	2	2	Nickel Sulfate Hexahydrate	5.0	0.5	10
3	2	2	Nickel Sulfate Hexahydrate	15.0	1.5	10
4	2	2	Nickel Sulfate Hexahydrate	25.0	2.5	10
5	2	2	Nickel Sulfate Hexahydrate	50.0	5.0	10
6	2	2	Nickel Sulfate Hexahydrate	75.0	7.5	10
7	2	2	Nickel Sulfate Hexahydrate	150.0	15.0	10

Dosing preparations were administered orally, by gavage, as a single dose for 14 consecutive days. Individual doses were adjusted based on the most recent body weight. Mortality/general health checks were performed twice daily, in the morning and afternoon. Detailed clinical observations were performed prior to study initiation (day -1) and cage-side observations were performed daily between one-half hour and two hours following dosing (days 1 to 14). Individual body weights were recorded for each animal on days 1, 8 and 15. All animals were subjected to an abbreviated gross necropsy at the time of death or euthanasia. Surviving

SLI Study No. 3472.3

animals were euthanized by carbon dioxide inhalation at study termination on day 15. The necropsy examination included evaluation of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. No tissues were retained at necropsy.

### III. RESULTS

One female in the 5.0 mg/kg/day group, one male in the 50.0 mg/kg/day group, one male in the 75.0 mg/kg/day group, and two females in the 150.0 mg/kg/day group died or were euthanized moribund during the study. The death at the 75.0 mg/kg/day level was clearly the result of a gavage accident. The death at the 5.0 mg/kg/day level was also suspected to be unrelated to the test article since no deaths occurred at the 15.0 and 25.0 mg/kg/day levels. In general, clinical signs were infrequent and randomly dispersed in the treated groups. Body weight gains appeared to be decreased in males at levels of 50.0 mg/kg/day and above, especially during the second week of treatment.

### IV. CONCLUSION

Based on the above results, dosage levels of 10, 20, 30, 50 and 75 mg/kg/day were selected for the one-generation reproduction range-finding study in rats.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

PAGE 1

	M A L E					
	1	2	3	4	5	6
GROUP:	0	5.0	15.0	25.0	50.0	75.0
LEVEL (MG/KG/DAY):						
DEAD	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	1/ 1
- FOUND DEAD	2/ 2	2/ 2	2/ 2	2/ 2	1/ 1	1/ 1
- SCHEDULED EUTHANASIA						
ACTIVITY						
- ACTIVITY DECREASED	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
- SALIVATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1
EYES						
- DARK MATERIAL AROUND EYE(S)	0/ 0	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

PAGE 2

----- M A L E -----

GROUP: 7  
LEVEL (MG/KG/DAY): 150.0

DEAD

- FOUND DEAD 0/ 0

- SCHEDULED EUTHANASIA 2/ 2

ACTIVITY

- ACTIVITY DECREASED 1/ 1

- SALIVATION 1/ 1

EYES

- DARK MATERIAL AROUND EYE(S) 0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

PAGE 3

----- F E M A L E -----

GROUP: LEVEL (MG/KG/DAY):	----- F E M A L E -----					
	1	2	3	4	5	6
DEAD	0	5.0	15.0	25.0	50.0	75.0
- FOUND DEAD	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
- UNSCHEDULED EUTHANASIA	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
- SCHEDULED EUTHANASIA	2/ 2	1/ 1	2/ 2	2/ 2	2/ 2	2/ 2
ACTIVITY						
- ACTIVITY DECREASED	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
EXCRETA/EMESIS						
- SOFT STOOLS	0/ 0	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0
BODY						
- UNKEMPT APPEARANCE	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
EYES						
- LACRIMATION	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0	0/ 0
- EYELID(S) - PARTIALLY CLOSED	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0
OTHER						
- UNKNOWN AMOUNT OF TEST ARTICLE EXPELLED FROM MOUTH	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0	0/ 0
- APPARENT TEST ARTICLE SEEN COMING FROM ANIMAL'S NOSE DURING DOSING	0/ 0	0/ 0	1/ 1	0/ 0	0/ 0	0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
SUMMARY OF SURVIVAL AND CLINICAL OBSERVATIONS (OCCURRENCE/ANIMALS AFFECTED)

PAGE 4

----- F E M A L E -----

GROUP:  
LEVEL (MG/KG/DAY): 150.0

-----  
DEAD  
- FOUND DEAD 2/ 2  
- UNSCHEDULED EUTHANASIA 0/ 0  
- SCHEDULED EUTHANASIA 0/ 0  
ACTIVITY  
- ACTIVITY DECREASED 2/ 2  
EXCRETA/EMESIS  
- SOFT STOOLS 0/ 0  
BODY  
- UNKEMPT APPEARANCE 1/ 1  
EYES  
- LACRIMATION 1/ 1  
- EYELID(S) - PARTIALLY CLOSED 0/ 0  
OTHER  
- UNKNOWN AMOUNT OF TEST ARTICLE EXPELLED FROM MOUTH 0/ 0  
- APPARENT TEST ARTICLE SEEN COMING FROM ANIMAL'S NOSE DURING DOSING 0/ 0

NOTE: DATA REFLECT THE TOTAL OCCURRENCE OF EACH FINDING OVER THE NUMBER OF ANIMALS EXHIBITING THE FINDING.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF BODY WEIGHT DATA (GRAMS)

		M A L E						
		1	2	3	4	5	6	7
GROUP:	LEVEL (MG/KG/DAY):	0	5.0	15.0	25.0	50.0	75.0	150.0
DAY 1	MEAN	375	376	370	382	370	381	372
	N	2	2	2	2	2	2	2
8	MEAN	403	402	402	422	401	389	397
	N	2	2	2	2	2	1	2
15	MEAN	426	416	418	448	401	372	397
	N	2	2	2	2	1	1	2

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF BODY WEIGHT DATA (GRAMS)

----- F E M A L E -----

DAY	GROUP:	1	2	3	4	5	6	7
	LEVEL (MG/KG/DAY):	0	5.0	15.0	25.0	50.0	75.0	150.0
1	MEAN	249	264	246	254	251	248	242
	N	2	2	2	2	2	2	2
8	MEAN	264	302	246	265	254	254	
	N	2	2	2	2	2	2	
15	MEAN	266	257	249	266	257	260	
	N	2	1	2	2	2	2	

NOTE: FEMALES IN GROUP 7 WERE FOUND DEAD ON OR BEFORE DAY 6.



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF BODY WEIGHT GAIN DATA (GRAMS)

		M A L E						
		1	2	3	4	5	6	7
GROUP:		0	5.0	15.0	25.0	50.0	75.0	150.0
DAY	1 TO 8	28	26	33	40	32	5	26
	MEAN	2	2	2	2	2	1	2
	N							
DAY	8 TO 15	23	14	16	26	4	-17	0
	MEAN	2	2	2	2	1	1	2
	N							

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF BODY WEIGHT GAIN DATA (GRAMS)

----- F E M A L E -----

GROUP:	1	2	3	4	5	6	7
LEVEL (MG/KG/DAY):	0	5.0	15.0	25.0	50.0	75.0	150.0
DAY 1 TO 8	15	39	-1	12	3	6	
MEAN	2	2	2	2	2	2	
N							
8 TO 15	3	-7	4	1	3	6	
MEAN	2	1	2	2	2	2	
N							

NOTE: FEMALES IN GROUP 7 WERE FOUND DEAD ON OR BEFORE DAY 6.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF GROSS NECROPSY OBSERVATIONS

GROUP: LEVEL (MG/KG/DAY):	FOUND DEAD OR EUTHANIZED MORIBUND													
	M A L E							F E M A L E						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
	0	5.0	15.0	25.0	50.0	75.0	150.0	0	5.0	15.0	25.0	50.0	75.0	150.0
NUMBER OF ANIMALS IN DOSE GROUP	2	2	2	2	2	2	2	2	2	2	2	2	2	2
NUMBER OF ANIMALS FOUND DEAD OR EUTHANIZED MORIBUND	0	0	0	0	1	1	0	0	1	0	0	0	0	2
EXTERNAL APPEARANCE														
-HAIRCOAT - WET MATTING	0	0	0	0	1	1	0	0	0	0	0	0	0	1
-HAIRCOAT - DARK MATERIAL	0	0	0	0	0	0	0	0	0	0	0	0	0	1
ESOPHAGUS														
-PERFORATION	0	0	0	0	0	1	0	0	0	0	0	0	0	0
LARGE INTESTINE														
-CONTENT ABNORMAL	0	0	0	0	0	0	0	0	0	0	0	0	0	1
LUNGS														
-DARK RED	0	0	0	0	1	0	0	0	0	0	0	0	0	0
SMALL INTESTINE														
-CONTENT ABNORMAL	0	0	0	0	0	0	0	0	0	0	0	0	0	2
STOMACH														
-CONTENT ABNORMAL	0	0	0	0	0	0	0	0	0	0	0	0	0	1
THORACIC CAVITY														
-FLUID CONTENTS	0	0	0	0	0	1	0	0	0	0	0	0	0	0
THYMUS														
-FOCI	0	0	0	0	1	0	0	0	0	0	0	0	0	0
UTERINE HORNS														
-IMPLANTATION SITE(S) PRESENT	0	0	0	0	0	0	0	0	1	0	0	0	0	0

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 SUMMARY OF GROSS NECROPSY OBSERVATIONS

SCHEDULED EUTHANASIA

GROUP: LEVEL (MG/KG/DAY):	M A L E							F E M A L E						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7
	0	5.0	15.0	25.0	50.0	75.0	150.0	0	5.0	15.0	25.0	50.0	75.0	150.0
NUMBER OF ANIMALS IN DOSE GROUP	2	2	2	2	2	2	2	2	2	2	2	2	2	2
NUMBER OF ANIMALS EXAMINED AT SCHEDULED EUTHANASIA	2	2	2	2	1	1	2	2	1	2	2	2	2	0
NO REMARKABLE FINDINGS	2	2	2	2	1	1	2	2	1	2	2	2	2	0

SLI STUDY NO.: 3472.3  
 CLIENT: NIPIERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL SURVIVAL AND CLINICAL OBSERVATIONS

PAGE 1

(POSITIVE FINDINGS)

ANIMAL NO.	GROUP	CATEGORY	STUDY DAY	GRADE OBSERVATIONS
16980	M 0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16987	M 0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16986	M 5.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16989	M 5.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16991	M 15.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16995	M 15.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16981	M 25.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16992	M 25.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
16984	M 50.0 MG/KG/DAY	DEAD	11	P FOUND DEAD
16994	M 50.0 MG/KG/DAY	EYES	3	P DARK MATERIAL AROUND EYE(S)
		DEAD	15	P SCHEDULED EUTHANASIA
16982	M 75.0 MG/KG/DAY	DEAD	5	P FOUND DEAD
16985	M 75.0 MG/KG/DAY	ACTIVITY	9	P SALIVATION
		ACTIVITY	11	P ACTIVITY DECREASED
		DEAD	15	P SCHEDULED EUTHANASIA
16983	M 150.0 MG/KG/DAY	ACTIVITY	11	P SALIVATION
		DEAD	15	P SCHEDULED EUTHANASIA
16988	M 150.0 MG/KG/DAY	ACTIVITY	11	P ACTIVITY DECREASED
		DEAD	15	P SCHEDULED EUTHANASIA
180	F 0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
186	F 0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
178	F 5.0 MG/KG/DAY	DEAD	9	P SCHEDULED EUTHANASIA
190	F 5.0 MG/KG/DAY	OTHER	12	P UNSCHEDULED EUTHANASIA a
		DEAD	15	P UNKNOWN AMOUNT OF TEST ARTICLE EXPELLED FROM MOUTH
179	F 15.0 MG/KG/DAY	OTHER	7	P SCHEDULED EUTHANASIA
		EYES	13	P APPARENT TEST ARTICLE SEEN COMING FROM ANIMAL'S NOSE DURING DOSING
		DEAD	15	P EYELID(S) - PARTIALLY CLOSED
				P SCHEDULED EUTHANASIA

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT  
 a ON STUDY DAY 9, FEMALE #178 WAS FOUND TO HAVE DELIVERED PUPS IN ITS CAGE. THIS FEMALE WAS EUTHANIZED AND NECROPSIED. THE SURVIVING OFFSPRING WERE EUTHANIZED AND DISCARDED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL SURVIVAL AND CLINICAL OBSERVATIONS

PAGE 2

(POSITIVE FINDINGS)

ANIMAL NO.	GROUP	CATEGORY	STUDY DAY	GRADE OBSERVATIONS
191	F 15.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
176	F 25.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
183	F 25.0 MG/KG/DAY	EXCRETA/EMESIS	2	P SOFT STOOLS
		DEAD	15	P SCHEDULED EUTHANASIA
185	F 50.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
189	F 50.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
182	F 75.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
187	F 75.0 MG/KG/DAY	DEAD	15	P SCHEDULED EUTHANASIA
181	F 150.0 MG/KG/DAY	ACTIVITY	1	P ACTIVITY DECREASED
		DEAD	2	P FOUND DEAD
184	F 150.0 MG/KG/DAY	EYES	4	P LACRIMATION
		ACTIVITY	5	P ACTIVITY DECREASED
		BODY	5	P UNKEMPT APPEARANCE
		DEAD	6	P FOUND DEAD

GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- SEVERE, P- PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL BODY WEIGHT DATA (GRAMS)

PAGE 1

DAY 1 8 15

GROUP 1: 0 MG/KG/DAY

16980 M	381	408	431
16987 M	368	397	420
MEAN	375	403	426
N	2	2	2

GROUP 2: 5.0 MG/KG/DAY

16986 M	381	405	423
16989 M	370	398	408
MEAN	376	402	416
N	2	2	2

GROUP 3: 15.0 MG/KG/DAY

16991 M	374	404	424
16995 M	365	400	411
MEAN	370	402	418
N	2	2	2

GROUP 4: 25.0 MG/KG/DAY

16981 M	372	403	416
16992 M	391	440	479
MEAN	382	422	448
N	2	2	2

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL BODY WEIGHT DATA (GRAMS)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

PAGE 2

DAY 1 8 15

GROUP 5: 50.0 MG/KG/DAY

16984 M	366	405	FOUND DEAD
16994 M	373	397	401
MEAN	370	401	401
N	2	2	1

GROUP 6: 75.0 MG/KG/DAY

16982 M	378	FOUND DEAD
16985 M	384	389
MEAN	381	389
N	2	1
		372
		372
		1
		1

GROUP 7: 150.0 MG/KG/DAY

16983 M	372	409	410
16988 M	371	385	384
MEAN	372	397	397
N	2	2	2



APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL BODY WEIGHT DATA (GRAMS)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

PAGE 3

DAY	1	8	15
<b>GROUP 1: 0 MG/KG/DAY</b>			
180 F	255	268	262
186 F	243	259	270
MEAN	249	264	266
N	2	2	2
<b>GROUP 2: 5.0 MG/KG/DAY</b>			
178 F	276	340	UNSCHEDULED EUTHANASIA
190 F	251	264	257
MEAN	264	302	257
N	2	2	1
<b>GROUP 3: 15.0 MG/KG/DAY</b>			
179 F	245	251	246
191 F	247	240	252
MEAN	246	246	249
N	2	2	2
<b>GROUP 4: 25.0 MG/KG/DAY</b>			
176 F	242	254	252
183 F	265	276	280
MEAN	254	265	266
N	2	2	2

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL BODY WEIGHT DATA (GRAMS)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

PAGE 4

DAY	1	8	15
GROUP 5: 50.0 MG/KG/DAY			
185 F	250	250	257
189 F	252	257	256
MEAN	251	254	257
N	2	2	2
GROUP 6: 75.0 MG/KG/DAY			
182 F	237	247	256
187 F	259	261	263
MEAN	248	254	260
N	2	2	2
GROUP 7: 150.0 MG/KG/DAY			
181 F	247	FOUND DEAD	
184 F	237	FOUND DEAD	
MEAN	242		
N	2		

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL BODY WEIGHT GAIN DATA (GRAMS)

DAY	1 TO 8	8 TO 15
GROUP 1: 0 MG/KG/DAY		
16980 M	27	23
16987 M	29	23
MEAN	28	23
N	2	2
GROUP 2: 5.0 MG/KG/DAY		
16986 M	24	18
16989 M	28	10
MEAN	26	14
N	2	2
GROUP 3: 15.0 MG/KG/DAY		
16991 M	30	20
16995 M	35	11
MEAN	33	16
N	2	2
GROUP 4: 25.0 MG/KG/DAY		
16981 M	31	13
16992 M	49	39
MEAN	40	26
N	2	2

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL BODY WEIGHT GAIN DATA (GRAMS)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

PAGE 2

DAY 1 TO 8 8 TO 15

GROUP 5: 50.0 MG/KG/DAY

16984 M	39	FOUND DEAD
16994 M	24	4
MEAN	32	4
N	2	1

GROUP 6: 75.0 MG/KG/DAY

16982 M	FOUND DEAD
16985 M	5 -17
MEAN	5 -17
N	1 1

GROUP 7: 150.0 MG/KG/DAY

16983 M	37	1
16988 M	14	-1
MEAN	26	0
N	2	2

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL BODY WEIGHT GAIN DATA (GRAMS)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

PAGE 3

DAY 1 TO 8 8 TO 15

GROUP 1: 0 MG/KG/DAY

180 F	13	-6
186 F	16	11
MEAN	15	3
N	2	2

GROUP 2: 5.0 MG/KG/DAY

178 F	64	UNSCHEDULED EUTHANASIA
190 F	13	-7
MEAN	39	-7
N	2	1

GROUP 3: 15.0 MG/KG/DAY

179 F	6	-5
191 F	-7	12
MEAN	-1	4
N	2	2

GROUP 4: 25.0 MG/KG/DAY

176 F	12	-2
183 F	11	4
MEAN	12	1
N	2	2

APPENDIX A  
 A PRELIMINARY PROBE STUDY IN RATS  
 INDIVIDUAL BODY WEIGHT GAIN DATA (GRAMS)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

PAGE 4

DAY 1 TO 8 8 TO 15

GROUP 5: 50.0 MG/KG/DAY

185 F	0	7
189 F	5	-1
MEAN	3	3
N	2	2

GROUP 6: 75.0 MG/KG/DAY

182 F	10	9
187 F	2	2
MEAN	6	6
N	2	2

GROUP 7: 150.0 MG/KG/DAY

181 F	FOUND DEAD
184 F	FOUND DEAD

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL GROSS NECROPSY OBSERVATIONS

PAGE 1

ANIMAL NO.	GROUP:	50.0 MG/KG/DAY	MALE	FOUND DEAD OR EUTHANIZED MORIBUND	7/24/98	STUDY DAY	11	GRADE
		LUNGS		FOUND DEAD GROSS: DARK RED				P
		THYMUS		GROSS: FOCI ALL LOBES				P
		EXT. APPEARANCE		GROSS: HAIRCOAT - WET MATTING AROUND NOSE AND MOUTH, TAN				P
16982	GROUP:	75.0 MG/KG/DAY	MALE	FOUND DEAD GROSS: PERFORATION ESOPHAGUS	7/18/98	STUDY DAY	5	P
		EXT. APPEARANCE		GROSS: HAIRCOAT - WET MATTING ANTERIOR TO THYMUS				P
		THORACIC CAVITY		GROSS: FLUID CONTENTS AROUND NOSE AND MOUTH; LIGHT YELLOW APPROXIMATELY 1.5 ML; CLEAR DARK RED				P
178	GROUP:	5.0 MG/KG/DAY	FEMALE	EUTHANIZED MORIBUND GROSS: IMPLANTATION SITE(S) - (LEFT, RIGHT)	7/22/98	STUDY DAY	9	P
		UTERINE HORNS						
181	GROUP:	150.0 MG/KG/DAY	FEMALE	FOUND DEAD GROSS: CONTENT ABNORMAL	7/15/98	STUDY DAY	2	P
		SMALL INTESTINE						
184	GROUP:	150.0 MG/KG/DAY	FEMALE	FOUND DEAD GROSS: CONTENT ABNORMAL	7/19/98	STUDY DAY	6	P
		SMALL INTESTINE						
		LARGE INTESTINE		GROSS: CONTENT ABNORMAL ENTIRE TRACT; DARK REDDISH-GREEN MUCOID MATERIAL				P
		STOMACH		GROSS: CONTENT ABNORMAL ENTIRE TRACT; DARK REDDISH-GREEN MUCOID MATERIAL				P
		EXT. APPEARANCE		GROSS: HAIRCOAT - WET MATTING DARK GREENISH-BROWN FLUID UROGENITAL AREA; DARK GREEN				P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL GROSS NECROPSY OBSERVATIONS

PAGE 2

ANIMAL NO.	EXT. APPEARANCE	FOUND DEAD OR EUTHANIZED MORIBUND	GRADE
184 (CONTINUED)	GROSS: HAIRCOAT - DARK MATERIAL AROUND EYES, NOSE, MOUTH AND FORELIMBS; RED		P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL GROSS NECROPSY OBSERVATIONS

GRADE

ANIMAL NO.	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	7/28/98 STUDY DAY	15
16980	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16987	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16986	GROUP:	5.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16989	GROUP:	5.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16991	GROUP:	15.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16995	GROUP:	15.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16981	GROUP:	25.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16992	GROUP:	25.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16994	GROUP:	50.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16985	GROUP:	75.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
16983	GROUP:	150.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL GROSS NECROPSY OBSERVATIONS

PAGE 4

GRADE

ANIMAL NO.	GROUP:	150.0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	7/28/98 STUDY DAY	15
ANIMAL NO. 16988	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 180	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 186	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 190	GROUP:	5.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 179	GROUP:	15.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 191	GROUP:	15.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 176	GROUP:	25.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 183	GROUP:	25.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 185	GROUP:	50.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 189	GROUP:	50.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15
ANIMAL NO. 182	GROUP:	75.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	7/28/98 STUDY DAY	15

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX A  
A PRELIMINARY PROBE STUDY IN RATS  
INDIVIDUAL GROSS NECROPSY OBSERVATIONS

PAGE 5

GRADE

ANIMAL NO.	187	GROUP:	75.0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	7/28/98	STUDY DAY	15	GRADE
					SCHEDULED EUTHANASIA				
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				

GROSS GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- MARKED, P- PRESENT

(100)

SLI Study No. 3472.3

## APPENDIX B

Protocol, Protocol Amendments and Protocol  
Deviations/Occurrences

**A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE**

**PROTOCOL**

Springborn Study No. 3472.3

Springborn Laboratories, Inc. (SLI)  
Ohio Research Center  
640 N. Elizabeth Street  
Spencerville, OH 45887

Joseph C. Siglin, Ph.D., DABT  
Study Director

For

NiPERA, Inc.  
2605 Meridian Parkway  
Suite 200  
Durham, NC 27713

SLI Study No. 3472.3

TABLE OF CONTENTS

PURPOSE ..... 1

RESPONSIBILITIES ..... 1

    Sponsor ..... 1

    Sponsor's Representative ..... 1

    Testing Location ..... 1

    Personnel Responsibilities ..... 2

PROPOSED STUDY SCHEDULE ..... 2

TEST ARTICLE AND CONTROL MATERIAL ..... 2

    Test Article ..... 2

        Identification ..... 2

        SLI Test Article Identification Number ..... 3

        Batch (Lot) Number ..... 3

        Source ..... 3

        Purity ..... 3

        Description ..... 3

        Shelf Life/Expiration Date ..... 3

        Characteristics ..... 3

        Storage Conditions ..... 3

        Handling Precautions ..... 3

    Retention Sample ..... 4

    Test Article Disposition ..... 4

    Vehicle Control Material ..... 4

        Identity ..... 4

    Method and Frequency of Test Article Preparation ..... 4

SLI Study No. 3472.3

TABLE OF CONTENTS

TEST SYSTEM ..... 5

    Justification of the Test System ..... 5

    Justification of the Route of Exposure and Number of Animals ..... 5

    Description ..... 6

        Species ..... 6

        Strain ..... 6

        Source ..... 6

        Age and Body Weight ..... 6

        Number of Animals/Sex on Study ..... 6

    Method of Identification ..... 6

    Animal Husbandry ..... 7

        Housing ..... 7

        Environment ..... 7

        Food ..... 7

        Water ..... 7

    Acclimation ..... 8

    Randomization ..... 8

EXPERIMENTAL DESIGN AND PROCEDURES ..... 9

    Study Group Design ..... 9

    Treatment ..... 9

    Parameters to be Evaluated ..... 10

        Clinical Signs--F0 Animals ..... 10

        Clinical Signs--Selected F1 Animals ..... 10

        Body Weights--F0 Animals ..... 10

        Body Weights--Selected F1 Animals ..... 11

        Food and Water Consumption--F0 Animals ..... 11

    Breeding--F0 Animals ..... 11

SLI Study No. 3472.3

TABLE OF CONTENTS

Parturition--F0 Females .....	11
Lactation--F0 Females .....	12
Method of Individual Pup Identification .....	12
F1 Offspring .....	12
Standardization of Litter Sizes .....	12
Selection of F1 Animals .....	12
Nonselected F1 Pups .....	13
Gross Necropsy .....	13
Unscheduled Deaths--F0 and Selected F1 Animals .....	14
Scheduled Euthanasia--F0 and Selected F1 Animals .....	14
Unscheduled Deaths--Nonselected F1 Pups .....	14
PROTOCOL AMENDMENT .....	14
DATA REPORTING .....	15
STATISTICAL ANALYSIS .....	16
MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS .....	16
REGULATORY COMPLIANCE .....	17
QUALITY ASSURANCE .....	17
ANIMAL WELFARE COMPLIANCE STATEMENT .....	17
DECLARATION OF INTENT .....	18
PROTOCOL APPROVAL .....	19
REFERENCES .....	20



SLI Study No. 3472.3

TABLE OF CONTENTS

ATTACHMENT 1 .....	21
A Preliminary Probe Study in Rats .....	21

## I. PURPOSE

The purpose of this range-finding study is to evaluate the potential effects of the test article when administered to rats by oral gavage over the course of one generation. Data from this study will be used to select dosage levels for a subsequent two-generation reproduction study in rats. This study will be conducted in accordance with the Principles of Good Laboratory Practice set forth by the OECD [C(97)186/FINAL].

## II. RESPONSIBILITIES

### A. Sponsor

Nickel Producers Environmental Research Association, Inc. (NiPERA, Inc.)  
2605 Meridian Parkway  
Suite 200  
Durham, NC 27713

### B. Sponsor's Representative

Hudson K. Bates, Ph.D., DABT  
Senior Health Scientist

Telephone: (919) 544-7722  
Fax: (919) 544-7507  
e-mail: [hbates@nipera.org](mailto:hbates@nipera.org)

### C. Testing Location

Springborn Laboratories, Inc.  
Ohio Research Center  
640 N. Elizabeth Street  
Spencerville, Ohio 45887  
Telephone: (419) 647-4196  
Fax: (419) 647-6560

D. Personnel Responsibilities

1. Joseph C. Siglin, Ph.D., DABT  
Study Director/Director of Toxicology
2. Bjorn A. Thorsrud, Ph.D.  
Alternate Contact/Manager of Developmental  
and Reproduction Toxicology
3. Malcolm Blair, Ph.D.  
Vice President and Managing Director
4. Robert C. Springborn, Ph.D.  
Chairman, President and CEO
5. J. Dale Thurman, D.V.M., M.S., DABT  
Director of Pathology
6. Anita M. Bosau, RQAP-GLP  
Director of Compliance Assurance

III. PROPOSED STUDY SCHEDULE

- A. Initiation of In-Life Phase: July, 1998
- B. Completion of In-Life Phase: October, 1998
- C. Audited Draft Report Date: January, 1999

IV. TEST ARTICLE AND CONTROL MATERIAL

A. Test Article

1. Identification  
  
Nickel(II) sulfate hexahydrate  
(CAS No. 10101-97-0)

2. SLI Test Article Identification Number

S98.001.3472

3. Batch (Lot) Number

08516TQ

4. Source

Aldrich Chemical Company

5. Purity

99%

6. Description

Blue green crystalline powder

7. Shelf Life/Expiration Date

None provided

8. Characteristics

The Sponsor is responsible for any necessary evaluations of the test article concerning chemical identity, purity, strength, stability, and other required data.

9. Storage Conditions

Ambient temperature; tightly closed container

10. Handling Precautions

Safety data regarding the test article will be provided [Material Safety Data Sheet (MSDS) or equivalent, if available]. Technical personnel are required to read this information prior to handling the test article. Any questions concerning this information should be referred to the Study Director.

Additional safety and handling information may be provided by the Study Director and/or Sponsor. Minimum safety requirements include safety glasses, impervious gloves, and laboratory attire. Material Safety Data Sheets (or equivalent) shall also be available for all other chemical entities utilized in the conduct of this study.

B. Retention Sample

A retention sample (1 g) of each lot of the test article will be taken and stored at SLI under the specified storage conditions.

C. Test Article Disposition

The test article will be properly disposed of following completion of all scheduled studies.

D. Vehicle Control Material

1. Identity

Reverse Osmosis-Deionized (RO-Di) Water  
(from SLI Pharmacy source)

E. Method and Frequency of Test Article Preparation

The test article will be dissolved in RO-Di water for administration by daily oral gavage. Gavage solutions will be prepared fresh at least every 21 days and stored refrigerated (approximately 2-8°C) until use. All procedures used in preparing the gavage solutions will be recorded and reported.

At the first preparation of dosing solutions for the range-finding study, duplicate 20 mL samples of each gavage solution, including the vehicle control, will be taken and stored at -70°C for possible analytical analysis. These samples will be discarded after conclusion of the study if analytical analysis is not considered necessary by the Sponsor and Study Director.

## V. TEST SYSTEM

### A. Justification of the Test System

The Sprague-Dawley rat was selected as the animal model for this study since:

1. This species/strain has a proven sensitivity to a variety of agents and therefore provides a suitable animal model for testing chemicals and drugs for human risk assessment.
2. Both the EPA and OECD recommend the rat for reproduction studies.
3. Reliable scientific methods currently exist for performing rat reproduction studies. In addition, extensive historical control data are available at SLI and in the published literature concerning fertility and general reproduction in the rat.
4. The Sprague-Dawley rat has been used extensively for reproduction testing. Thus, data from this study may be compared and contrasted to other studies performed in rats.
5. Healthy rats may be obtained from USDA approved and regulated suppliers.
6. Laboratory rats may be safely handled and manipulated by trained laboratory personnel.

### B. Justification of the Route of Exposure and Number of Animals

1. Oral administration of the test article was selected since this is a potential route of human exposure. In addition, this route is recommended by EPA and OECD Guidelines for reproduction studies.
2. This study was designed to use the fewest number of animals possible, consistent with the objectives of the study, the scientific needs of the Sponsor, contemporary scientific standards and in consideration of applicable regulatory requirements.

C. Description

1. Species

Rat

2. Strain

Sprague-Dawley CrI:CD®BR VAF/Plus®

3. Source

Charles River Laboratories, Inc.  
St. Constant, Quebec  
Canada

4. Age and Body Weight (at Receipt)

Approximately 10 to 11 weeks old and at least 200 g (males) or 175 g (females). Actual body weights will be documented in the study records.

5. Number of Animals/Sex on Study

48 males and 48 females (range-finding study)  
14 males and 14 females (preliminary probe)

A minimum of 70 rats per sex will be obtained. The females will be nulliparous and nonpregnant at receipt. Males and females will have different birth dates to avoid potential sibling pairings.

D. Method of Identification

Metal ear tags displaying unique identification numbers will be used as the method of identification. Color coded cage cards displaying the study number, animal number and group number will be affixed to each cage.

## E. Animal Husbandry

### 1. Housing

The animals will be housed individually in suspended stainless steel cages (except during cohabitation for mating) or plastic nesting boxes (F0 females) for parturition and lactation. All housing and care will be based on the standards recommended by the Guide for the Care and Use of Laboratory Animals [1].

### 2. Environment

The environmental controls for the animal room will be set to maintain room temperature and relative humidity ranges of  $72 \pm 7^{\circ}\text{F}$  and  $50 \pm 20\%$ , respectively. Environmental control equipment will be monitored and adjusted as necessary to minimize fluctuations in the animal room environment. Light timers will be set to maintain a 12-hour light/12-hour dark cycle and the room ventilation will be set to produce 10-15 air changes/hour. The room temperature and relative humidity will be recorded a minimum of once daily.

### 3. Food

PMI Certified Rodent Chow® #5002 (Purina Mills, Inc.) will be provided ad libitum throughout the study. The feed is analyzed by the supplier for nutritional components and environmental contaminants. The lot number and expiration date of each batch of diet used during the study will be recorded. Dietary limitations for various environmental contaminants, including heavy metals, pesticides, polychlorinated biphenyls and total aflatoxin are set by the manufacturer. Within these limits, there are no contaminants reasonably expected in the diet which would interfere with the conduct of this study. Results of the dietary analyses (Certificates of Analysis) are provided by the manufacturer for each lot of diet. These will be maintained by the testing laboratory.

### 4. Water

Municipal tap water following treatment by reverse osmosis will be available ad libitum throughout the study. The purified water will be supplied by an automatic watering system or in water bottles for measurement of water consumption. Monitoring of the drinking water for contaminants will be conducted by the testing laboratory and the records will be available for inspection. Levels of contaminants which may be present are not expected to compromise the purpose of the study.



#### F. Acclimation

Upon receipt, 10-11 week old Charles River CD VAF/Plus® rats will be removed randomly from the shipping cartons, housed individually and eartagged. The animals will be weighed on the day after receipt and allowed to acclimate for a minimum of 10 days. During the acclimation period, the rats will be observed on a daily basis for overt physical and behavioral abnormalities. General health/mortality and moribundity checks will be performed twice daily, in the morning and afternoon, throughout the acclimation period. Any animals exhibiting abnormal signs will not be used on the study.

#### G. Randomization

On study day -1, the animals will be weighed and examined in detail for signs of physical disorder (detailed clinical observations). Animals determined to be suitable as test subjects will be assigned randomly to groups. The animal numbers and the respective body weight values will be entered into the computer. Homogeneity of groups by weight will be the criterion for acceptance of the randomization. Disposition of animals not selected for study will be documented in the study records. At the commencement of the study, the weight variation of the animals used will not exceed  $\pm 20\%$  of the mean weight for that sex.

## VI. EXPERIMENTAL DESIGN AND PROCEDURES

### A. Study Group Design

The experimental design for the range-finding study is as follows:

Group	No. of Parental Animals		Dosage Material <sup>a</sup>	Dosage Level (mg/kg/day) <sup>b</sup>	Dosage Conc. (mg/mL)	Dosage Volume (mL/kg)
	Male	Female				
1	8	8	Vehicle	0	0	TBD
2	8	8	NSH	TBD	TBD	TBD
3	8	8	NSH	TBD	TBD	TBD
4	8	8	NSH	TBD	TBD	TBD
5	8	8	NSH	TBD	TBD	TBD
6	8	8	NSH	TBD	TBD	TBD

<sup>a</sup>Vehicle = RO-Di water; NSH = Nickel sulfate hexahydrate (in aqueous solution).  
<sup>b</sup>Dosage levels for the range-finding study will be selected based upon results of a preliminary probe study (see Attachment 1).  
 TBD = To Be Determined.

### B. Treatment

Oral (gavage) administration. The test article and vehicle will be administered once daily, by oral gavage, to F0 parents and selected F1 offspring. The gavage needle will be wiped with gauze just prior to each dose administration. All attempts will be made to complete dosing by 10:00 a.m. on each day. Individual doses will be based on the most recent body weights. Study animals will receive continuous exposure to the control or test article throughout the study, at the appropriate levels, up to and including the day prior to scheduled euthanasia. F0 parental animals will be treated daily, beginning two weeks (14 days) prior to mating. Dosing of F1 offspring will begin on postnatal day (PND) 22 and will continue for 1, 2 or 3 weeks, depending on findings.

### C. Parameters to be Evaluated

#### 1. Clinical Signs--F0 Animals

F0 male and female animals will be checked for mortality/general health and moribundity twice daily during the study, in the morning and afternoon. Detailed clinical observations will be performed once weekly. In addition, cage-side observations for overt signs of toxicity will be performed a minimum of once daily, within approximately one-half to two hours following dosing. During gestation and lactation, F0 females will receive detailed clinical observations on a daily basis. All F0 animals will receive a detailed clinical observation on the day of scheduled euthanasia.

#### 2. Clinical Signs--Selected F1 Animals

Beginning on PND 22, selected F1 animals will be checked daily for mortality/general health and moribundity twice daily, in the morning and afternoon. Detailed clinical observations will be performed a minimum of once weekly. In addition, cage-side observations for overt signs of toxicity will be performed a minimum of once daily, within approximately one-half to two hours following dosing. All selected F1 animals will receive a detailed clinical observation on the day of scheduled euthanasia.

#### 3. Body Weights--F0 Animals

- a. Males--recorded once per week and on the day of scheduled euthanasia.
- b. Females--recorded once per week prior to confirmation of copulation. Females with positive evidence of mating and females that deliver will be weighed as follows:

Gestation--days 0, 7, 14 and 21.

Lactation--days 1, 4, 7, 10, 14 and 21.

Females with no evidence of copulation will be weighed weekly and on the day of scheduled euthanasia.

#### 4. Body Weights--Selected F1 Animals

Beginning on PND 22, body weights will be recorded on a weekly basis for all selected F1 animals until termination. A final body weight will be recorded for each animal on the day of scheduled euthanasia.

#### 5. Food and Water Consumption--F0 Animals

a. Males--recorded on a weekly basis, except during cohabitation, until the start of scheduled euthanasia for males.

b. Females--recorded on a weekly basis (except during cohabitation), on gestation days 0, 7, 14, and 21; and on lactation days 1, 4, 7 and 10.

For females with no evidence of copulation, food and water bottle weights will be recorded on a weekly basis.

#### D. Breeding--F0 Animals

After 14 days of treatment, each F0 female will be cohabitated with a single randomly selected F0 male from the same treatment group (1:1 pairings). The female will be placed in the male's cage. Each mating pair will be observed for evidence of copulation once daily during cohabitation. Detection of a vaginal copulatory plug or the presence of sperm in a vaginal smear will be the methods used to confirm copulation. The day on which confirmation of mating is made will be designated as day 0 of gestation, and will result in separation of the mating pair. The female will be returned to her individual cage. If after 14 days of mating no evidence of copulation is observed, the female will be separated from the male and placed in a plastic cage containing nesting material.

#### E. Parturition--F0 Females

Females with confirmed copulation will be transferred to plastic cages containing nesting material on gestation day 18 and observed at least twice daily for signs of parturition. Females with no evidence of mating will be examined for signs of parturition beginning 19 days following initiation of cohabitation. When parturition is first detected, the time will be recorded. The day when parturition is judged complete will be designated lactation day 0. Any signs of difficult or prolonged parturition will be recorded.

## F. Lactation--F0 Females

The lactation period will extend from days 0 to 21 during which time the dam and litter will remain together. Any abnormal nursing or nesting behaviors will be noted.

### 1. Method of Individual Pup Identification

Tail tattooing will be used to individually identify each pup in the litter. On lactation day 0, pups in each litter will be consecutively numbered beginning with the male offspring.

### 2. F1 Offspring

The following parameters will be evaluated for each pup during lactation:

- a. Viability: daily from days 0 to 21.
- b. External Examinations: days 0, 4, 7, 14 and 21.
- c. Sex Determinations: days 0, 4, 7, 14 and 21.
- d. Body Weights: days 1, 4, 7, 14 and 21.

### 3. Standardization of Litter Sizes

On lactation day 4, the size of each litter will be adjusted by random selection of pups to yield, as nearly as possible, 4 males and 4 females per litter. Whenever the number of male and female pups prevents having 4 of each sex per litter, partial adjustment will be undertaken. No adjustments will be made for litters of 8 pups or less.

## G. Selection of F1 Animals

At least 1 pup per sex per litter will be randomly selected (when possible) for oral dosing which will begin for selected F1 rats on PND 22 and continue for 1 to 3 weeks. The selection procedure will be performed when the pups are between postpartum days 4 and 21. Prior to the selection process, each pup will be externally examined and the sex verified. Only animals of suitable health will be acceptable for selection. A total of 8 male and 8 female F1 pups per group will be randomly selected. Following selection, F1 pups will

be individually ear tagged and then gang housed (2 or 3 per cage) in stainless steel caging for approximately 3 days to allow the animals to adapt to the automatic watering system.

#### H. Nonselected F1 Pups

Following weaning, all surviving nonselected F1 pups will be euthanized by carbon dioxide inhalation and discarded without necropsy.

#### I. Gross Necropsy

##### 1. Unscheduled Deaths--F0 and Selected F1 Animals

All F0 and selected F1 animals found dead or euthanized moribund during the study will be subjected to an abbreviated gross necropsy examination which will include examination of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. For F0 females found dead or euthanized following mating, uterine contents will be examined and the number of implantation sites and number of corpora lutea on each ovary will be recorded. Uteri of F0 females with no macroscopic implantations will be opened and placed in 10% aqueous ammonium sulfide solution as described by Salewski [2]. If present, uterine implantation scars will be counted and recorded. Moribund animals will be euthanized by carbon dioxide inhalation. Any animal found dead after working hours will be refrigerated until the next scheduled work day. No tissues will be saved.

##### 2. Scheduled Euthanasia--F0 and Selected F1 Animals

Parental female animals will be euthanized and necropsied according to the following schedule:

- a. Females that Deliver: on lactation day 21
- b. Females with Total Litter Loss: at the time of discovered total litter loss
- c. Females that Fail to Deliver (with evidence of mating): 25 days after evidence of mating is detected.

- d. Females that Fail to Deliver (with no evidence of mating): 25 days after completion of the breeding period.

Surviving F0 and selected F1 animals will be euthanized by carbon dioxide inhalation and subjected to an abbreviated gross necropsy examination which will include examination of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. Uterine contents of F0 females will be examined and the number of implantation scars will be recorded. Uteri of F0 females with no macroscopic implantations will be opened and placed in 10% aqueous ammonium sulfide solution as described by Salewski [2]. If present, uterine implantation scars will be counted and recorded. No tissues will be saved.

If all the pups in a litter die prior to lactation day 21, the dam will be euthanized and necropsied as described above, and the number of uterine implantation scars will be recorded.

In general, F0 males will be euthanized following completion of female parturition, and F0 females will be euthanized following completion of weaning. Selected F1 animals will be euthanized following termination of the F1 dosing phase.

### 3. Unscheduled Deaths--Nonselected F1 Pups

All nonselected F1 pups found dead or euthanized moribund will be submitted to necropsy for a gross examination, with emphasis on developmental morphology. Pups with deformities which are expected to affect survival, or pups partially cannibalized but viable will be euthanized by carbon dioxide inhalation and necropsied similar to dead pups. Partially cannibalized nonviable pups will be examined externally and discarded if they appear normal, or submitted to necropsy for further examination if they appear abnormal. No tissues will be saved.

## VII. PROTOCOL AMENDMENT

Alterations to this protocol may be made as the study progresses. No changes in the protocol will be made without the specific consent of the Sponsor's Representative. A protocol amendment will be prepared and signed by the Study Director, SLI Quality Assurance and Sponsor's Representative for any such changes.

## VIII. DATA REPORTING

One copy of the draft report and two copies of the final report (one bound and one unbound) will be submitted to the Sponsor. The final report will include all information necessary to provide a complete and accurate description of the experimental procedures and results.

The report will include at least the following information, tables and appendices:

- Table of Contents
- Regulatory Compliance
- Summary
- Introduction and Objectives
- Experimental Design and Test Procedures
- Presentation and Discussion of Results
- Conclusion
- References

### Tables:

- Summary of F0 Survival and Incidence of Clinical Signs
- Summary of F0 Body Weights and Body Weight Changes
- Summary of F0 Food and Water Consumption (g/animal/day)
- Summary of F0 Gestation and Lactation Body Weights and Body Weight Changes
- Summary of F0 Gestation Food and Water Consumption (g/animal/day)
- Summary of F0 Lactation Food and Water Consumption (g/animal/day)
- Summary of F0 Fertility Indices and Gestation Lengths
- Summary of F1 Litter Data (Survival, Size and Sex Ratios)
- Summary of F1 Litter Weights
- Summary of F1 Pup Observations
- Summary of Selected F1 Survival and Incidence of Clinical Signs
- Summary of Selected F1 Body Weights and Body Weight Changes
- Summary of F0 Gross Necropsy Findings
- Summary of F0 Implantation Data and Post-Implantation Loss
- Summary of Selected F1 Gross Necropsy Findings

### Appendices:

- Individual F0 Survival and Incidence of Clinical Signs
- Individual F0 Body Weights and Body Weight Changes
- Individual F0 Food and Water Consumption (g/animal/day)



- Individual F0 Gestation and Lactation Body Weights and Body Weight Changes
- Individual F0 Gestation Food and Water Consumption (g/animal/day)
- Individual F0 Lactation Food and Water Consumption (g/animal/day)
- Individual F0 Fertility Indices and Gestation Lengths.
- Individual F1 Litter Data (Survival)
- Individual F1 Litter Weights
- Individual F0 Gross Necropsy Findings
- Individual F0 Implantation Data and Post-Implantation Loss
- Individual Selected F1 Gross Necropsy Findings
- Protocol and any Amendments
- Historical Control Data (if applicable)
- SLI Personnel Responsibilities

## IX. STATISTICAL ANALYSIS

Statistical analyses will be performed using a Digital MicroVax 3100 computer. The level of significance will be a minimum of 5% ( $p < 0.05$ ) and all tests will be two-tailed. The summary tables will indicate the level of significance detected. The sample size, mean and standard deviation will be presented. The control group data will be compared to the treated data using all groups or by an individual group by group comparison depending on the test. Data including body weights, body weight gains, food consumption, gestation length, pup body weights and mean live litter size will be analyzed by one way analysis of variance. If significance is detected, control to treatment group comparison will proceed with Dunnett's test. Count data will be tested using Chi-Square for copulation and fertility indices, pup sex ratios, the number of live and dead pups per group (on lactation day 0), and pup survival (after lactation day 0).

## X. MAINTENANCE OF RAW DATA, RECORDS AND SPECIMENS

All original data, specimens and reports from this study are the property of the Sponsor. These materials shall be available at SLI to facilitate auditing of the study during its progress and prior to acceptance of the final report. Following study completion, all original paper data, magnetically encoded records, tissues, tissue blocks, slides and the final report will be transferred to the SLI archives and stored for a minimum of 10 years. The Sponsor will be contacted prior to the final disposition of these materials. Records to be maintained shall include the following, as applicable:

- Protocol and any amendments
- Animal receipt, acclimation, randomization and final disposition
- In-life records such as mortality/general health checks, animal husbandry, clinical observations, body weights, and other relevant in-life data
- Computer records such as computer protocols, operator lists, edits and edit checks
- Necropsy, histology and pathology records
- Clinical pathology records and QC results
- Pharmacy records including test article receipt, inventory, preparation, dispensation and disposition
- Analytical analyses related to the test article
- Water and feed analyses/certifications
- Specimen retention and inventory records
- All correspondence related to the study
- QA inspections and related reports

#### XI. REGULATORY COMPLIANCE

The study will be conducted in accordance with the Principles of Good Laboratory Practice set forth by the OECD [C(97)186/FINAL].

#### XII. QUALITY ASSURANCE

At least one critical phase of this study will be inspected by Springborn Laboratories, Inc., Quality Assurance Unit while in progress to assure compliance with Good Laboratory Practices, SLI's Standard Operating Procedures and for conformance with the protocol and protocol amendments. The final report will be audited prior to submission to the Sponsor to ensure that it completely and accurately describes the test procedures and results of the study.

#### XIII. ANIMAL WELFARE COMPLIANCE STATEMENT

In order to ensure the welfare of the animals used on this project, this study will comply with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). All procedures conducted on the

animals have been approved by the Springborn Laboratories, Inc. Institutional Animal Care and Use Committee (SLI IACUC) and are described in the study protocol and/or the standard operating procedures of this institution. These procedures are based on the most currently available regulatory accepted technologies. The SLI IACUC has approved the use of a maximum of 250 F0 animals on this study.

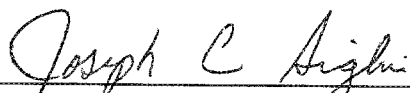
In order to reduce the possibility of animals being exposed to overt pain/distress, the animals used on this study will be observed daily by the technical staff and monitored as necessary by the Study Director or Facility Veterinarian. If an animal is determined to be in overt pain/distress, the animal will be euthanized for humane reasons in accordance with the Report of the AVMA on Euthanasia [3]. In addition, if an animal appears moribund and is beyond the point where recovery appears reasonable, the animal will be euthanized for humane reasons. Anesthetics/analgesics will not be used on this study since such treatment could interfere with the study and confound the results.

#### XIV. DECLARATION OF INTENT

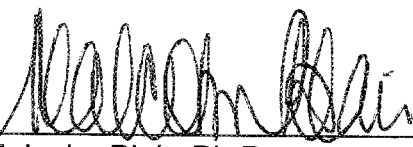
This study will be listed on the SLI Quality Assurance Master Schedule for the OECD.

XV. PROTOCOL APPROVAL

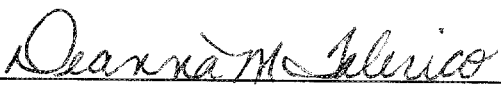
The Sponsor's signature below documents that there are no acceptable non-animal alternatives for this study, and that since this study is required by the relevant supervising government agency, it does not unnecessarily duplicate any previous experiments.

  
\_\_\_\_\_  
Joseph C. Siglin, Ph.D., DABT  
Study Director (SLI)

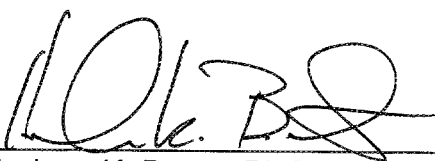
Date: 7/9/98

  
\_\_\_\_\_  
Malcolm Blair, Ph.D.  
Vice President and Managing Director (SLI)

Date: 7/9/98

  
\_\_\_\_\_  
Deanna M. Merico  
Quality Assurance Unit (SLI)

Date: 7-9-98

  
\_\_\_\_\_  
Hudson K. Bates, Ph.D., DABT  
Sponsor's Representative  
(Principal Investigator)

Date: 7/10/98

XVI. REFERENCES

1. Guide for the Care and Use of Laboratory Animals, DHHS Publication No. (NIH) 96-03, 1996.
2. Salewski, V.E. Färbemethode zum makroskopischen Nachweis von Implantations-stellen am Uterus der Ratte, Naunyn-Schm. Archiv. Für Exper. Pathologie und Pharm., 247:367, 1964.
3. 1993 Report of the American Veterinary Medical Assoc. Panel on Euthanasia, JAVMA, Vol. 202, No. 2, pp. 229-249, January 15, 1993.

## ATTACHMENT 1

## A Preliminary Probe Study in Rats

A preliminary probe study will be performed to assist in dosage level selection for the one-generation reproduction range-finding study. Receipt, animal husbandry and acclimation will be as described in the main study protocol, with the following additional procedures specified below.

## A. Acclimation and Randomization

Animals designated for possible assignment to the probe study will be acclimated for a minimum of 5 days. On study day -1, rats will be weighed and examined in detail for signs of physical disorder (detailed clinical observations). Animals determined to be suitable as test subjects will be assigned randomly to groups in stratified block design based on body weights. Disposition of animals not selected for study will be documented in the study records.

## B. Study Group Design

The experimental design for the probe study is as follows:

Group	No. of Animals		Dosage Material	Dosage Level (mg/kg/day)	Dosage Conc. (mg/mL)	Dosage Volume (mL/kg)
	Male	Female				
1	2	2	Vehicle <sup>a</sup>	0	0	10
2	2	2	NSH <sup>b</sup>	5.0	0.5	10
3	2	2	NSH	15.0	1.5	10
4	2	2	NSH	25.0	2.5	10
5	2	2	NSH	50.0	5.0	10
6	2	2	NSH	75.0	7.5	10
7	2	2	NSH	150.0	15.0	10

<sup>a</sup>RO-Di water.  
<sup>b</sup>NSH = Nickel sulfate hexahydrate (in aqueous solution).

### C. Treatment

Oral (gavage) administration. The test article and vehicle will be administered once daily, by oral gavage, for 14 consecutive days. Control animals will receive the vehicle at a dosage volume comparable to that received by the test animals. The gavage needle will be wiped with gauze just prior to each dose administration. All attempts will be made to complete dosing by 10:00 a.m. on each day. Individual doses will be based on the most recent body weight. If severe toxicity develops, dosing may be discontinued and the affected group(s) may be euthanized and necropsied as described below.

### D. Clinical Signs

The animals will be checked for general health/mortality and moribundity twice daily, in the morning and afternoon. The rats will be examined daily for clinical signs of toxicity (cage-side observations) between one-half and two hours after dosing.

### E. Body Weights

Each animal will be weighed prior to the initiation of treatment on day -1. During the study period, the individual body weights will be recorded on days 1, 8 and 15.

### F. Unscheduled Deaths and Scheduled Euthanasia

Any animals showing signs of severe debility or toxicity, particularly if death appears imminent, will be euthanized moribund (carbon dioxide inhalation). Any animal found dead after routine working hours will be refrigerated until the next scheduled work day. All surviving animals will be euthanized on study day 15 (carbon dioxide inhalation).

All animals will be subjected to an abbreviated gross necropsy examination at the time of death or scheduled euthanasia. The necropsy examination will include examination of the external surfaces of the body and major tissues and organs in the thoracic, abdominal and pelvic cavities. No tissues will be retained.

G. Data Reporting

Results of this preliminary study will be reported in a separate appendix within the one-generation study report. This information will be provided to the Sponsor for selection of dosage levels for the one-generation study. No inferential statistical analyses will be performed on the probe data.



A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE

PROTOCOL AMENDMENT NO. 1

1) PART TO BE CHANGED/REVISED (Effective July 7, 1998):

V.C.5. Number of Animals/Sex on Study

CHANGE/REVISION:

Delete the following sentence: "Males and females will have different birth dates to avoid potential sibling pairings."

REASON FOR CHANGE/REVISION:

Sibling matings will be avoided by obtaining males and females from different production rooms within the supplier's facility, not by different birth dates.

2) PART TO BE CHANGED/REVISED (Effective July 31, 1998):

VI.A. Study Group Design

CHANGE/REVISION:

Dose levels, concentrations and volume for the study will be as follows:

Group	No. of Parental Animals		Dosage Material <sup>a</sup>	Dosage Level (mg/kg/day) <sup>b</sup>	Dosage Conc. (mg/mL)	Dosage Volume (mL/kg)
	Male	Female				
1	8	8	Vehicle	0	0	10
2	8	8	NSH	10	1.0	10
3	8	8	NSH	20	2.0	10
4	8	8	NSH	30	3.0	10
5	8	8	NSH	50	5.0	10
6	8	8	NSH	75	7.5	10

<sup>a</sup>Vehicle = RO-Di water; NSH = Nickel sulfate hexahydrate (in aqueous solution).

<sup>b</sup>Dosage levels for the range-finding study will be selected based upon results of a preliminary probe study (see Attachment 1).

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE

PROTOCOL AMENDMENT NO. 1

REASON FOR CHANGE/REVISION:

To reflect dose levels selected by the Sponsor, and related concentrations and volume information.

3) PART TO BE CHANGED/REVISED (Effective August 17, 1998):

VI.C.3.b. Body Weights--F0 Animals

CHANGE/REVISION:

Change gestation day 21 to gestation day 20.

REASON FOR CHANGE/REVISION:

To avoid missing any late gestation body weights due to delivery.

4) PART TO BE CHANGED/REVISED:

VI.C.5.b. Food and Water Consumption--F0 Animals (Effective August 17, 1998):

CHANGE/REVISION:

Change reference from gestation day 21 to gestation day 20.

REASON FOR CHANGE/REVISION:

To parallel body weight days.

5) PART TO BE CHANGED/REVISED:

VI.F.1. Method of Individual Pup Identification (Effective July 7, 1998):

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE

PROTOCOL AMENDMENT NO. 1

CHANGE/REVISION:

Replace this section with the following:

On lactation day 0 each pup will be individually identified by tail tattooing.

REASON FOR CHANGE/REVISION:

Because dead pups are assigned numbers first, consecutive numbering does not always begin with the male offspring.




Joseph C. Siglin, Ph.D., DABT  
Study Director (SLI)

Date: 8/20/98



Deanna M. Salerio  
Quality Assurance Unit (SLI)

Date: 8-20-98



Hudson K. Bates, Ph.D., DABT  
Sponsor's Representative  
(Principal Investigator)

Date: 8-28-98

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE

PROTOCOL AMENDMENT NO. 2

1) PART TO BE CHANGED/REVISED (Effective July 14, 1998):

IV.E. Method and Frequency of Test Article Preparations

CHANGE/REVISION:

Delete the second paragraph from this section and replace it with the following:

Homogeneity of the test article in the vehicle will be evaluated by analyzing duplicate 10 mL samples taken from the top, middle, and bottom of two concentrations: 0.1 mg/mL and 7.5 mg/mL. These concentrations are expected to encompass the high and low concentrations for the range-finding study. Stability of the test article in the vehicle will be assessed by analyzing duplicate 10 mL samples taken from the middle of each concentration (0.1 and 7.5 mg/mL) following 24 hours of room temperature storage, and following 7, 14 and 21 days of refrigerated storage.

At the first preparation of dosing solutions for the range-finding study, duplicate 10 mL samples will be taken from each gavage solution, including the vehicle, and submitted for analytical analysis.

The analytical samples will be packed in ice and shipped by overnight courier to Lancaster Laboratories for analysis by Atomic Absorption. The stability samples will be sent in separate shipments, at the time points indicated above. The samples will be shipped to the following address:

Lancaster Laboratories  
2425 New Holland Pike  
P.O. Box 12425  
Lancaster, PA 17605-2425  
Attention: Sample Administration

REASON FOR CHANGE/REVISION:

Analytical chemistry analyses were added to the protocol to verify homogeneity, stability and concentration of the test article in the vehicle.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE

PROTOCOL AMENDMENT NO. 2

2) PART TO BE CHANGED/REVISED (Effective July 7, 1998):


V.C.2. Strain

CHANGE/REVISION:

Change the rat strain designation from CrI:CD®BR VAF/Plus® to  
CrI:CD®(SD)IGS BR

REASON FOR CHANGE/REVISION:

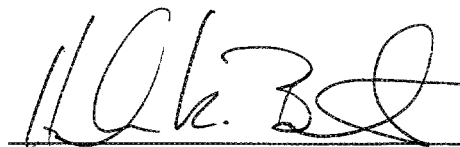
This is the supplier's new strain designation for Sprague-Dawley rats  
derived from their "International Genetic Standard" stock.

  
\_\_\_\_\_  
Joseph C. Siglin, Ph.D., DABT  
Study Director (SLI)

Date: 8/26/98

  
\_\_\_\_\_  
Deanna M. Salerico  
Quality Assurance Unit (SLI)

Date: 8-26-98

  
\_\_\_\_\_  
Hudson K. Bates, Ph.D., DABT  
Sponsor's Representative  
(Principal Investigator)

Date: 8-28-98

**A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE**

**PROTOCOL AMENDMENT NO. 3**

- 1) PART TO BE CHANGED/REVISED (Effective March 25, 1999):

III. PROPOSED STUDY SCHEDULE

CHANGE/REVISION:

Replace this section with the following:

- A. Initiation of In-Life Phase: July 14, 1998
- B. Completion of In-Life Phase: October 30, 1998
- C. Audited Draft Report Date: March 25, 1999

REASON FOR CHANGE/REVISION:

To include the study dates.

- 2) PART TO BE CHANGED/REVISED (Effective October 23, 1998):

VI.B. Treatment

CHANGE/REVISION:

Replace the sixth sentence in this section with the following:

Study animals will receive continuous exposure to the control or test article throughout the study, at the appropriate levels, until the day prior to or the day of scheduled euthanasia.

REASON FOR CHANGE/REVISION:

Surviving selected F1 pups will be euthanized and necropsied on the day after each pup receives its 21<sup>st</sup> dose. The necropsies will begin on October 23, 1998. Animals to be necropsied on this day will have received 22 doses since they were dosed on October 23, 1998. All other animals will not be dosed on the day of scheduled euthanasia.

**A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE**

**PROTOCOL AMENDMENT NO. 3**

3) PART TO BE CHANGED/REVISED (Effective September 11, 1998):

Protocol Amendment No. 1, Part 5

CHANGE/REVISION:

Replace the first sentence in this section with the following:

On lactation day 0, each viable pup will be identified by tail tattooing and nonviable pups will be identified by indelible ink.

REASON FOR CHANGE/REVISION:

Live pups and dead pups will be identified differently.

4) PART TO BE CHANGED/REVISED (Effective September 22, 1998):

VI.I.1. Unscheduled Deaths--F0 and Selected Animals

CHANGE/REVISION:

Add the following paragraph to this section:

The litter for F0 group 3 female #177 (found dead on September 22, 1998) will be euthanized by carbon dioxide inhalation and discarded without necropsy. No tissues will be retained.

REASON FOR CHANGE/REVISION:

Additional information was provided.

**A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY  
IN RATS WITH NICKEL SULFATE HEXAHYDRATE**

**PROTOCOL AMENDMENT NO. 3**

5) PART TO BE CHANGED/REVISED (Effective July 9, 1998):

IX. STATISTICAL ANALYSIS

CHANGE/REVISION:

Replace the sixth sentence and add the following sentence:

Data including body weights, body weight gains, food consumption, water consumption, gestation length, pup body weights and mean live litter size will be analyzed by one way analysis of variance.

The Mann-Whitney U test will be used to compare post-implantation loss.

REASON FOR CHANGE/REVISION:

The statistical method for water consumption and post-implantation loss was omitted from the original protocol.



Joseph C. Siglin, Ph.D., DABT  
Study Director (SLI)

Date 3-25-99



Quality Assurance Unit (SLI)

Date 3-25-99



Hudson K. Bates, Ph.D., DABT  
Sponsor's Representative  
(Principal Investigator)

Date 12-18-00



SLI Study No. 3472.3

The following protocol deviations and occurrences were noted during the conduct of the study. None of the noted deviations or occurrences impacted the validity or integrity of the study.

1. Acclimation observations were not performed on one occasion due to a power outage.
2. On two days during the preliminary probe study, the animal room temperature was outside the specified range of 65 to 79°F. The actual animal room temperature ranged from 63 to 70°F. On two days during the preliminary probe study, the animal room relative humidity was outside the specified range of 30 to 70%. The actual animal room relative humidity was recorded as 36 to 102% (102% on two occasions). On eight days during the range-finding study, the animal room relative humidity was outside the specified range of 30 to 70%. The actual animal room relative humidity ranged from 17 to 63%.
3. It was not documented that the gavage needle was wiped with gauze just prior to each dose administration for the preliminary probe study and the range-finding study.
4. On study day 9 of the preliminary probe study, group 2 female #178 was found to have delivered pups in its cage. This animal was euthanized and necropsied. The surviving offspring were euthanized and discarded. The animal supplier was notified of this occurrence, since these animals were supposed to be nulliparous and nonpregnant.
5. On two days during the range-finding study, three mortality checks, rather than two, were performed.
6. It was not documented on gestation day 13 of the range-finding study that F0 group 3 female #242 was dosed.
7. The start day of parturition was recorded as lactation day 0, rather than the completion day of parturition, for F0 group 6 females #244 and #245 in the range-finding study. Parturition for these females was initiated on one day and completed on the following day. Pups that died on either day were recorded as dead on lactation day 0.
8. On lactation day 6 of the range-finding study, F0 group 5 female #194 was dosed 2.2 mL more than the intended dose.

SLI Study No. 3472.3

9. On study day 17 of the range-finding study, group 4 (30 mg/kg/day) F1 animals were dosed with a dosing solution from another study. However, the animals did not exhibit any adverse clinical signs following dosing. The Sponsor was informed of this error when it was discovered. Dosing of the correct dosing solution was resumed the following day.
10. Positive evidence of copulation was not observed for F0 group 5 female #227 after 14 days of mating. The female was separated from the male, however, the female was not placed in a plastic cage containing nesting material. This female was later found to be nonpregnant.
11. The method of euthanasia was not recorded for group 2 female #178 in the preliminary probe study; F0 group 1 female #219, F0 group 4 female #222 and F0 group 5 female #227 in the range-finding study; and the F1 selected pups in the range-finding study.

SLI Study No. 3472.3

APPENDIX C

Certificate of Analysis (as Provided by Aldrich Chemical  
Company) and Analytical Chemistry Results  
(as Provided by Lancaster Laboratories)

# CERTIFICATE OF ANALYSIS

Page 1 of 2

SPRINGBORN LABORATORIES  
419 647 4438  
PENNY KAPUT

PO NBR:

PRODUCT NUMBER: 22767-6

LOT NUMBER: 08516TQ

PRODUCT NAME: NICKEL(II) SULFATE HEXAHYDRATE, 99%,  
A.C.S. REAGENT

FORMULA:  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$ 

FORMULA WEIGHT: 262.84

APPEARANCE

BLUE-GREEN CRYSTALS

TITRATION

98.5% (COMPLEXOMETRIC)

ICP ASSAY

CONFIRMS NICKEL AND SULFUR COMPONENTS.

SUITABLE IDENTIFICATION IN LIEU OF XRAY.

INSOLUBLE MATTER

&lt;0.001% \*

SOLUBILITY

1 GM IN 7.5ML H<sub>2</sub>O; CLEAR, GREEN SOLUTION.

ACS TESTS

&lt;0.001% CO \*

CALCIUM

&lt;0.0001% \*

CHLORIDE

&lt;0.001% \*

COPPER

&lt;0.0001% \*

IRON

0.0006% \*

POTASSIUM

&lt;0.001% \*

MAGNESIUM

&lt;0.0001% \*

MANGANESE

&lt;0.0001% \*

CONTINUED ON NEXT PAGE

ALDRICH CHEMICAL COMPANY  
DAVID SWESSEL  
JULY 10, 1998



chemists helping chemists in research &amp; industry

## aldrich chemical co.

P.O. Box 365, Milwaukee, Wisconsin 53201 USA • (414) 273-3850 • FAX (414) 273-4879

ALDRICH warrants that its products conform to the information contained in this and other Aldrich publications. Purchaser must determine the suitability of the product for its particular use. See reverse side of invoice or packing slip for additional terms and conditions of sale.

(141)

SLI Study No. 3472.3

# CERTIFICATE OF ANALYSIS

Page 2 of 2

SPRINGBORN LABORATORIES  
419 647 4438  
PENNY KAPUT

PO NBR:

PRODUCT NUMBER: 22767-6

LOT NUMBER: 08516TQ

PRODUCT NAME: NICKEL(II) SULFATE HEXAHYDRATE, 99%,  
A.C.S. REAGENT

FORMULA:  $\text{NiSO}_4 \cdot 6\text{H}_2\text{O}$

FORMULA WEIGHT: 262.84

CONTINUED FROM PREVIOUS PAGE

SODIUM

<0.001% \*

NITROGEN COMPOUNDS

<0.001% \*

\* SUPPLIER CERTIFICATE

ALDRICH CHEMICAL COMPANY  
DAVID SWESSEL  
JULY 10, 1998



chemists helping chemists in research & industry  
**aldrich chemical co.**

P.O. Box 355, Milwaukee, Wisconsin 53201 USA • (414) 273-3860 • FAX (414) 273-4979

ALDRICH warrants that its products conform to the information contained in this and other Aldrich publications. Purchaser must determine the suitability of the product for its particular use. See reverse side of invoice or packing slip for additional terms and conditions of sale.



### Quality Assurance Statement

Springborn Study Number: 3472.3

This study was inspected by the Lancaster Laboratories' Quality Assurance Unit on July 30 and August 27, 1998. The inspection reports were circulated to Lancaster Laboratories' management on September 8, 1998. The inspection reports were sent to the study director and study director management on September 9, 1998.

The analysis reports and raw data for Springborn Study Number 3472.3(Lancaster Laboratories' sample numbers: 2965531-5542, 2967458-461, 2969792-795, 2974207-210, 2978139-142, and 2986512-523) were compared and audited for accuracy by the Lancaster Laboratories' Quality Assurance Unit.

Jill E. Angie, M.S.  
Quality Assurance Senior Specialist

11/16/98  
Date



**Springborn Laboratories**

**Nickel Sulfate Hexahydrate  
Homogeneity Study**

Designation	LL Sample Number	Concentration Nickel Sulfate Hexahydrate (mg/mL)	Statistics Summary
0.1 mg/mL Bottom	2965535	0.108	Average mg/mL = 0.108 RSD = 0.66%
0.1 mg/mL Bottom Duplicate	2965536	0.107	
0.1 mg/mL Middle	2965533	0.108	Average mg/mL = 0.108 RSD = 0.00%
0.1 mg/mL Middle Duplicate	2965534	0.108	
0.1 mg/mL Top	2965531	0.109	Average mg/mL = 0.108 RSD = 1.31%
0.1 mg/mL Top Duplicate	2965532	0.107	

Overall Average mg/mL = 0.108  
RSD = 0.70%

Designation	LL Sample Number	Concentration Nickel Sulfate Hexahydrate (mg/mL)	Statistics Summary
7.5 mg/mL Bottom	2965541	7.614	Average mg/mL = 7.588 RSD = 0.49%
7.5 mg/mL Bottom Duplicate	2965542	7.561	
7.5 mg/mL Middle	2965539	7.561	Average mg/mL = 7.509 RSD = 0.99%
7.5 mg/mL Middle Duplicate	2965540	7.456	
7.5 mg/mL Top	2965537	7.561	Average mg/mL = 7.482 RSD = 1.49%
7.5 mg/mL Top Duplicate	2965538	7.403	

Overall Average mg/mL = 7.526  
RSD = 1.05%

Lancaster Labs sample numbers:

2974207-10

RESULTS ARE IN DATA PACKAGE NSH 02

2978139-42

RESULTS ARE IN DATA PACKAGE NSH 03

2969792-95

RESULTS ARE IN DATA PACKAGE NSH 02

*Handwritten initials/signature*

*Handwritten signature*

811

*Handwritten signature*

8-27-98

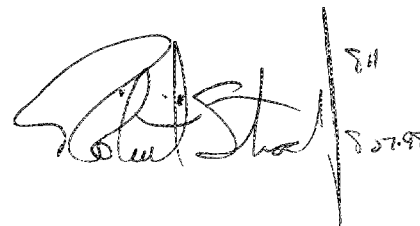
**Springborn Laboratories****Nickel Sulfate Hexahydrate  
Stability Study**

Designation	LL Sample Number	Concentration Nickel Sulfate Hexahydrate (mg/mL)	Statistics Summary
0.1 mg/mL 24 Hour RT	2967458	0.108	Average mg/mL = 0.108
0.1 mg/mL 24 Hour RT Duplic	2967459	0.107	RSD = 0.66%
0.1 mg/mL Day 7	2969792	0.107	Average mg/mL = 0.108
0.1 mg/mL Day 7 Duplicate	2969793	0.109	RSD = 1.31%
0.1 mg/mL Day 14	2974207	0.105	Average mg/mL = 0.103
0.1 mg/mL Day 14 Duplicate	2974208	0.101	RSD = 2.75%
0.1 mg/mL Day 21	2978139	0.105	Average mg/mL = 0.104
0.1 mg/mL Day 21 Duplicate	2978140	0.103	RSD = 1.36%

Overall Average mg/mL = 0.106  
RSD = 2.53%

Designation	LL Sample Number	Concentration Nickel Sulfate Hexahydrate (mg/mL)	Statistics Summary
7.5 mg/mL 24 Hour RT	2967460	7.403	Average mg/mL = 7.456
7.5 mg/mL 24 Hour RT Duplic	2967461	7.509	RSD = 1.01%
7.5 mg/mL Day 7	2969794	7.403	Average mg/mL = 7.245
7.5 mg/mL Day 7 Duplicate	2969795	7.086	RSD = 3.09%
7.5 mg/mL Day 14	2974209	7.661	Average mg/mL = 7.552
7.5 mg/mL Day 14 Duplicate	2974210	7.443	RSD = 2.04%
7.5 mg/mL Day 21	2978141	7.661	Average mg/mL = 7.661
7.5 mg/mL Day 21 Duplicate	2978142	7.661	RSD = 0.00%

Overall Average mg/mL = 7.478  
RSD = 2.61%

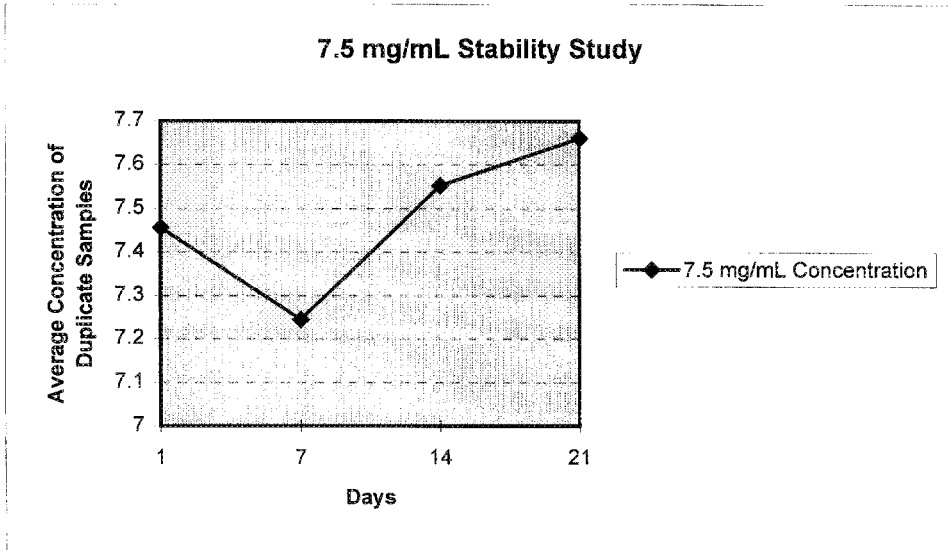
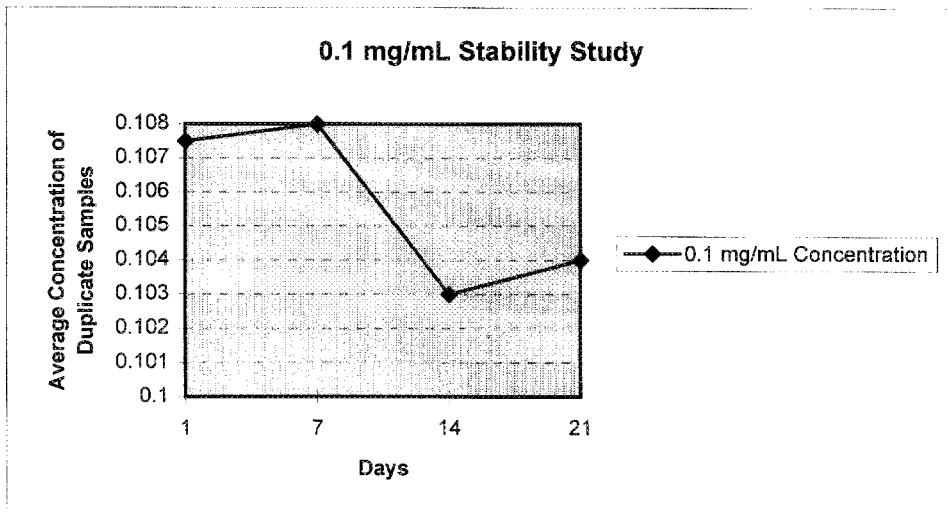


Handwritten signature and date: 8/27/98



**Springborn Laboratories**

**Nickel Sulfate Hexahydrate  
Stability Study**



**Springborn Laboratories****Nickel Sulfate Hexahydrate  
Concentration Verification - RF Study**

<b>Designation</b>	<b>LL Sample Number</b>	<b>Concentration Nickel Sulfate Hexahydrate (mg/mL)</b>	<b>Statistics Summary</b>
0 mg/mL 0 mg/mL Duplicate	2986512 2986513	0.000 0.000	Average mg/mL = 0.000 RSD = 0.00% Recovery = N/A
1.0 mg/mL 1.0 mg/mL Duplicate	2986514 2986515	1.053 1.064	Average mg/mL = 1.059 RSD = 0.73% Recovery = 105.9%
2.0 mg/mL 2.0 mg/mL Duplicate	2986516 2986517	2.058 2.129	Average mg/mL = 2.094 RSD = 2.40% Recovery = 104.7%
3.0 mg/mL 3.0 mg/mL Duplicate	2986518 2986519	3.118 3.136	Average mg/mL = 3.127 RSD = 0.41% Recovery = 104.2%
5.0 mg/mL 5.0 mg/mL Duplicate	2986520 2986521	5.31 5.298	Average mg/mL = 5.304 RSD = 0.16% Recovery = 106.1%
7.5 mg/mL 7.5 mg/mL Duplicate	2986522 2986523	8.013 8.013	Average mg/mL = 8.013 RSD = 0.00% Recovery = 106.8%

*Robert A. Stead* 8-31-98

SLI Study No. 3472.3

APPENDIX D

Individual F0 Survival and Clinical Observations  
(Positive Findings)

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
16996	M 0 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
16997	M 0 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 29	P DARK MATERIAL AROUND NOSE
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17010	M 0 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17018	M 0 MG/KG/DAY	BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	STUDY DAY 29	1 HAIRLOSS
		BODY	STUDY DAY 49	1 HAIRLOSS
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17032	M 0 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 22	P DARK MATERIAL AROUND NOSE
		NOSE/MOUTH	STUDY DAY 29	P INCISOR(S) - BROKEN
		NOSE/MOUTH	STUDY DAY 49	P INCISOR(S) - BROKEN
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
		NOSE/MOUTH	STUDY DAY 8	P MALALIGNMENT
		NOSE/MOUTH	STUDY DAY 8	P SCAB(S) - AROUND MOUTH
		EYES	STUDY DAY 8	P DARK MATERIAL AROUND EYE(S)
		NOSE/MOUTH	STUDY DAY 15	P MALALIGNMENT
		NOSE/MOUTH	STUDY DAY 15	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	STUDY DAY 15	P INCISOR(S) TRIMMED
		NOSE/MOUTH	STUDY DAY 22	P MALALIGNMENT
		NOSE/MOUTH	STUDY DAY 29	P MALALIGNMENT
		EYES	STUDY DAY 29	P INCISOR(S) TRIMMED
		NOSE/MOUTH	STUDY DAY 30	P DARK MATERIAL AROUND EYE(S)
		NOSE/MOUTH	STUDY DAY 31	P DARK MATERIAL AROUND NOSE
		ACTIVITY	STUDY DAY 31	P REDDISH NASAL DISCHARGE
		ACTIVITY	STUDY DAY 31	P LABORED BREATHING
		EYES	STUDY DAY 31	P SALIVATION
		EYES	STUDY DAY 31	P DARK MATERIAL AROUND EYE(S)

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
17035	M 0 MG/KG/DAY	EXCRETA/EMESIS	STUDY DAY 31	P FEW FECES
		BODY	STUDY DAY 31	P SWELLING - RIGHT LATERAL THORACIC
		DEAD	STUDY DAY 31	P UNSCHEDULED EUTHANASIA - MORIBUND
17036	M 0 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17009	M 10 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 8	P DARK MATERIAL AROUND NOSE
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17011	M 10 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 29	P DARK MATERIAL AROUND NOSE
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17015	M 10 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 15	P DARK MATERIAL AROUND NOSE
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17017	M 10 MG/KG/DAY	BODY	STUDY DAY 1	1 HAIRLOSS
		BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 29	1 HAIRLOSS
		BODY	STUDY DAY 36	P SCAB(S) - RIGHT FORELIMB
		BODY	STUDY DAY 36	P SCAB(S) - LEFT FORELIMB
		BODY	STUDY DAY 43	1 HAIRLOSS
		BODY	STUDY DAY 49	1 HAIRLOSS
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17020	M 10 MG/KG/DAY	BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	STUDY DAY 22	1 HAIRLOSS
		BODY	STUDY DAY 29	1 HAIRLOSS
		BODY	STUDY DAY 36	1 HAIRLOSS
		BODY	STUDY DAY 43	1 HAIRLOSS
		BODY	STUDY DAY 49	1 HAIRLOSS
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17044	M 10 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17046	M 10 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17048	M 10 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
16990	M 20 MG/KG/DAY	BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	STUDY DAY 22	1 HAIRLOSS
16999	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
		BODY	STUDY DAY 22	P SCAB(S) - LEFT PINNA
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17002	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17008	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17039	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17040	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17042	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17045	M 20 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17001	M 30 MG/KG/DAY	BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 8	P SCAB(S) - RIGHT FORELIMB
		BODY	STUDY DAY 15	1 HAIRLOSS
		NOSE/MOUTH	STUDY DAY 29	P DARK MATERIAL AROUND NOSE
		BODY	STUDY DAY 49	1 HAIRLOSS
17005	M 30 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17007	M 30 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17012	M 30 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17013	M 30 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 22	P DARK MATERIAL AROUND NOSE
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17023	M 30 MG/KG/DAY	BODY	STUDY DAY 22	P ENLARGEMENT - TAIL
		BODY	STUDY DAY 29	P ENLARGEMENT - TAIL
		BODY	STUDY DAY 36	P ENLARGEMENT - TAIL
		NOSE/MOUTH	STUDY DAY 36	P DARK MATERIAL AROUND NOSE
		BODY	STUDY DAY 49	P ENLARGEMENT - TAIL
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA

GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- SEVERE, P- PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
17041	M 30 MG/KG/DAY	BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	STUDY DAY 22	1 HAIRLOSS
		BODY	STUDY DAY 29	1 HAIRLOSS
17049	M 30 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17004	M 50 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17024	M 50 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17026	M 50 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17028	M 50 MG/KG/DAY	NOSE/MOUTH	STUDY DAY 15	P INCISOR(S) - BROKEN
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17029	M 50 MG/KG/DAY	BODY	STUDY DAY 43	P SWELLING - LEFT HINDLIMB DIGIT(S)
		BODY	STUDY DAY 43	P PURPLE DISCOLORATION - LEFT HINDLIMB DIGIT(S)
		BODY	STUDY DAY 49	P PURPLE DISCOLORATION - LEFT HINDLIMB DIGIT(S)
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17034	M 50 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17043	M 50 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17047	M 50 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17000	M 75 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17014	M 75 MG/KG/DAY	BODY	STUDY DAY 15	1 FECAL STAIN
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17016	M 75 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17019	M 75 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17021	M 75 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17022	M 75 MG/KG/DAY	POST-DOSE OBS	STUDY DAY 2	P ACTIVITY DECREASED
		POST-DOSE OBS	STUDY DAY 3	P SALIVATION
		BODY	STUDY DAY 36	1 URINE STAIN
17025	M 75 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
17027	M 75 MG/KG/DAY	DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA
		DEAD	STUDY DAY 49	P SCHEDULED EUTHANASIA

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
192	F 0 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
196	F 0 MG/KG/DAY	BODY	STUDY DAY 21	2 URINE STAIN
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS
		BODY	LACTATION DAY 9	1 HAIRLOSS
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
206	F 0 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
219	F 0 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
221	F 0 MG/KG/DAY	BODY	LACTATION DAY 1	P REDDISH VAGINAL DISCHARGE
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
231	F 0 MG/KG/DAY	BODY	GESTATION DAY 11	1 HAIRLOSS
		BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS
		NOSE/MOUTH	GESTATION DAY 14	P DARK MATERIAL AROUND NOSE
		BODY	GESTATION DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

PAGE 6

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
231	F 0 MG/KG/DAY	BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 4	1 HAIRLOSS
		BODY	LACTATION DAY 5	1 HAIRLOSS
		BODY	LACTATION DAY 6	1 HAIRLOSS
		BODY	LACTATION DAY 7	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS
		BODY	LACTATION DAY 9	1 HAIRLOSS
		BODY	LACTATION DAY 10	1 HAIRLOSS
		BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
		BODY	LACTATION DAY 15	1 HAIRLOSS
		BODY	LACTATION DAY 16	1 HAIRLOSS
		BODY	LACTATION DAY 17	P SCAB(S) - RIGHT FORELIMB
		BODY	LACTATION DAY 17	P SCAB(S) - LEFT FORELIMB
		BODY	LACTATION DAY 17	1 HAIRLOSS
		BODY	LACTATION DAY 18	1 HAIRLOSS
		BODY	LACTATION DAY 18	P SCAB(S) - RIGHT FORELIMB
		BODY	LACTATION DAY 18	P SCAB(S) - LEFT FORELIMB
		233	F 0 MG/KG/DAY	BODY
BODY	LACTATION DAY 19			P SCAB(S) - RIGHT FORELIMB
BODY	LACTATION DAY 20			P SCAB(S) - RIGHT FORELIMB
BODY	LACTATION DAY 20			1 HAIRLOSS
DEAD	LACTATION DAY 21			P SCHEDULED EUTHANASIA
BODY	STUDY DAY 8			1 HAIRLOSS
BODY	STUDY DAY 15			1 HAIRLOSS
BODY	GESTATION DAY 0			1 HAIRLOSS
BODY	GESTATION DAY 1			1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX D  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
233	F 0 MG/KG/DAY	BODY	GESTATION DAY 2	1 HAIRLOSS
		BODY	GESTATION DAY 3	1 HAIRLOSS
		BODY	GESTATION DAY 4	1 HAIRLOSS
		BODY	GESTATION DAY 5	1 HAIRLOSS
		BODY	GESTATION DAY 6	1 HAIRLOSS
		BODY	GESTATION DAY 7	1 HAIRLOSS
		BODY	GESTATION DAY 8	1 HAIRLOSS
		BODY	GESTATION DAY 9	1 HAIRLOSS
		BODY	GESTATION DAY 10	1 HAIRLOSS
		BODY	GESTATION DAY 11	1 HAIRLOSS
		BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS
		BODY	GESTATION DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 4	1 HAIRLOSS
		BODY	LACTATION DAY 5	1 HAIRLOSS
		BODY	LACTATION DAY 6	1 HAIRLOSS
		BODY	LACTATION DAY 7	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX D  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
233	F 0 MG/KG/DAY	BODY	LACTATION DAY 9	1 HAIRLOSS
		BODY	LACTATION DAY 10	1 HAIRLOSS
		BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
		BODY	LACTATION DAY 15	1 HAIRLOSS
		BODY	LACTATION DAY 16	1 HAIRLOSS
		BODY	LACTATION DAY 17	1 HAIRLOSS
		BODY	LACTATION DAY 18	1 HAIRLOSS
		BODY	LACTATION DAY 19	1 HAIRLOSS
		BODY	LACTATION DAY 20	1 HAIRLOSS
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
237	F 0 MG/KG/DAY	BODY	STUDY DAY 16	1 URINE STAIN
		NOSE/MOUTH	GESTATION DAY 2	P DARK MATERIAL AROUND NOSE
		NOSE/MOUTH	GESTATION DAY 8	P DARK MATERIAL AROUND NOSE
		NOSE/MOUTH	GESTATION DAY 9	P DARK MATERIAL AROUND NOSE
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
188	F 10 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
195	F 10 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
224	F 10 MG/KG/DAY	NOSE/MOUTH	GESTATION DAY 2	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 3	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 4	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 5	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 6	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 6	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 6	P SWELLING - UPPER LIP
		NOSE/MOUTH	GESTATION DAY 7	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 7	P SCAB(S) - AROUND MOUTH

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

APPENDIX D

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
224	F 10 MG/KG/DAY	NOSE/MOUTH	GESTATION DAY 7	P SWELLING - UPPER LIP
		NOSE/MOUTH	GESTATION DAY 8	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 8	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 9	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 10	P INCISOR(S) - BROKEN
		NOSE/MOUTH	GESTATION DAY 11	P INCISOR(S) - BROKEN
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
		BODY	STUDY DAY 8	1 HAIRLOSS
229	F 10 MG/KG/DAY	DEAD	LACTATION DAY 0	P SCHEDULED EUTHANASTIA
234	F 10 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
236	F 10 MG/KG/DAY	BODY	LACTATION DAY 0	P REDDISH VAGINAL DISCHARGE
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
238	F 10 MG/KG/DAY	NOSE/MOUTH	GESTATION DAY 1	P DARK MATERIAL AROUND NOSE
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
243	F 10 MG/KG/DAY	BODY	STUDY DAY 1	1 HAIRLOSS
		BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 0	1 HAIRLOSS
		BODY	GESTATION DAY 1	1 HAIRLOSS
		BODY	GESTATION DAY 2	1 HAIRLOSS
		BODY	GESTATION DAY 3	1 HAIRLOSS
		BODY	GESTATION DAY 4	1 HAIRLOSS
		BODY	GESTATION DAY 5	1 HAIRLOSS
		BODY	GESTATION DAY 6	1 HAIRLOSS
		BODY	GESTATION DAY 7	1 HAIRLOSS
		BODY	GESTATION DAY 8	1 HAIRLOSS
		BODY	GESTATION DAY 9	1 HAIRLOSS
		BODY	GESTATION DAY 10	1 HAIRLOSS
		BODY	GESTATION DAY 11	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
243	F 10 MG/KG/DAY	BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS
		BODY	GESTATION DAY 15	1 HAIRLOSS
		NOSE/MOUTH	GESTATION DAY 15	P DARK MATERIAL AROUND NOSE
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 4	1 HAIRLOSS
		BODY	LACTATION DAY 5	1 HAIRLOSS
		BODY	LACTATION DAY 6	1 HAIRLOSS
		BODY	LACTATION DAY 7	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS
		BODY	LACTATION DAY 9	1 HAIRLOSS
		BODY	LACTATION DAY 10	1 HAIRLOSS
		BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
		BODY	LACTATION DAY 15	1 HAIRLOSS
		BODY	LACTATION DAY 16	1 HAIRLOSS
		BODY	LACTATION DAY 17	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
243 F	10 MG/KG/DAY	BODY	LACTATION DAY 18	1 HAIRLOSS
		BODY	LACTATION DAY 20	1 HAIRLOSS
		BODY	LACTATION DAY 21	1 HAIRLOSS
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		ACTIVITY	GESTATION DAY 6	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	GESTATION DAY 8	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	GESTATION DAY 9	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	GESTATION DAY 10	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	GESTATION DAY 11	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	GESTATION DAY 12	P INCREASED SENSITIVITY TO TOUCH
177 F	20 MG/KG/DAY	ACTIVITY	GESTATION DAY 13	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	LACTATION DAY 1	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	LACTATION DAY 2	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	LACTATION DAY 3	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	LACTATION DAY 4	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	LACTATION DAY 5	P INCREASED SENSITIVITY TO TOUCH
		ACTIVITY	LACTATION DAY 8	P INCREASED SENSITIVITY TO TOUCH
		POST-DOSE OBS	LACTATION DAY 9	P CONVULSIONS
		DEAD	LACTATION DAY 9	P FOUND DEAD
		NOSE/MOUTH	LACTATION DAY 14	P DARK MATERIAL AROUND NOSE
198 F	20 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		BODY	STUDY DAY 1	1 HAIRLOSS
		BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 0	1 HAIRLOSS
		BODY	GESTATION DAY 1	1 HAIRLOSS
		EYES	GESTATION DAY 1	P DARK MATERIAL AROUND EYE(S)
		BODY	GESTATION DAY 2	1 HAIRLOSS
		BODY	GESTATION DAY 3	1 HAIRLOSS
		205 F	20 MG/KG/DAY	BODY
BODY	LACTATION DAY 8			1 HAIRLOSS
BODY	LACTATION DAY 15			1 HAIRLOSS
BODY	GESTATION DAY 0			1 HAIRLOSS
BODY	GESTATION DAY 1			1 HAIRLOSS
EYES	GESTATION DAY 1			P DARK MATERIAL AROUND EYE(S)
BODY	GESTATION DAY 2			1 HAIRLOSS
BODY	GESTATION DAY 3			1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
205	F 20 MG/KG/DAY	BODY	GESTATION DAY 4	1 HAIRLOSS
		BODY	GESTATION DAY 5	1 HAIRLOSS
		BODY	GESTATION DAY 6	1 HAIRLOSS
		BODY	GESTATION DAY 7	1 HAIRLOSS
		BODY	GESTATION DAY 8	1 HAIRLOSS
		BODY	GESTATION DAY 9	1 HAIRLOSS
		BODY	GESTATION DAY 10	1 HAIRLOSS
		BODY	GESTATION DAY 11	1 HAIRLOSS
		EYES	GESTATION DAY 11	P DARK MATERIAL AROUND EYE(S)
		BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS
		BODY	GESTATION DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 4	1 HAIRLOSS
		BODY	LACTATION DAY 5	1 HAIRLOSS
		BODY	LACTATION DAY 6	1 HAIRLOSS
		BODY	LACTATION DAY 7	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS
		BODY	LACTATION DAY 9	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
205	F 20 MG/KG/DAY	BODY	LACTATION DAY 10	1 HAIRLOSS
		BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
		BODY	LACTATION DAY 15	1 HAIRLOSS
		BODY	LACTATION DAY 16	1 HAIRLOSS
		BODY	LACTATION DAY 17	1 HAIRLOSS
		BODY	LACTATION DAY 18	1 HAIRLOSS
		BODY	LACTATION DAY 19	1 HAIRLOSS
		BODY	LACTATION DAY 20	1 HAIRLOSS
		BODY	LACTATION DAY 21	1 HAIRLOSS
		208	F 20 MG/KG/DAY	DEAD
218	F 20 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
239	F 20 MG/KG/DAY	BODY	LACTATION DAY 21	P SCHEDULED EUTHANASTIA
		BODY	STUDY DAY 1	1 HAIRLOSS
		BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 0	1 HAIRLOSS
		BODY	GESTATION DAY 1	1 HAIRLOSS
		BODY	GESTATION DAY 2	1 HAIRLOSS
		BODY	GESTATION DAY 3	1 HAIRLOSS
		NOSE/MOUTH	GESTATION DAY 3	P DARK MATERIAL AROUND NOSE
		BODY	GESTATION DAY 4	1 HAIRLOSS
		BODY	GESTATION DAY 5	1 HAIRLOSS
		BODY	GESTATION DAY 6	1 HAIRLOSS
		BODY	GESTATION DAY 7	1 HAIRLOSS
		BODY	GESTATION DAY 8	1 HAIRLOSS
		BODY	GESTATION DAY 9	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
239	F	20 MG/KG/DAY	GESTATION DAY 10	1 HAIRLOSS
		BODY	GESTATION DAY 11	1 HAIRLOSS
		BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS
		BODY	GESTATION DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		EYES	LACTATION DAY 1	P EYE(S) PALE IN COLOR
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 4	1 HAIRLOSS
		BODY	LACTATION DAY 5	1 HAIRLOSS
		BODY	LACTATION DAY 6	1 HAIRLOSS
		BODY	LACTATION DAY 7	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS
		BODY	LACTATION DAY 9	1 HAIRLOSS
		BODY	LACTATION DAY 10	1 HAIRLOSS
		BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
		BODY	LACTATION DAY 15	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

APPENDIX D

SLI STUDY NO.: 3472.3 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS WITH NICKEL SULFATE HEXAHYDRATE INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
239	F 20 MG/KG/DAY	BODY	LACTATION DAY 16	1 HAIRLOSS
		BODY	LACTATION DAY 17	1 HAIRLOSS
		NOSE/MOUTH	LACTATION DAY 17	P DARK MATERIAL AROUND NOSE
		BODY	LACTATION DAY 18	1 HAIRLOSS
		BODY	LACTATION DAY 19	1 HAIRLOSS
		BODY	LACTATION DAY 20	1 HAIRLOSS
		BODY	LACTATION DAY 21	1 HAIRLOSS
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		NOSE/MOUTH	GESTATION DAY 4	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 5	P MALALIGNMENT
241	F 20 MG/KG/DAY	NOSE/MOUTH	GESTATION DAY 6	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 7	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 8	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 9	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 10	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 11	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 12	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 13	P MALALIGNMENT
		NOSE/MOUTH	GESTATION DAY 14	P MALALIGNMENT
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
242	F 20 MG/KG/DAY	BODY	STUDY DAY 1	1 HAIRLOSS
		BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	STUDY DAY 15	P SCAB(S) - LEFT FORELIMB
		BODY	GESTATION DAY 0	1 HAIRLOSS
		BODY	GESTATION DAY 1	1 HAIRLOSS
		BODY	GESTATION DAY 2	1 HAIRLOSS
		BODY	GESTATION DAY 3	1 HAIRLOSS
		BODY	GESTATION DAY 4	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
242 F	20 MG/KG/DAY	BODY	GESTATION DAY 5	1 HAIRLOSS
		BODY	GESTATION DAY 6	1 HAIRLOSS
		BODY	GESTATION DAY 7	1 HAIRLOSS
		BODY	GESTATION DAY 8	1 HAIRLOSS
		BODY	GESTATION DAY 9	P SCAB(S) - RIGHT FORELIMB
		BODY	GESTATION DAY 10	1 HAIRLOSS
		BODY	GESTATION DAY 11	1 HAIRLOSS
		BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS
		BODY	GESTATION DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
BODY	LACTATION DAY 4	1 HAIRLOSS		
BODY	LACTATION DAY 5	1 HAIRLOSS		
BODY	LACTATION DAY 6	1 HAIRLOSS		
BODY	LACTATION DAY 7	1 HAIRLOSS		
BODY	LACTATION DAY 8	1 HAIRLOSS		
BODY	LACTATION DAY 9	1 HAIRLOSS		
BODY	LACTATION DAY 10	1 HAIRLOSS		

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX D  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
242	F 20 MG/KG/DAY	BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
		BODY	LACTATION DAY 15	1 HAIRLOSS
		BODY	LACTATION DAY 16	1 HAIRLOSS
		BODY	LACTATION DAY 17	1 HAIRLOSS
		BODY	LACTATION DAY 18	1 HAIRLOSS
		BODY	LACTATION DAY 19	1 HAIRLOSS
		BODY	LACTATION DAY 20	1 HAIRLOSS
		BODY	LACTATION DAY 21	1 HAIRLOSS
200	F 30 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
204	F 30 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
207	F 30 MG/KG/DAY	DEAD	GESTATION DAY 25	P SCHEDULED EUTHANASIA
212	F 30 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
217	F 30 MG/KG/DAY	NOSE/MOUTH	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		NOSE/MOUTH	GESTATION DAY 1	P DARK MATERIAL AROUND NOSE
		NOSE/MOUTH	GESTATION DAY 2	P DARK MATERIAL AROUND NOSE
		NOSE/MOUTH	GESTATION DAY 4	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 5	P SCAB(S) - AROUND MOUTH
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
222	F 30 MG/KG/DAY	EXCRETA/EMESIS	GESTATION DAY 11	P FEW FECES
		BODY	LACTATION DAY 0	P REDDISH VAGINAL DISCHARGE
		BODY	LACTATION DAY 20	P SWELLING - ABDOMINAL MAMMARY(IES)
		BODY	LACTATION DAY 21	P SWELLING - ABDOMINAL MAMMARY(IES)
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
230	F 30 MG/KG/DAY	BODY	GESTATION DAY 12	1 HAIRLOSS
		BODY	GESTATION DAY 13	1 HAIRLOSS
		BODY	GESTATION DAY 14	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
230 F	30 MG/KG/DAY	BODY	GESTATION DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 16	1 HAIRLOSS
		BODY	GESTATION DAY 17	1 HAIRLOSS
		BODY	GESTATION DAY 18	1 HAIRLOSS
		BODY	GESTATION DAY 19	1 HAIRLOSS
		BODY	GESTATION DAY 20	1 HAIRLOSS
		BODY	GESTATION DAY 21	1 HAIRLOSS
		BODY	LACTATION DAY 0	1 HAIRLOSS
		BODY	LACTATION DAY 1	1 HAIRLOSS
		BODY	LACTATION DAY 2	1 HAIRLOSS
		BODY	LACTATION DAY 3	1 HAIRLOSS
		BODY	LACTATION DAY 4	1 HAIRLOSS
		BODY	LACTATION DAY 6	1 HAIRLOSS
		BODY	LACTATION DAY 7	1 HAIRLOSS
		BODY	LACTATION DAY 8	1 HAIRLOSS
		BODY	LACTATION DAY 9	1 HAIRLOSS
		BODY	LACTATION DAY 10	1 HAIRLOSS
		BODY	LACTATION DAY 11	1 HAIRLOSS
		BODY	LACTATION DAY 12	1 HAIRLOSS
		BODY	LACTATION DAY 13	1 HAIRLOSS
		BODY	LACTATION DAY 14	1 HAIRLOSS
BODY	LACTATION DAY 15	1 HAIRLOSS		
BODY	LACTATION DAY 16	1 HAIRLOSS		
BODY	LACTATION DAY 17	1 HAIRLOSS		
BODY	LACTATION DAY 18	1 HAIRLOSS		
BODY	LACTATION DAY 19	1 HAIRLOSS		
BODY	LACTATION DAY 21	1 HAIRLOSS		
240 F	30 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F0 SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
194	F 50 MG/KG/DAY	BODY	STUDY DAY 16	2 URINE STAIN
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
199	F 50 MG/KG/DAY	BODY	STUDY DAY 1	1 HAI RLOSS
		BODY	STUDY DAY 8	1 HAI RLOSS
		BODY	STUDY DAY 15	1 HAI RLOSS
		BODY	GESTATION DAY 0	1 HAI RLOSS
		BODY	GESTATION DAY 1	1 HAI RLOSS
		BODY	GESTATION DAY 2	1 HAI RLOSS
		BODY	GESTATION DAY 3	1 HAI RLOSS
		BODY	GESTATION DAY 4	1 HAI RLOSS
		BODY	GESTATION DAY 5	1 HAI RLOSS
		BODY	GESTATION DAY 6	1 HAI RLOSS
		BODY	GESTATION DAY 7	1 HAI RLOSS
		BODY	GESTATION DAY 8	1 HAI RLOSS
		BODY	GESTATION DAY 9	1 HAI RLOSS
		BODY	GESTATION DAY 10	1 HAI RLOSS
		BODY	GESTATION DAY 11	1 HAI RLOSS
		BODY	GESTATION DAY 12	1 HAI RLOSS
		BODY	GESTATION DAY 13	1 HAI RLOSS
		BODY	GESTATION DAY 14	1 HAI RLOSS
		BODY	GESTATION DAY 15	1 HAI RLOSS
		BODY	GESTATION DAY 16	1 HAI RLOSS
		BODY	GESTATION DAY 17	1 HAI RLOSS
		BODY	GESTATION DAY 18	1 HAI RLOSS
		BODY	GESTATION DAY 19	1 HAI RLOSS
		BODY	GESTATION DAY 20	1 HAI RLOSS
		BODY	GESTATION DAY 21	1 HAI RLOSS
		BODY	LACTATION DAY 0	1 HAI RLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F0 SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
199	F	50 MG/KG/DAY	LACTATION DAY 1	1 HAI RLOSS
		BODY	LACTATION DAY 2	1 HAI RLOSS
		BODY	LACTATION DAY 3	1 HAI RLOSS
		BODY	LACTATION DAY 4	1 HAI RLOSS
		BODY	LACTATION DAY 5	1 HAI RLOSS
		BODY	LACTATION DAY 6	1 HAI RLOSS
		BODY	LACTATION DAY 7	1 HAI RLOSS
		BODY	LACTATION DAY 8	1 HAI RLOSS
		BODY	LACTATION DAY 9	1 HAI RLOSS
		BODY	LACTATION DAY 10	1 HAI RLOSS
		BODY	LACTATION DAY 11	1 HAI RLOSS
		BODY	LACTATION DAY 12	1 HAI RLOSS
		BODY	LACTATION DAY 13	1 HAI RLOSS
		BODY	LACTATION DAY 14	1 HAI RLOSS
		BODY	LACTATION DAY 15	1 HAI RLOSS
		BODY	LACTATION DAY 16	1 HAI RLOSS
		BODY	LACTATION DAY 17	1 HAI RLOSS
		BODY	LACTATION DAY 18	1 HAI RLOSS
		BODY	LACTATION DAY 19	1 HAI RLOSS
		BODY	LACTATION DAY 21	1 HAI RLOSS
202	F	50 MG/KG/DAY	LACTATION DAY 21	P SCHEDULED EUTHANASIA
215	F	50 MG/KG/DAY	LACTATION DAY 21	P SCHEDULED EUTHANASIA
216	F	50 MG/KG/DAY	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		NOSE/MOUTH	STUDY DAY 15	P DARK MATERIAL AROUND NOSE
		BODY	STUDY DAY 16	2 URINE STAIN
226	F	50 MG/KG/DAY	LACTATION DAY 21	P SCHEDULED EUTHANASIA
227	F	50 MG/KG/DAY	LACTATION DAY 21	P SCHEDULED EUTHANASIA
232	F	50 MG/KG/DAY	STUDY DAY 54	P SCHEDULED EUTHANASIA
		NOSE/MOUTH	GESTATION DAY 17	P SCAB(S) - AROUND MOUTH

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

APPENDIX D

SLI STUDY NO.: 3472.3 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS WITH NICKEL SULFATE HEXAHYDRATE  
CLIENT: NIPERA, INC. INDIVIDUAL F0 SURVIVAL AND CLINICAL OBSERVATIONS

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
232	F 50 MG/KG/DAY	NOSE/MOUTH	GESTATION DAY 18	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 19	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 20	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 21	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	GESTATION DAY 22	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	LACTATION DAY 0	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	LACTATION DAY 1	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	LACTATION DAY 2	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	LACTATION DAY 3	P SCAB(S) - AROUND MOUTH
		NOSE/MOUTH	LACTATION DAY 4	P SCAB(S) - AROUND MOUTH
197	F 75 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		POST-DOSE OBS	LACTATION DAY 11	P SALIVATION
210	F 75 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
213	F 75 MG/KG/DAY	BODY	LACTATION DAY 1	1 FECAL STAIN
		BODY	LACTATION DAY 1	P DARK MATERIAL AROUND MOUTH
		BODY	LACTATION DAY 1	P SKIN PALE IN COLOR - ALL EXTREMITIES
		BODY	LACTATION DAY 1	P COOL TO THE TOUCH
		EXCRETA/EMESIS	LACTATION DAY 1	P DIARRHEA
		EYES	LACTATION DAY 1	P EYE(S) PALE IN COLOR
		EXCRETA/EMESIS	LACTATION DAY 2	P FEW FECES
		BODY	LACTATION DAY 2	1 FECAL STAIN
		BODY	LACTATION DAY 2	1 URINE STAIN
		BODY	LACTATION DAY 2	P SKIN PALE IN COLOR - ALL EXTREMITIES
EYES	NOSE/MOUTH	NOSE/MOUTH	LACTATION DAY 2	P DARK MATERIAL - FORELIMB(S)
			LACTATION DAY 2	P EYE(S) PALE IN COLOR
			LACTATION DAY 2	P DARK MATERIAL AROUND MOUTH
			LACTATION DAY 2	P SALIVATION

GRADE CODE: 1- SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX D  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
213	F 75 MG/KG/DAY	BODY	LACTATION DAY 2	P HUNCHED POSTURE
		BODY	LACTATION DAY 2	P DEHYDRATION
		DEAD	LACTATION DAY 2	P SCHEDULED EUTHANASIA
220	F 75 MG/KG/DAY	BODY	STUDY DAY 16	1 URINE STAIN
		NOSE/MOUTH	GESTATION DAY 15	P DARK MATERIAL AROUND NOSE
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
228	F 75 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
235	F 75 MG/KG/DAY	BODY	STUDY DAY 1	P SCHEDULED EUTHANASIA
		BODY	STUDY DAY 8	1 HAIRLOSS
		BODY	STUDY DAY 15	1 HAIRLOSS
		BODY	GESTATION DAY 0	1 HAIRLOSS
		BODY	GESTATION DAY 1	1 HAIRLOSS
		BODY	GESTATION DAY 2	1 HAIRLOSS
		BODY	GESTATION DAY 3	1 HAIRLOSS
		BODY	GESTATION DAY 4	1 HAIRLOSS
		BODY	GESTATION DAY 5	1 HAIRLOSS
		EXCRETA/EMESIS	GESTATION DAY 22	P SOFT STOOLS
		DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
244	F 75 MG/KG/DAY	BODY	GESTATION DAY 0	P SCAB(S) - FACIAL AREA
		BODY	GESTATION DAY 1	P SCAB(S) - FACIAL AREA
		BODY	GESTATION DAY 2	P SCAB(S) - FACIAL AREA
		BODY	GESTATION DAY 3	P SCAB(S) - FACIAL AREA
		BODY	GESTATION DAY 4	P SCAB(S) - FACIAL AREA
		BODY	GESTATION DAY 4	1 HAIRLOSS
		BODY	GESTATION DAY 5	1 HAIRLOSS
		BODY	GESTATION DAY 5	P SCAB(S) - FACIAL AREA
		BODY	GESTATION DAY 6	1 HAIRLOSS
		BODY	GESTATION DAY 7	1 HAIRLOSS
		BODY	GESTATION DAY 8	1 HAIRLOSS

GRADE CODE: 1 - SLIGHT, 2 - MODERATE, 3 - SEVERE, P - PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX D  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO SURVIVAL AND CLINICAL OBSERVATIONS

PAGE 23

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	DAY	GRADE OBSERVATIONS
244	F 75 MG/KG/DAY	BODY	GESTATION DAY 9	1 HAIRLOSS
		PARTURITION OBS	LACTATION DAY 1	P REDDISH VAGINAL DISCHARGE
245	F 75 MG/KG/DAY	DEAD	LACTATION DAY 21	P SCHEDULED EUTHANASIA
		PARTURITION OBS	LACTATION DAY 0	P SKIN PALE IN COLOR - ALL EXTREMITIES
		PARTURITION OBS	LACTATION DAY 0	P EYE(S) PALE IN COLOR
		PARTURITION OBS	LACTATION DAY 1	P SKIN PALE IN COLOR - ALL EXTREMITIES
		PARTURITION OBS	LACTATION DAY 1	P EYE(S) PALE IN COLOR
		EYES	LACTATION DAY 1	P EYE(S) PALE IN COLOR
		BODY	LACTATION DAY 1	P SKIN PALE IN COLOR - ALL EXTREMITIES
		DEAD	LACTATION DAY 1	P SCHEDULED EUTHANASIA

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

(171)

SLI Study No. 3472.3

## APPENDIX E

Individual F0 Body Weight Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
16996 M	420	455	466	475	496	510	506	531
16997 M	440	445	461	470	484	494	487	505
17010 M	466	477	499	502	507	527	517	527
17018 M	522	545	569	573	582	601	613	633
17032 M	495	516	542	547	563	578	582	580
17033 M	486	508	533	543	562	572	579	587
17035 M	486	490	520	538	560	UNSCHEDULED	EUTHANASIA	- MORI BUND
17036 M	464	469	492	504	539	556	555	576
MEAN	472	488	510	519	537	548	548	563
S. D.	32.2	33.5	37.6	36.8	36.3	39.1	46.3	44.0
N	8	8	8	8	8	7	7	7

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

GROUP 2: 10 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
17009 M	470	481	514	520	530	538	523	536
17011 M	452	451	468	479	490	500	476	486
17015 M	470	481	486	493	510	535	536	521
17017 M	442	452	464	472	485	498	489	490
17020 M	477	476	498	513	520	541	540	534
17044 M	485	497	515	525	544	558	567	582
17046 M	505	502	531	548	560	576	582	609
17048 M	444	457	465	477	490	506	486	500
MEAN	468	475	493	503	516	532	525	532
S. D.	21.6	19.7	25.9	27.3	27.5	28.3	38.9	43.9
N	8	8	8	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

GROUP 3: 20 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
16990 M	515	531	547	548	556	582	584	607
16999 M	453	440	466	467	481	497	490	501
17002 M	460	470	484	506	531	550	544	546
17008 M	482	501	512	523	547	558	572	584
17039 M	423	428	453	462	479	490	471	484
17040 M	468	493	510	520	531	543	541	541
17042 M	493	497	514	530	553	574	562	576
17045 M	445	475	494	503	518	526	527	545
MEAN	467	479	498	507	525	540	536	548
S. D.	29.0	33.6	29.9	29.9	30.2	33.6	39.3	41.3
N	8	8	8	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

GROUP 4: 30 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
17001 M	470	481	493	508	526	541	530	536
17005 M	478	485	501	510	530	538	548	562
17007 M	473	485	502	500	502	515	520	540
17012 M	473	485	499	507	520	527	532	557
17013 M	420	430	443	464	467	478	462	468
17023 M	496	513	539	524	560	590	604	624
17041 M	460	470	486	480	503	515	523	536
17049 M	449	465	482	493	499	502	502	520
MEAN	465	477	493	498	513	526	528	543
S. D.	22.6	23.6	26.6	18.9	27.4	32.9	40.2	43.7
N	8	8	8	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

GROUP 5: 50 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
17004 M	471	478	497	509	527	541	507	539
17024 M	465	482	478	510	522	529	523	539
17026 M	485	495	512	520	533	544	546	563
17028 M	451	452	456	460	469	487	477	487
17029 M	489	510	511	511	518	521	522	540
17034 M	462	472	488	492	508	517	517	526
17043 M	472	486	504	507	518	529	530	546
17047 M	445	454	457	475	493	503	489	506
MEAN	468	479	488	498	511	521	514	531
S. D.	15.2	19.6	22.4	20.7	20.9	19.1	22.3	24.0
N	8	8	8	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

GROUP 6: 75 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
17000 M	454	465	475	489	504	523	513	539
17014 M	443	447	463	478	493	484	459	482
17016 M	431	461	477	486	482	486	470	496
17019 M	476	487	511	512	525	539	516	541
17021 M	460	452	474	479	491	517	503	523
17022 M	483	482	497	509	508	506	524	554
17025 M	473	474	502	487	509	532	514	520
17027 M	531	546	574	579	595	609	619	656
MEAN	469	477	497	502	513	525	515	539
S. D.	30.5	31.2	35.3	33.4	35.5	39.5	48.1	53.0
N	8	8	8	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT DATA (GRAMS)

PAGE 7

GROUP 1: 0 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
192 F	253	262	267					
196 F	273	282	288					
206 F	264	262	270					
219 F	269	268	266	271				
221 F	277	287	293					
231 F	299	287	298					
233 F	274	271	274					
237 F	288	298	303					
MEAN	275	277	282	271				
S. D.	14.1	13.3	14.8	--				
N	8	8	8	1				

NOTE: FBW = FINAL BODY WEIGHT. BODY WEIGHTS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX G.  
 STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

PAGE 8

GROUP 2: 10 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
188 F	267	273	278					
195 F	263	272	268					
224 F	300	289	299					
229 F	257	250	249					
234 F	284	274	287					
236 F	276	279	280					
238 F	258	266	260					
243 F	286	285	298					
MEAN	274	274	277					
S. D.	15.3	12.0	17.7					
N	8	8	8					

NOTE: FBW = FINAL BODY WEIGHT. BODY WEIGHTS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX G.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

PAGE 9

GROUP 3: 20 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
177 F	279	278	280					
198 F	270	272	281					
205 F	275	275	283					
208 F	264	264	276					
218 F	283	291	300					
239 F	268	255	270					
241 F	279	288	293					
242 F	290	305	309					
MEAN	276	279	287					
S. D.	8.5	15.9	13.1					
N	8	8	8					

NOTE: FBW = FINAL BODY WEIGHT. BODY WEIGHTS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX G.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX E  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO BODY WEIGHT DATA (GRAMS)

PAGE 10

GROUP 4: 30 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
200 F	268	286	284					
204 F	282	277	278					
207 F	280	281	277					
212 F	255	260	265					
217 F	269	271	271					
222 F	304	308	313					
230 F	255	260	261					
240 F	286	286	300					
MEAN	275	279	281					
S. D.	16.6	15.7	17.6					
N	8	8	8					

NOTE: FBW = FINAL BODY WEIGHT. BODY WEIGHTS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX G.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT DATA (GRAMS)  
 GROUP 5: 50 MG/KG/DAY  
 PAGE 11

WEEK	1	2	3	4	5	6	7	8	FBW
194 F	280	271	275						
199 F	267	267	271						
202 F	263	265	278						
215 F	295	295	299						
216 F	284	278	287						
226 F	254	246	242						
227 F	262	266	274	279	274	277	279	277	283
232 F	298	300	299						
MEAN	275	274	278	279	274	277	279	277	283
S. D.	16.3	17.4	18.3	--	--	--	--	--	--
N	8	8	8	1	1	1	1	1	1

NOTE: FBW = FINAL BODY WEIGHT. BODY WEIGHTS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX G.  
 STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX E  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 BODY WEIGHT DATA (GRAMS)

PAGE 12

GROUP 6: 75 MG/KG/DAY

WEEK	1	2	3	4	5	6	7	FBW
197 F	271	263	268					
210 F	281	289	289					
213 F	260	255	269					
220 F	284	292	295					
228 F	278	287	286					
235 F	257	264	269					
244 F	265	265	270					
245 F	290	300	311					
MEAN	273	277	282					
S. D.	11.9	16.9	15.8					
N	8	8	8					

NOTE: FBW = FINAL BODY WEIGHT. BODY WEIGHTS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX G.

SLI Study No. 3472.3

APPENDIX F

Individual F0 Body Weight Gain Data



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 1

GROUP 1: 0 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
16996 M	35	11	9	21	14	-4	25
16997 M	5	16	9	14	10	-7	18
17010 M	11	22	3	5	20	-10	10
17018 M	23	24	4	9	19	12	20
17032 M	21	26	5	16	15	4	-2
17033 M	22	25	10	19	10	7	8
17035 M	4	30	18	22	UNSCHEДУLED	EUTHANASIA -	MORI BUND
17036 M	5	23	12	35	17	-1	21
MEAN	16	22	9	18	15	0	14
S. D.	11.2	6.0	4.9	9.1	4.0	7.9	9.4
N	8	8	8	8	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

GROUP 2: 10 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17009 M	11	33	6	10	8	-15	13
17011 M	-1	17	11	11	10	-24	10
17015 M	11	5	7	17	25	1	-15
17017 M	10	12	8	13	13	-9	1
17020 M	-1	22	15	7	21	-1	-6
17044 M	12	18	10	19	14	9	15
17046 M	-3	29	17	12	16	6	27
17048 M	13	8	12	13	16	-20	14
MEAN	7	18	11	13	15	-7	7
S. D.	6.8	9.8	3.8	3.8	5.6	12.2	13.3
N	8	8	8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

GROUP 3: 20 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
16990 M	16	16	1	8	26	2	23
16999 M	-13	26	1	14	16	-7	11
17002 M	10	14	22	25	19	-6	2
17008 M	19	11	11	24	11	14	12
17039 M	5	25	9	17	11	-19	13
17040 M	25	17	10	11	12	-2	0
17042 M	4	17	16	23	21	-12	14
17045 M	30	19	9	15	8	1	18
MEAN	12	18	10	17	16	-4	12
S. D.	13.6	5.1	7.0	6.3	6.1	9.9	7.6
N	8	8	8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 4

GROUP 4: 30 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17001 M	11	12	15	18	15	-11	6
17005 M	7	16	9	20	8	10	14
17007 M	12	17	-2	2	13	5	20
17012 M	12	14	8	13	7	5	25
17013 M	10	13	21	3	11	-16	6
17023 M	17	26	-15	36	30	14	20
17041 M	10	16	-6	23	12	8	13
17049 M	16	17	11	6	3	0	18
MEAN	12	16	5	15	12	2	15
S. D.	3.3	4.3	11.9	11.6	8.1	10.4	6.8
N	8	8	8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 5

GROUP 5: 50 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17004 M	7	19	12	18	14	-34	32
17024 M	17	-4	32	12	7	-6	16
17026 M	10	17	8	13	11	2	17
17028 M	1	4	4	9	18	-10	10
17029 M	21	1	0	7	3	1	18
17034 M	10	16	4	16	9	0	9
17043 M	14	18	3	11	11	1	16
17047 M	9	3	18	18	10	-14	17
MEAN	11	9	10	13	10	-8	17
S. D.	6.2	9.2	10.5	4.1	4.5	12.2	7.0
N	8	8	8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

GROUP 6: 75 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17000 M	11	10	14	15	19	-10	26
17014 M	4	16	15	15	-9	-25	23
17016 M	30	16	9	-4	4	-16	26
17019 M	11	24	1	13	14	-23	25
17021 M	-8	22	5	12	26	-14	20
17022 M	-1	15	12	-1	-2	18	30
17025 M	1	28	-15	22	23	-18	6
17027 M	15	28	5	16	14	10	37
MEAN	8	20	6	11	11	-10	24
S. D.	11.7	6.6	9.7	8.9	12.4	15.6	8.9
N	8	8	8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
192 F	9	5					
196 F	9	6					
206 F	-2	8					
219 F	-1	-2	5				
221 F	10	6					
231 F	-12	11					
233 F	-3	3					
237 F	10	5					
MEAN	3	5					
S. D.	8.2	3.8	--				
N	8	8					

NOTE: BODY WEIGHT GAINS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX H.  
 STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 8

GROUP 2: 10 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
188 F	6	5					
195 F	9	-4					
224 F	-11	10					
229 F	-7	-1					
234 F	-10	13					
236 F	3	1					
238 F	8	-6					
243 F	-1	13					

MEAN 0 4  
 S. D. 8.1 7.5  
 N 8 8

NOTE: BODY WEIGHT GAINS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX H.



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 9

GROUP 3: 20 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
177 F	-1	2					
198 F	2	9					
205 F	0	8					
208 F	0	12					
218 F	8	9					
239 F	-13	15					
241 F	9	5					
242 F	15	4					
MEAN	3	8					
S. D.	8.4	4.3					
N	8	8					

NOTE: BODY WEIGHT GAINS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX H.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
200 F	18	-2					
204 F	-5	1					
207 F	1	-4					
212 F	5	5					
217 F	2	0					
222 F	4	5					
230 F	5	1					
240 F	0	14					
MEAN	4	3					
S. D.	6.6	5.6					
N	8	8					

NOTE: BODY WEIGHT GAINS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX H.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX F  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 11

GROUP 5: 50 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
194 F	-9	4					
199 F	0	4					
202 F	2	13					
215 F	0	4					
216 F	-6	9					
226 F	-8	-4	5	-5	3	2	-2
227 F	4	8					
232 F	2	-1					
MEAN	-2	5	5	-5	3	2	-2
S. D.	5.0	5.4	--	--	--	--	--
N	8	8	1	1	1	1	1

NOTE: BODY WEIGHT GAINS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX H.  
 STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX F  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO BODY WEIGHT GAIN DATA (GRAMS)

PAGE 12

GROUP 6: 75 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4	4 TO 5	5 TO 6	6 TO 7	7 TO 8
197 F	-8	5					
210 F	8	0					
213 F	-5	14					
220 F	8	3					
228 F	9	-1					
235 F	7	5					
244 F	0	5					
245 F	10	11					
MEAN	4	5					
S. D.	7.0	5.1					
N	8	8					

NOTE: BODY WEIGHT GAINS FOR FEMALES WITH POSITIVE EVIDENCE OF MATING ARE PRESENTED IN APPENDIX H.

SLI Study No. 3472.3

APPENDIX G

Individual F0 Gestation Body Weight Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX G  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT DATA (GRAMS)

PAGE 1

GROUP 1: 0 MG/KG/DAY

PREGNANCY STATUS	DAY				
	0	7	14	20	
192 G	271	300	326	412	
196 G	279	307	330	431	
206 G	266	294	319	414	
219 G	271	284	306	362	
221 G	295	309	332	415	
231 G	311	335	369	447	
233 G	278	312	337	412	
237 G	302	339	360	434	
MEAN	284	310	335	416	
S. D.	16.5	18.9	20.7	25.2	
N	8	8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX G  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT DATA (GRAMS)

PAGE 2

GROUP 2: 10 MG/RG/DAY

PREGNANCY STATUS	DAY				
	0	7	14	20	
188 G	256	299	321	362	
195 G	272	297	317	389	
224 G	270	314	342	421	
229 G	245	296	327	402	
234 G	292	326	346	407	
236 G	289	313	335	426	
238 G	255	293	314	376	
243 G	313	327	364	430	
MEAN	274	308	333	402	
S. D.	22.7	13.7	17.0	24.5	
N	8	8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX G  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT DATA (GRAMS)

GROUP 3: 20 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0	7	14	20
177 G	285	316	343	419
198 G	272	307	336	420
205 G	291	312	334	407
208 G	272	303	330	395
218 G	279	315	327	387
239 G	264	299	328	400
241 G	292	322	339	384
242 G	306	328	353	419
MEAN	283	313	336	404
S. D.	13.6	9.6	8.7	14.6
N	8	8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX G  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0	7	14	20
200 G	286	318	341	411
204 G	290	321	332	351
207 G	287	315	342	423
212 G	272	312	328	425
217 G	275	297	323	406
222 G	317	350	356	431
230 G	252	284	309	389
240 G	293	320	350	436
MEAN	284	315	335	409
S. D.	18.8	19.2	15.3	27.9
N	8	8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX G  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO GESTATION BODY WEIGHT DATA (GRAMS)

PAGE 5

GROUP 5: 50 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0	7	14	20
194 G	268	312	337	397
199 G	255	296	318	379
202 G	270	313	351	419
215 G	299	321	342	403
216 G	267	296	312	384
226 G	248	291	302	370
232 G	310	342	377	429
MEAN	274	310	334	397
S. D.	22.6	17.8	25.7	21.5
N	7	7	7	7

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX G  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT DATA (GRAMS)

PAGE 6

GROUP 6: 75 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0	7	14	20
197 G	277	287	283	342
210 G	285	325	355	441
213 G	262	305	318	390
220 G	298	319	326	421
228 G	289	343	374	438
235 G	269	290	308	372
244 G	251	288	329	420
245 G	308	341	358	397
MEAN	280	312	331	403
S. D.	18.9	23.2	29.7	34.2
N	8	8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI Study No. 3472.3

APPENDIX H

Individual F0 Gestation Body Weight Gain Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX H  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

PAGE 1

GROUP 1: 0 MG/KG/DAY

PREGNANCY STATUS	DAY			
	0- 7	7-14	14-20	
192 G	29	26	86	
196 G	28	23	101	
206 G	28	25	95	
219 G	13	22	56	
221 G	14	23	83	
231 G	24	34	78	
233 G	34	25	75	
237 G	37	21	74	
MEAN	26	25	81	
S. D.	8.6	4.1	13.9	
N	8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX H  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 2: 10 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0- 7	7-14	14-20	
188 G	43	22	41	
195 G	25	20	72	
224 G	44	28	79	
229 G	51	31	75	
234 G	34	20	61	
236 G	24	22	91	
238 G	38	21	62	
243 G	14	37	66	
MEAN	34	25	68	
S. D.	12.3	6.2	14.8	
N	8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX H  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 3: 20 MG/RG/DAY

PREGNANCY STATUS		DAY	0- 7	7-14	14-20
177	G		31	27	76
198	G		35	29	84
205	G		21	22	73
208	G		31	27	65
218	G		36	12	60
239	G		35	29	72
241	G		30	17	45
242	G		22	25	66
MEAN			30	24	68
S. D.			5.8	6.1	11.7
N			8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX H  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0- 7	7-14	14-20	
200 G	32	23	70	
204 G	31	11	19	
207 G	28	27	81	
212 G	40	16	97	
217 G	22	26	83	
222 G	33	6	75	
230 G	32	25	80	
240 G	27	30	86	
MEAN	31	21	74	
S. D.	5.2	8.5	23.5	
N	8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX H  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 5: 50 MG/RG/DAY

PREGNANCY STATUS	DAY			
	0-7	7-14	14-20	
194 G	44	25	60	
199 G	41	22	61	
202 G	43	38	68	
215 G	22	21	61	
216 G	29	16	72	
226 G	43	11	68	
232 G	32	35	52	
MEAN	36	24	63	
S. D.	8.6	9.7	6.7	
N	7	7	7	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX H  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 6: 75 MG/RG/DAY

PREGNANCY STATUS	DAY		
	0- 7	7-14	14-20
197 G	10	-4	59
210 G	40	30	86
213 G	43	13	72
220 G	21	7	95
228 G	54	31	64
235 G	21	18	64
244 G	37	41	91
245 G	33	17	39
MEAN	32	19	71
S. D.	14.2	14.5	18.8
N	8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

(211)

SLI Study No. 3472.3

## APPENDIX I

Individual F0 Lactation Body Weight Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX I  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 LACTATION BODY WEIGHT DATA (GRAMS)

PAGE 1

GROUP 1: 0 MG/KG/DAY

ANIMAL NO.	DAY	1	4	7	10	14	21
192		286	299	306	318	338	318
196		303	313	328	339	335	336
206		305	316	316	325	357	345
219		275	296	318	333	325	316
221		277	324	321	330	347	362
231		322	331	336	348	355	368
233		321	334	334	358	371	366
237		327	329	339	332	346	348
MEAN		302	318	325	335	347	345
S. D.		20.7	14.4	11.4	12.8	14.4	20.4
N		8	8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX I  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 LACTATION BODY WEIGHT DATA (GRAMS)

GROUP 2: 10 MG/RG/DAY

ANIMAL NO.	DAY	1	4	7	10	14	21
188		317	309	317	324	325	324
195		287	309	318	332	349	331
224		309	335	328	353	363	342
229		EUTHANIZED - TOTAL LITTER LOSS					
234		309	323	326	328	329	327
236		307	323	343	359	360	343
238		287	288	286	293	305	303
243		329	341	335	344	366	345
MEAN		306	318	322	333	342	331
S. D.		15.2	17.9	18.3	22.0	23.2	14.8
N		7	7	7	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX I  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 LACTATION BODY WEIGHT DATA (GRAMS)

PAGE 3

GROUP 3: 20 MG/RG/DAY

ANIMAL NO.	DAY 1	DAY 4	DAY 7	DAY 10	DAY 14	DAY 21
177	312	331	344	344	357	353
198	303	323	326	345	357	328
205	276	301	303	316	331	328
208	299	308	311	323	353	332
218	248	292	316	323	335	324
239	294	309	318	328	351	349
241	313	317	325	335	350	341
242	312	333	318	323	336	353
MEAN	295	314	320	328	345	340
S. D.	22.5	14.4	12.1	9.6	10.4	12.1
N	8	8	8	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX I  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 LACTATION BODY WEIGHT DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

ANIMAL NO.	DAY	1	4	7	10	14	21
200		308	332	336	347	370	345
207		314	310	320	323	365	355
212		306	329	326	338	364	342
217		286	291	288	304	305	319
222		332	324	321	345	350	345
230		285	304	319	336	358	355
240		326	350	341	344	367	365
MEAN		308	320	322	334	354	347
S. D.		18.0	19.7	17.0	15.4	22.7	14.5
N		7	7	7	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX I  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 LACTATION BODY WEIGHT DATA (GRAMS)

GROUP 5: 50 MG/RG/DAY

ANIMAL NO.	DAY	1	4	7	10	14	21
194		310	293	295	306	310	324
199		303	308	321	330	346	338
202		309	318	333	334	352	334
215		322	337	332	337	346	362
216		289	303	330	329	353	321
226		262	275	277	313	327	306
232		304	329	338	340	373	349
MEAN		300	309	318	327	344	333
S. D.		19.4	21.3	23.0	12.7	20.2	18.6
N		7	7	7	7	7	7



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX I  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F0 LACTATION BODY WEIGHT DATA (GRAMS)

GROUP 6: 75 MG/RG/DAY

ANIMAL NO.	DAY	1	4	7	10	14	21	
197		255	273	285	294	300	290	
210		308	326	328	344	360	335	
213		260	EUTHANIZED - TOTAL LITTER LOSS					
220		320	318	325	328	343	350	
228		318	312	322	338	357	348	
235		274	297	315	322	337	319	
244		308	323	325	336	342	340	
245		323	EUTHANIZED - TOTAL LITTER LOSS					
MEAN		296	308	317	327	340	330	
S. D.		28.1	20.1	16.1	17.9	21.5	22.7	
N		8	6	6	6	6	6	

SLI Study No. 3472.3

APPENDIX J

Individual F0 Lactation Body Weight Gain Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX J  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

PAGE 1

GROUP 1: 0 MG/KG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7-10	10-14	14-21
192		13	7	12	20	-20
196		10	15	11	-4	1
206		11	0	9	32	-12
219		21	22	15	-8	-9
221		47	-3	9	17	15
231		9	5	12	7	13
233		13	0	24	13	-5
237		2	10	-7	14	2
MEAN		16	7	11	11	-2
S. D.		13.7	8.5	8.6	12.9	12.1
N		8	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX J  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 2: 10 MG/RG/DAY

ANIMAL NO.	DAY	1-4	4-7	7-10	10-14	14-21
188		-8	8	7	1	-1
195		22	9	14	17	-18
224		26	-7	25	10	-21
229		EUTHANIZED - TOTAL LITTER LOSS				
234		14	3	2	1	-2
236		16	20	16	1	-17
238		1	-2	7	12	-2
243		12	-6	9	22	-21
MEAN		12	4	11	9	-12
S. D.		11.8	9.6	7.6	8.5	9.5
N		7	7	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX J  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 3: 20 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10	10- 14	14- 21
177		19	13	FOUND DEAD		
198		20	3	19	12	-4
205		25	2	13	15	-3
208		9	3	12	30	-21
218		44	24	7	12	-11
239		15	9	10	23	-2
241		4	8	10	15	-9
242		21	-15	5	13	17
MEAN		20	6	11	17	-5
S. D.		12.0	11.1	4.5	6.8	11.6
N		8	8	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX J  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7-10	10-14	14-21
200		24	4	11	23	-25
207		-4	10	3	42	-10
212		23	-3	12	26	-22
217		5	-3	16	1	14
222		-8	-3	24	5	-5
230		19	15	17	22	-3
240		24	-9	3	23	-2
MEAN		12	2	12	20	-8
S. D.		13.9	8.5	7.6	13.7	13.2
N		7	7	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX J  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 5: 50 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7-10	10-14	14-21
194		-17	2	11	4	14
199		5	13	9	16	-8
202		9	15	1	18	-18
215		15	-5	5	9	16
216		14	27	-1	24	-32
226		13	2	36	14	-21
232		25	9	2	33	-24
MEAN		9	9	9	17	-10
S. D.		13.1	10.6	12.7	9.6	18.8
N		7	7	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX J  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION BODY WEIGHT GAIN DATA (GRAMS)

GROUP 6: 75 MG/RG/DAY

ANIMAL NO.	DAY	1-4	4-7	7-10	10-14	14-21
197		18	12	9	6	-10
210		18	2	16	16	-25
213		EUTHANIZED - TOTAL LITTER LOSS				
220		-2	7	3	15	7
228		-6	10	16	19	-9
235		23	18	7	15	-18
244		15	2	11	6	-2
245		EUTHANIZED - TOTAL LITTER LOSS				
MEAN		11	9	10	13	-10
S. D.		12.0	6.2	5.1	5.5	11.3
N		6	6	6	6	6



SLI Study No. 3472.3

APPENDIX K

Individual F0 Food Consumption Data  
(grams/animal/day)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1

GROUP 1: 0 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
16996 M	23	24	27	29	27	28
16997 M	22	22	25	26	25	25
17010 M	24	26	28	28	23	23
17018 M	29	32	a	33	33	34
17032 M	27	27	30	29	27	26
17033 M	24	26	28	30	28	28
17035 M	25	26	30	UNSCHEDULED EUTHANASIA - MORIBUND		
17036 M	23	26	31	32	29	30
MEAN	25	26	28	30	27	27
S. D.	2.3	2.9	2.0	2.3	3.2	3.6
N	8	8	7	7	7	7

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).  
 a ANIMAL WAS MATING.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 2: 10 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17009 M	21	25	26	26	23	25
17011 M	21	21	24	25	23	23
17015 M	24	24	27	30	27	18
17017 M	23	23	26	27	25	24
17020 M	22	24	26	27	25	25
17044 M	26	27	29	30	31	30
17046 M	28	28	28	30	28	31
17048 M	22	22	25	26	23	24
MEAN	23	24	26	28	26	25
S. D.	2.5	2.3	1.7	1.8	2.6	4.0
N	8	8	8	8	8	8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 3: 20 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
16990 M	24	25	28	31	29	29
16999 M	19	24	25	26	25	25
17002 M	24	25	32	32	28	26
17008 M	26	25	29	29	29	30
17039 M	22	27	30	30	25	27
17040 M	26	26	28	29	28	27
17042 M	24	25	31	31	29	29
17045 M	24	26	29	29	27	29
MEAN	24	25	29	30	27	28
S. D.	2.3	0.9	2.0	1.9	1.8	1.8
N	8	8	8	8	8	8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 4: 30 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17001 M	20	22	29	30	24	24
17005 M	26	23	25	25	27	30
17007 M	25	25	26	26	27	28
17012 M	24	24	29	28	27	31
17013 M	22	22	26	26	23	24
17023 M	27	29	33	35	33	34
17041 M	25	25	29	28	27	28
17049 M	24	23	25	25	24	27
MEAN	24	24	28	28	27	28
S. D.	2.3	2.3	2.9	3.3	3.1	3.4
N	8	8	8	8	8	8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 5: 50 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17004 M	23	24	29	29	23	29
17024 M	26	24	27	27	25	28
17026 M	26	25	26	28	27	28
17028 M	23	24	26	27	24	25
17029 M	25	27	31	29	29	31
17034 M	25	24	28	27	27	27
17043 M	26	26	a	27	27	28
17047 M	22	23	28	29	27	28
MEAN	24	25	28	28	26	28
S.D.	1.3	1.3	1.7	1.0	1.8	1.9
N	8	8	7	8	8	8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).  
 a ANIMAL WAS MATING.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 6: 75 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
17000 M	24	25	30	32	29	31
17014 M	21	24	27	23	23	26
17016 M	23	24	24	24	24	27
17019 M	24	26	28	29	25	28
17021 M	23	26	29	31	27	33
17022 M	23	25	27	18	34	33
17025 M	24	29	30	31	29	27
17027 M	31	31	33	31	34	36
MEAN	24	26	29	28	28	30
S. D.	2.8	2.6	2.8	5.0	4.3	3.6
N	8	8	8	8	8	8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 1: 0 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
192 F	15	16				
196 F	18	18				
206 F	17	18				
219 F	15	15				
221 F	19	19				
231 F	17	18				
233 F	16	15				
237 F	19	18				

MEAN 17 17  
 S. D. 1.6 1.6  
 N 8 8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4). FOOD CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX L.



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX K  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 2: 10 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
188 F	17	17				
195 F	15	15				
224 F	18	23				
229 F	14	16				
234 F	15	19				
236 F	16	17				
238 F	16	17				
243 F	19	20				

MEAN 16 18  
S. D. 1.5 2.7  
N 8 8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4). FOOD CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX L.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX K  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 9

GROUP 3: 20 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
177 F	15	16				
198 F	16	16				
205 F	18	18				
208 F	16	18				
218 F	17	19				
239 F	18	19				
241 F	18	18				
242 F	19	19				

MEAN 17 18  
S.D. 1.3 1.1  
N 8 8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4). FOOD CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX L.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 10

GROUP 4: 30 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
200 F	19	17				
204 F	16	17				
207 F	17	16				
212 F	17	17				
217 F	16	15				
222 F	18	19				
230 F	16	14				
240 F	17	18				

MEAN 17 17  
 S.D. 1.1 1.4  
 N 8 8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4). FOOD CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX L.

APPENDIX K  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

GROUP 5: 50 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
194 F	16	17				
199 F	16	17				
202 F	18	19				
215 F	18	18				
216 F	18	18				
226 F	15	15	a	17	16	18
227 F	16	16				
232 F	20	20				
MEAN	17	17		17	16	18
S. D.	1.4	1.6		--	--	--
N	8	8		1	1	1

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4). FOOD CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX L. STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.  
 a ANIMAL WAS MATING.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX K  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 6: 75 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	4 TO 5	5 TO 6	6 TO 7	7 TO 8
197 F	14	15				
210 F	18	18				
213 F	14	17				
220 F	18	18				
228 F	19	19				
235 F	17	17				
244 F	16	17				
245 F	19	19				

MEAN 17 17  
S.D. 2.0 1.3  
N 8 8

NOTE: FOOD CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4). FOOD CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX L.

SLI Study No. 3472.3

APPENDIX L

Individual F0 Gestation Food Consumption Data  
(grams/animal/day)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX L  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1

GROUP 1: 0 MG/KG/DAY

PREGNANCY		DAY			
STATUS	DAY	0- 7	7-14	14-20	
192	G	20	21	22	
196	G	22	21	25	
206	G	23	24	26	
219	G	17	18	20	
221	G	21	21	24	
231	G	23	26	26	
233	G	21	23	24	
237	G	25	25	23	
MEAN		22	22	24	
S. D.		2.4	2.6	2.1	
N		8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX L  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 2: 10 MG/RG/DAY

PREGNANCY		DAY	0- 7	7-14	14-20
STATUS					
188	G	22	25	24	
195	G	20	21	22	
224	G	25	24	23	
229	G	25	26	26	
234	G	26	25	23	
236	G	21	22	24	
238	G	24	23	22	
243	G	24	26	24	
MEAN		23	24	24	
S. D.		2.1	1.9	1.3	
N		8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX L  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 3: 20 MG/RG/DAY

PREGNANCY		DAY			
STATUS	DAY	0- 7	7-14	14-20	
177	G	22	21	24	
198	G	23	23	26	
205	G	23	24	22	
208	G	25	24	24	
218	G	22	19	17	
239	G	24	24	24	
241	G	25	25	24	
242	G	23	23	22	
MEAN		23	23	23	
S. D.		1.2	2.0	2.7	
N		8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX L  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 4: 30 MG/RG/DAY

PREGNANCY		DAY			
STATUS	0- 7	7-14	14-20		
200 G	25	25	25		
204 G	22	24	24		
207 G	23	24	26		
212 G	26	27	28		
217 G	22	24	24		
222 G	26	17	26		
230 G	21	23	24		
240 G	22	25	25		
MEAN	23	24	25		
S. D.	2.0	2.9	1.4		
N	8	8	8		

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX L  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 5: 50 MG/RG/DAY

PREGNANCY		DAY	0- 7	7-14	14-20
STATUS					
194	G		25	28	25
199	G		24	22	24
202	G		26	29	24
215	G		21	22	23
216	G		21	20	21
226	G		23	21	23
232	G		27	27	24
MEAN			24	24	23
S. D.			2.3	3.7	1.3
N			7	7	7

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX L  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 6: 75 MG/RG/DAY

PREGNANCY		DAY	0- 7	7-14	14-20
STATUS					
197	G		17	14	19
210	G		26	27	28
213	G		23	23	21
220	G		21	21	25
228	G		31	32	21
235	G		21	19	23
244	G		24	29	27
245	G		24	26	25
MEAN			23	24	24
S. D.			4.1	5.8	3.2
N			8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI Study No. 3472.3

APPENDIX M

Individual F0 Lactation Food Consumption Data  
(grams/animal/day)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX M  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1

GROUP 1: 0 MG/KG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
192		42	47	56
196		35	43	56
206		38	40	53
219		37	45	47
221		37	39	51
231		35	41	56
233		39	42	55
237		25	33	41
MEAN		36	41	52
S. D.		5.0	4.2	5.4
N		8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX M  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 2: 10 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
188		195	41	44
195		35	38	52
224		34	42	55
229		EUTHANIZED - TOTAL LITTER LOSS		
234		37	40	53
236		40	51	57
238		29	37	46
243		41	47	54
MEAN		59	42	52
S. D.		60.2	5.0	4.8
N		7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX M  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 3

GROUP 3: 20 MG/RG/DAY

ANIMAL NO.	DAY 1- 4	4- 7	7-10
177	37	47	FOUND DEAD
198	38	45	55
205	31	57	49
208	33	43	57
218	37	48	50
239	34	40	57
241	20	31	43
242	31	34	43
MEAN	33	43	51
S. D.	5.8	8.2	6.1
N	8	8	7



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX M  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 4: 30 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
200		39	47	56
207		27	39	47
212		44	48	59
217		22	31	41
222		25	35	52
230		37	44	58
240		34	37	46
MEAN		33	40	51
S. D.		8.1	6.4	6.8
N		7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX M  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 5: 50 MG/RG/DAY

ANIMAL NO.	DAY 1- 4	4- 7	7- 10
194	19	30	46
199	33	42	56
202	31	50	57
215	34	35	47
216	38	51	55
226	52	42	53
232	45	50	54
MEAN	36	43	53
S. D.	10.6	8.1	4.4
N	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX M  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION FOOD CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 6: 75 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
197		24	36	44
210		39	51	59
213		EUTHANIZED - TOTAL LITTER LOSS		
220		37	58	43
228		22	43	52
235		38	48	56
244		30	42	53
245		EUTHANIZED - TOTAL LITTER LOSS		
MEAN		32	46	51
S. D.		7.4	7.7	6.4
N		6	6	6

SLI Study No. 3472.3

APPENDIX N

Individual F0 Water Consumption Data  
(grams/animal/day)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1  
 WEEK 1 TO 2

GROUP: LEVEL:	M A L E										
	1 0 MG/KG/DAY	2 10 MG/KG/DAY	3 20 MG/KG/DAY	4 30 MG/KG/DAY	5 50 MG/KG/DAY	6 75 MG/KG/DAY	6 17000=				
16996=	37	17009=	28	16990=	41	17001=	36	17004=	42	17000=	85
16997=	34	17011=	28	16999=	39	17005=	24	17024=	46	17014=	39
17010=	34	17015=	38	17002=	27	17007=	31	17026=	34	17016=	30
17018=	49	17017=	31	17008=	31	17012=	41	17028=	32	17019=	42
17032=	27	17020=	27	17039=	27	17013=	29	17029=	86	17021=	41
17033=	31	17044=	37	17040=	46	17023=	39	17034=	32	17022=	30
17035=	35	17046=	36	17042=	48	17041=	39	17043=	34	17025=	39
17036=	33	17048=	33	17045=	36	17049=	30	17047=	44	17027=	37
MEAN	35		32		37		34		44		43
S. D.	6.5		4.5		7.9		6.1		18.2		17.8
N	8		8		8		8		8		8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 2  
 WEEK 2 TO 3

GROUP: LEVEL:	M A L E										
	1 0 MG/KG/DAY	2 10 MG/KG/DAY	3 20 MG/KG/DAY	4 30 MG/KG/DAY	5 50 MG/KG/DAY	6 75 MG/KG/DAY					
16996=	41	17009=	36	16990=	43	17001=	38	17004=	44	17000=	a
16997=	35	17011=	24	16999=	42	17005=	25	17024=	47	17014=	45
17010=	37	17015=	37	17002=	27	17007=	29	17026=	33	17016=	34
17018=	60	17017=	31	17008=	31	17012=	38	17028=	34	17019=	33
17032=	28	17020=	30	17039=	29	17013=	31	17029=	88	17021=	43
17033=	33	17044=	36	17040=	49	17023=	39	17034=	31	17022=	32
17035=	38	17046=	37	17042=	50	17041=	35	17043=	33	17025=	41
17036=	33	17048=	34	17045=	33	17049=	31	17047=	51	17027=	38
MEAN	38	33	33	38	38	33	33	45	45	38	38
S. D.	9.6	4.5	4.5	9.1	9.1	5.0	5.0	18.8	18.8	5.3	5.3
N	8	8	8	8	8	8	8	8	8	8	7

NOTE: WATER CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).  
 a ELIMINATED DUE TO LEAKING WATER BOTTLE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 3  
 WEEK 4 TO 5

GROUP: LEVEL:	M A L E													
	1 0 MG/KG/DAY	2 10 MG/KG/DAY	3 20 MG/KG/DAY	4 30 MG/KG/DAY	5 50 MG/KG/DAY	6 75 MG/KG/DAY	6 17000=	6 17014=	6 17016=	6 17019=	6 17021=	6 17022=	6 17025=	6 17027=
	16996=	45	17009=	38	16990=	41	17001=	41	17004=	58	17000=	123		
	16997=	36	17011=	33	16999=	41	17005=	26	17024=	52	17014=	46		
	17010=	35	17015=	42	17002=	33	17007=	29	17026=	35	17016=	32		
	17018=	a	17017=	34	17008=	34	17012=	45	17028=	34	17019=	36		
	17032=	27	17020=	27	17039=	31	17013=	29	17029=	b	17021=	44		
	17033=	35	17044=	33	17040=	48	17023=	42	17034=	32	17022=	34		
	17035=	40	17046=	37	17042=	52	17041=	41	17043=	a	17025=	47		
	17036=	35	17048=	32	17045=	34	17049=	29	17047=	58	17027=	40		
MEAN	36		34		39		35		45		50			
S. D.	5.4		4.8		7.5		7.4		12.4		29.8			
N	7		8		8		8		6		8			

a ANIMAL WAS MATING.  
 b ELIMINATED DUE TO LEAKING WATER BOTTLE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 4  
 WEEK 5 TO 6

GROUP: LEVEL:	M A L E										
	1 0 MG/KG/DAY	2 10 MG/KG/DAY	3 20 MG/KG/DAY	4 30 MG/KG/DAY	5 50 MG/KG/DAY	6 75 MG/KG/DAY					
16996=	58	17009=	37	16990=	47	17001=	40	17004=	57	17000=	b
16997=	39	17011=	32	16999=	41	17005=	28	17024=	47	17014=	40
17010=	32	17015=	44	17002=	32	17007=	27	17026=	35	17016=	31
17018=	67	17017=	33	17008=	33	17012=	45	17028=	31	17019=	34
17032=	27	17020=	28	17039=	35	17013=	30	17029=	97	17021=	42
17033=	39	17044=	34	17040=	45	17023=	39	17034=	29	17022=	26
17035=	a	17046=	40	17042=	48	17041=	38	17043=	30	17025=	43
17036=	40	17048=	33	17045=	32	17049=	28	17047=	53	17027=	36
MEAN	43		35	39	39	34	34	47	47	36	
S. D.	14.2		5.0	6.9	6.9	6.7	6.7	22.8	22.8	6.4	
N	7		8	8	8	8	8	8	8	7	

a UNSCHEDULED EUTHANASIA - MORIBUND.  
 b ELIMINATED DUE TO BROKEN WATER BOTTLE.



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 5  
 WEEK 6 TO 7

GROUP: LEVEL:	M A L E										
	1 0 MG/KG/DAY	2 10 MG/KG/DAY	3 20 MG/KG/DAY	4 30 MG/KG/DAY	5 50 MG/KG/DAY	6 75 MG/KG/DAY					
16996=	51	17009=	32	16990=	46	17001=	37	17004=	44	17000=	100
16997=	35	17011=	28	16999=	39	17005=	29	17024=	50	17014=	51
17010=	31	17015=	40	17002=	27	17007=	28	17026=	37	17016=	31
17018=	60	17017=	35	17008=	35	17012=	46	17028=	31	17019=	35
17032=	26	17020=	28	17039=	27	17013=	27	17029=	105	17021=	37
17033=	34	17044=	34	17040=	45	17023=	36	17034=	33	17022=	43
17035=	a	17046=	37	17042=	45	17041=	38	17043=	32	17025=	41
17036=	36	17048=	33	17045=	29	17049=	27	17047=	53	17027=	39
MEAN	39	33	37	37	34	47			48	47	
S. D.	11.9	4.4	8.2	8.2	6.7	22.2			24.5	22.2	
N	7	8	8	8	8	8			8	8	

a UNSCHEDULED EUTHANASIA - MORTIBUND.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 6  
 WEEK 7 TO 8

GROUP: LEVEL:	M A L E										
	1 0 MG/KG/DAY	2 10 MG/KG/DAY	3 20 MG/KG/DAY	4 30 MG/KG/DAY	5 50 MG/KG/DAY	6 75 MG/KG/DAY					
16996=	52	17009=	32	16990=	42	17001=	36	17004=	45	17000=	111
16997=	33	17011=	26	16999=	36	17005=	31	17024=	b	17014=	46
17010=	26	17015=	17	17002=	27	17007=	29	17026=	36	17016=	36
17018=	58	17017=	33	17008=	34	17012=	48	17028=	31	17019=	34
17032=	24	17020=	25	17039=	30	17013=	27	17029=	109	17021=	39
17033=	34	17044=	28	17040=	43	17023=	36	17034=	28	17022=	40
17035=	a	17046=	40	17042=	41	17041=	36	17043=	33	17025=	42
17036=	41	17048=	31	17045=	31	17049=	31	17047=	53	17027=	40
MEAN	38		29		35		34		48		48
S. D.	12.7		6.9		6.1		6.6		28.3		25.7
N	7		8		8		8		7		8

a UNSCHEDULED EUTHANASIA - MORIBUND.  
 b ELIMINATED DUE TO BROKEN WATER BOTTLE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 7  
 WEEK 1 TO 2

GROUP: LEVEL:	F E M A L E												
	1	2	3	4	5	6	7	8	9	10	11	12	
	0 MG/KG/DAY	10 MG/KG/DAY	20 MG/KG/DAY	30 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY	100 MG/KG/DAY	150 MG/KG/DAY	200 MG/KG/DAY	300 MG/KG/DAY	450 MG/KG/DAY	600 MG/KG/DAY	750 MG/KG/DAY
	192=	188=	177=	25	194=	34	197=	21	200=	25	194=	34	197=
	196=	195=	198=	28	199=	30	210=	36	204=	33	199=	30	210=
	206=	224=	205=	25	202=	28	213=	24	207=	26	202=	28	213=
	219=	229=	208=	30	215=	40	220=	38	212=	38	215=	40	220=
	221=	234=	218=	31	216=	24	228=	33	217=	28	216=	24	228=
	231=	236=	239=	22	226=	22	235=	30	222=	28	226=	22	235=
	233=	238=	241=	37	227=	18	244=	25	230=	27	227=	18	244=
	237=	243=	242=	26	232=	a	245=	25	240=	24	232=	a	245=
MEAN	27	26	28	28	29	28	29	29	29	29	28	28	29
S. D.	5.7	6.2	4.5	4.5	4.5	7.5	6.1	6.1	4.5	4.5	7.5	6.1	6.1
N	8	7	8	8	8	7	8	8	8	8	7	8	8

a ELIMINATED DUE TO LEAKING WATER BOTTLE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX N  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 8  
 WEEK 2 TO 3

GROUP: LEVEL:	F E M A L E												
	1	2	3	4	5	6	7	8	9	10	11	12	
	0 MG/KG/DAY	10 MG/KG/DAY	20 MG/KG/DAY	30 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY	100 MG/KG/DAY	150 MG/KG/DAY	200 MG/KG/DAY	300 MG/KG/DAY	450 MG/KG/DAY	600 MG/KG/DAY	750 MG/KG/DAY
	192=	188=	177=	200=	194=	197=	222=	222=	200=	194=	197=	222=	222=
	196=	195=	198=	204=	199=	210=	33=	33=	204=	199=	210=	63=	63=
	206=	224=	205=	207=	202=	213=	21=	21=	207=	202=	213=	24=	24=
	219=	229=	208=	212=	215=	220=	32=	32=	212=	215=	220=	33=	33=
	221=	234=	218=	217=	216=	228=	21=	21=	217=	216=	228=	33=	33=
	231=	236=	239=	222=	226=	235=	30=	30=	222=	226=	235=	28=	28=
	233=	238=	241=	230=	227=	244=	28=	28=	230=	227=	244=	26=	26=
	237=	243=	242=	240=	232=	245=	22=	22=	240=	232=	245=	28=	28=
MEAN	26	26	29	26	28	32	26	26	29	28	32	32	32
S. D.	5.8	6.9	4.4	5.2	7.7	13.2	5.2	5.2	4.4	7.7	13.2	13.2	13.2
N	8	7	8	8	7	8	8	8	8	7	8	8	8

NOTE: WATER CONSUMPTION WAS NOT MEASURED DURING MATING (WEEK 3 TO 4).  
 a ELIMINATED DUE TO LEAKING WATER BOTTLE.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX N  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 9  
WEEK 5 TO 6

GROUP:	1	2	3	4	5	6
LEVEL:	0 MG/KG/DAY	10 MG/KG/DAY	20 MG/KG/DAY	30 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY

----- F E M A L E -----

227= 19

MEAN  
S. D.  
N

19  
--  
1

NOTE: WATER CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX O.  
STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX N  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 10  
WEEK 6 TO 7

GROUP:	1	2	3	4	5	6
LEVEL:	0 MG/KG/DAY	10 MG/KG/DAY	20 MG/KG/DAY	30 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY

227= 20

MEAN 20  
S. D. --  
N 1

NOTE: WATER CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX O.  
STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX N  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 11  
WEEK 7 TO 8

GROUP:	1	2	3	4	5	6
LEVEL:	0 MG/KG/DAY	10 MG/KG/DAY	20 MG/KG/DAY	30 MG/KG/DAY	50 MG/KG/DAY	75 MG/KG/DAY

227= 20

MEAN 20  
S. D. --  
N 1

NOTE: WATER CONSUMPTION FOR FEMALES WITH POSITIVE EVIDENCE OF MATING IS PRESENTED IN APPENDIX O.  
STANDARD DEVIATION WAS NOT CALCULATED WHEN N < 2.

SLI Study No. 3472.3

APPENDIX O

Individual F0 Gestation Water Consumption Data  
(grams/animal/day)



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX 0  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 1: 0 MG/KG/DAY

PREGNANCY		DAY			
STATUS	DAY	0- 7	7-14	14-20	
192	G	29	33	36	
196	G	38	41	47	
206	G	48	63	59	
219	G	31	33	45	
221	G	40	45	54	
231	G	30	34	48	
233	G	42	41	56	
237	G	33	35	46	
MEAN		36	41	49	
S. D.		6.7	10.1	7.3	
N		8	8	8	

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX 0  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 2: 10 MG/RG/DAY

PREGNANCY		DAY	0- 7	7-14	14-20
STATUS					
188	G		34	41	44
195	G		49	45	69
224	G		55	59	70
229	G		38	40	47
234	G		43	a	67
236	G		32	38	46
238	G		27	28	35
243	G		a	a	a
MEAN			40	42	54
S. D.			9.9	10.1	14.3
N			7	6	7

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN  
 a ELIMINATED DUE TO LEAKING WATER BOTTLE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX 0  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 3

GROUP 3: 20 MG/RG/DAY

PREGNANCY		DAY	0- 7	7-14	14-20
STATUS					
177	G		38	46	55
198	G		49	54	59
205	G		38	39	48
208	G		50	48	51
218	G		44	45	60
239	G		35	35	35
241	G		46	55	58
242	G		31	31	35
MEAN			41	44	50
S. D.			6.9	8.6	10.2
N			8	8	8

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX 0  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 4: 30 MG/RG/DAY

PREGNANCY				
STATUS	DAY	0- 7	7-14	14-20
200 G		57	38	43
204 G		55	59	60
207 G		46	51	b
212 G		57	64	77
217 G		39	45	73
222 G		55	33	81
230 G		44	48	52
240 G		32	a	49
MEAN		48	48	62
S. D.		9.4	11.0	14.9
N		8	7	7

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN  
 a ELIMINATED DUE TO BROKEN WATER BOTTLE.  
 b ELIMINATED DUE TO ABERRANT VALUE.

APPENDIX 0  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

GROUP 5: 50 MG/RG/DAY

PREGNANCY		DAY	0- 7	7-14	14-20
STATUS					
194	G		46	50	64
199	G		47	47	62
202	G		42	b	48
215	G		45	51	64
216	G		37	42	51
226	G		36	34	45
232	G		a	a	53
MEAN			42	45	55
S. D.			4.7	7.0	8.0
N			6	5	7

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN

a ELIMINATED DUE TO LEAKING WATER BOTTLE.

b ELIMINATED DUE TO BROKEN WATER BOTTLE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX 0  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 6: 75 MG/RG/DAY

PREGNANCY		DAY		
STATUS	0- 7	7-14	14-20	
197	G	28	24	49
210	G	90	87	a
213	G	41	40	50
220	G	47	81	74
228	G	53	56	a
235	G	35	35	46
244	G	64	68	66
245	G	33	36	41
MEAN		49	53	54
S. D.		20.3	23.3	12.8
N		8	8	6

G = GRAVID NG = NONGRAVID; NOT INCLUDED IN CALCULATION OF MEAN  
 a ELIMINATED DUE TO EMPTY WATER BOTTLE.

(271)

SLI Study No. 3472.3

APPENDIX P

Individual F0 Lactation Water Consumption Data  
(grams/animal/day)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX P  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

PAGE 1

GROUP 1: 0 MG/KG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
192		54	58	68
196		51	56	68
206		70	58	75
219		50	59	61
221		66	62	74
231		54	56	72
233		53	48	66
237		41	48	51
MEAN		55	56	67
S. D.		9.2	5.1	7.9
N		8	8	8



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX P  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 2: 10 MG/RG/DAY

ANIMAL NO.	DAY	1-4	4-7	7-10
188		a	60	63
195		66	64	86
224		58	62	78
229		EUTHANIZED - TOTAL LITTER LOSS		
234		60	62	80
236		64	74	88
238		45	53	68
243		63	71	83
MEAN		59	64	78
S. D.		7.6	7.0	9.3
N		6	7	7

a ELIMINATED DUE TO ABERRANT VALUE.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX P  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 3: 20 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
177		68	72	FOUND DEAD
198		60	66	84
205		56	59	67
208		65	75	83
218		67	65	69
239		53	61	80
241		40	54	72
242		45	48	57
MEAN		57	63	73
S. D.		10.3	9.0	9.8
N		8	8	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX P  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 4: 30 MG/RG/DAY

ANIMAL NO.	DAY 1- 4	4- 7	7- 10
200	60	67	90
207	42	58	80
212	73	76	94
217	38	43	55
222	37	60	90
230	59	62	82
240	53	55	73
MEAN	52	60	81
S. D.	13.4	10.2	13.4
N	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX P  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 5: 50 MG/RG/DAY

ANIMAL NO.	DAY 1- 4	4- 7	7- 10
194	39	51	74
199	52	67	86
202	54	74	84
215	61	54	78
216	56	66	73
226	51	60	79
232	89	88	95
MEAN	57	66	81
S. D.	15.5	12.6	7.7
N	7	7	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX P  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO LACTATION WATER CONSUMPTION DATA (GRAMS/ANIMAL/DAY)

GROUP 6: 75 MG/RG/DAY

ANIMAL NO.	DAY	1- 4	4- 7	7- 10
197		46	50	60
210		71	70	82
213		EUTHANIZED - TOTAL LITTER LOSS		
220		76	102	122
228		46	60	81
235		68	79	86
244		51	65	75
245		EUTHANIZED - TOTAL LITTER LOSS		
MEAN		60	71	84
S. D.		13.5	18.0	20.6
N		6	6	6

SLI Study No. 3472.3

APPENDIX Q

Individual F0 Reproductive Performance Data

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX Q  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO REPRODUCTIVE PERFORMANCE DATA

PAGE 1

GROUP 1: 0 MG/KG/DAY

FEMALE NO.	MALE NO.	PRECOITAL INTERVAL (DAYS)	PREGNANCY STATUS
192	16996	3	G
196	16997	2	G
206	17010	3	G
219	17018	8	G
221	17032	3	G
231	17033	3	G
233	17035	4	G
237	17036	2	G

G = GRAVID NG = NONGRAVID

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX Q  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO REPRODUCTIVE PERFORMANCE DATA

PAGE 2

GROUP 2: 10 MG/RG/DAY

FEMALE NO.	MALE NO.	PRECOITAL INTERVAL (DAYS)	PREGNANCY STATUS
188	17009	3	G
195	17011	3	G
224	17015	4	G
229	17017	3	G
234	17020	2	G
236	17044	3	G
238	17046	1	G
243	17048	3	G

G = GRAVID NG = NONGRAVID



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

GROUP 3: 20 MG/KG/DAY

APPENDIX Q  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO REPRODUCTIVE PERFORMANCE DATA

PAGE 3

FEMALE NO.	MALE NO.	PRECOITAL INTERVAL (DAYS)	PREGNANCY STATUS
177	16990	4	G
198	16999	2	G
205	17002	3	G
208	17008	1	G
218	17039	2	G
239	17040	1	G
241	17042	3	G
242	17045	1	G

G = GRAVID NG = NONGRAVID

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

GROUP 4: 30 MG/RG/DAY

APPENDIX Q  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO REPRODUCTIVE PERFORMANCE DATA

FEMALE NO.	MALE NO.	PRECOITAL INTERVAL (DAYS)	PREGNANCY STATUS
200	17001	3	G
204	17005	4	G
207	17007	3	G
212	17012	2	G
217	17013	3	G
222	17023	7	G
230	17041	3	G
240	17049	2	G

G = GRAVID NG = NONGRAVID

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

GROUP 5: 50 MG/KG/DAY

APPENDIX Q  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO REPRODUCTIVE PERFORMANCE DATA

FEMALE NO.	MALE NO.	PRECOITAL INTERVAL (DAYS)	PREGNANCY STATUS
194	17004	2	G
199	17024	3	G
202	17026	2	G
215	17028	2	G
216	17029	3	G
226	17034	4	G
227	17043	a	NG
232	17047	4	G

G = GRAVID NG = NONGRAVID  
a PRESENCE OF SPERM WAS NOT DETECTED.

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

GROUP 6: 75 MG/RG/DAY

APPENDIX Q  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO REPRODUCTIVE PERFORMANCE DATA

PAGE 6

FEMALE NO.	MALE NO.	PRECOITAL INTERVAL (DAYS)	PREGNANCY STATUS
197	17000	4	G
210	17014	3	G
213	17016	2	G
220	17019	3	G
228	17021	3	G
235	17022	1	G
244	17025	3	G
245	17027	2	G

G = GRAVID NG = NONGRAVID

SLI Study No. 3472.3

APPENDIX R

Individual F0 Gestation Length Data

APPENDIX R  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION LENGTH DATA (DAYS)

GROUP 1: 0 MG/KG/DAY		GROUP 2: 10 MG/KG/DAY		GROUP 3: 20 MG/KG/DAY		GROUP 4: 30 MG/KG/DAY	
ANIMAL NO.	GESTATION LENGTH	ANIMAL NO.	GESTATION LENGTH	ANIMAL NO.	GESTATION LENGTH	ANIMAL NO.	GESTATION LENGTH
192	22	188	24	177	22	200	23
196	22	195	22	198	22	207	22
206	22	224	22	205	22	212	22
219	22	229	23	208	22	217	22
221	22	234	22	218	23	222	22
231	22	236	23	239	22	230	22
233	22	238	22	241	22	240	22
237	22	243	22	242	22		
MEAN	22.0	MEAN	22.5	MEAN	22.1	MEAN	22.1
S. D.	0.0	S. D.	0.8	S. D.	0.4	S. D.	0.4
N	8	N	8	N	8	N	7

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX R  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GESTATION LENGTH DATA (DAYS)

PAGE 2

GROUP 5: 50 MG/KG/DAY		GROUP 6: 75 MG/KG/DAY	
ANIMAL NO.	GESTATION LENGTH	ANIMAL NO.	GESTATION LENGTH
194	22	197	22
199	22	210	23
202	22	213	23
215	22	220	22
216	23	228	22
226	23	235	23
232	23	244	22
		245	23
MEAN	22.4	MEAN	22.5
S. D.	0.5	S. D.	0.5
N	7	N	8

SLI Study No. 3472.3

APPENDIX S

Individual F0 Gross Necropsy Observations



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 1

ANIMAL NO.	17035	GROUP:	0 MG/KG/DAY	MALE	EUTHANIZED MORIBUND	9/ 3/98	STUDY DAY	31	GRADE
				ESOPHAGUS	GROSS: PERFORATION				P
					TWO DISTINCT OPENINGS APPROXIMATELY 1.0 CM APART IN CRANIAL PORTION APPROXIMATELY 0.2 CM AND 0.4 CM IN LENGTH; SURROUNDING PERFORATION AND EXTENDING INTO SUBCUTANEOUS TISSUE OF RIGHT AXILLARY AREA IS LARGE QUANTITY OF LIGHT GREEN CASEOUS MATERIAL AND INGESTA				
				EXT. APPEARANCE	GROSS: HAIRCOAT - DARK MATERIAL				P
				EXT. APPEARANCE	GROSS: AROUND EYES, NOSE, MOUTH AND FOREPAWS, RED HAIRCOAT - WET MATTING				P
				THORACIC CAVITY	GROSS: AROUND MOUTH, CLEAR COLORLESS FLUID CONTENTS				P
				GENERAL COMMENT	GROSS: APPROXIMATELY 3.0 ML, CLOUDY RED GI TRACT - NO DIGESTA, INGESTA OR FECAL MATERIAL PRESENT ENTIRE TRACT				P
				SUBCUTANEOUS TIS	GROSS: EDEMA RIGHT AXILLARY AREA, POSSIBLY ASSOCIATED WITH ESOPHAGEAL PERFORATIONS				P
ANIMAL NO.	177	GROUP:	20 MG/KG/DAY	FEMALE	FOUND DEAD	9/22/98	LACTATION DAY	9	P
			BRAIN		GROSS: HEMORRHAGE				
			LUNGS		GROSS: BLOOD PRESENT ON SURFACE OF MENINGES MOTTLED				P
			OVARIES		GROSS: ALL LOBES; RED AND DARK RED CORPORA LUTEA - REGRESSING				P
			TRACHEA		GROSS: PRESENT BUT IN REGRESSION - ACCURATE COUNT NOT POSSIBLE CONTENT ABNORMAL				P
			UTERINE HORNS		GROSS: WHITE FOAM IMPLANTATION SCARS (LEFT, RIGHT)				P
			EXT. APPEARANCE		GROSS: HAIRCOAT - WET MATTING AROUND NOSE AND MOUTH, LIGHT RED				P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO. : 3472.3  
CLIENT: NIPERA, INC.

APPENDIX S  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

PAGE 2

ANIMAL NO.	FOUND DEAD OR EUTHANIZED MORIBUND	THORACIC CAVITY	GROSS: CONTENT ABNORMAL	GRADE
177 (CONTINUED)			APPROXIMATELY 3.0 ML OF DARK RED FLUID	P
		SUBCUTANEOUS TIS	GROSS: HEMORRHAGIC AREA DORSAL SKULL, WITH ASSOCIATED FRACTURE OF RIGHT PARIETAL	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

ANIMAL NO.	GROUP	DOSE	SEX	SCHEDULED EUTHANASIA	STUDY DAY	GRADE
16996	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
16997	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
17010	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
17018	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
17032	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY ORAL CAVITY	MALE	SCHEDULED EUTHANASIA GROSS: INCISOR(S) - BROKEN UPPER RIGHT	9/21/98 STUDY DAY 49	P
17033	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
17036	GROUP: 0 MG/KG/DAY	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
17009	GROUP: 10 MG/KG/DAY	10 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	
17011	GROUP: 10 MG/KG/DAY	10 MG/KG/DAY KIDNEYS	MALE	SCHEDULED EUTHANASIA GROSS: CYST(S) LEFT, CORTICAL AND CUT SURFACES, TWO, BOTH 0.2 CM DIAMETER	9/21/98 STUDY DAY 49	P
17015	GROUP: 10 MG/KG/DAY	10 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	9/21/98 STUDY DAY 49	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

APPENDIX S

GRADE

ANIMAL NO.	GROUP	DOSE (MG/KG/DAY)	SEX	EXT. APPEARANCE	STUDY DAY	GRADE
17017	GROUP:	10 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
17020	GROUP:	10 MG/KG/DAY	MALE	HAIRCOAT - HAIRLOSS FORELIMBS	9/21/98 STUDY DAY 49	P
GROSS: HAIRCOAT - HAIRLOSS						
17044	GROUP:	10 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
17046	GROUP:	10 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
17048	GROUP:	10 MG/KG/DAY	MALE	STOMACH	9/21/98 STUDY DAY 49	P
GROSS: REDDENED GLANDULAR MUCOSA						
16990	GROUP:	20 MG/KG/DAY	MALE	KIDNEYS	9/21/98 STUDY DAY 49	P
GROSS: DILATED PELVIS BILATERAL; BOTH CLEAR FLUID FILLED						
16999	GROUP:	20 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
17002	GROUP:	20 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
17008	GROUP:	20 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
17039	GROUP:	20 MG/KG/DAY	MALE		9/21/98 STUDY DAY 49	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

APPENDIX S

GRADE

ANIMAL NO.	GROUP	DOSE (MG/KG/DAY)	SEX	ORGAN/TISSUE	DATE	OBSERVATIONS	GRADE
17040	GROUP	20	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED			
17042	GROUP	20	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED			
17045	GROUP	20	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED			
17001	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: CONTENT ABNORMAL CLEAR YELLOW MUCOID MATERIAL			P
17005	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED			
17007	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED			
17012	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED			
17013	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: REDDENED GLANDULAR MUCOSA			P
17023	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: TAIL - ENLARGEMENT PROXIMAL PORTION; 0.6 CM DIAMETER			P
17041	GROUP	30	MALE	SCHEDULED EUTHANASIA	9/21/98	STUDY DAY 49	
				GROSS: FOCI RIGHT DIAPHRAGMATIC AND LEFT LOBES; MULTIPLE; PINPOINT TO 0.3 CM; TAN			P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 6

ANIMAL NO.	GROUP	MG/KG/DAY	SEX	ORGAN	DATE	STUDY DAY	GRADE
17049	GROUP:	30	MALE		9/21/98	STUDY DAY 49	
SCHEDULED EUTHANASIA							
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
17004	GROUP:	50	MALE	KIDNEYS	9/21/98	STUDY DAY 49	1
GROSS: DILATED PELVIS RIGHT							
17024	GROUP:	50	MALE		9/21/98	STUDY DAY 49	
SCHEDULED EUTHANASIA							
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
17026	GROUP:	50	MALE	URINARY BLADDER	9/21/98	STUDY DAY 49	P
GROSS: CONTENT ABNORMAL YELLOWISH-CLEAR MUCOID MATERIAL							
17028	GROUP:	50	MALE	LUNGS	9/21/98	STUDY DAY 49	P
GROSS: FOCI ALL LOBES; MULTIPLE; PINPOINT TO 0.4 CM; TAN; APPEAR RAISED							
GROSS: CONTENT ABNORMAL YELLOWISH-CLEAR MUCOID MATERIAL							
17029	GROUP:	50	MALE	KIDNEYS	9/21/98	STUDY DAY 49	P
GROSS: ENLARGED BILATERAL; LEFT - 3.2 X 1.6 X 1.5 CM; RIGHT - 2.6 X 1.8 X 1.6 CM							
GROSS: DILATED PELVIS BILATERAL; LEFT - WITH CLEAR FLUID; RIGHT - WITH YELLOW FLUID							
GROSS: CALCULI BILATERAL, MULTIPLE, UP TO 0.5 CM DIAMETER							
GROSS: DISTENDED BILATERAL							
GROSS: CALCULI BILATERAL, MULTIPLE, UP TO 0.3 CM DIAMETER							

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

ANIMAL NO.	17029 (CONTINUED)	URINARY BLADDER	SCHEDULED EUTHANASIA	GRADE
		URINARY BLADDER	GROSS: DISTENDED 2.8 X 2.2 X 1.1 CM	P
		URINARY BLADDER	GROSS: CALCULI	P
		URINARY BLADDER	GROSS: THICKENED MULTIPLE, UP TO 0.4 CM DIAMETER	P
ANIMAL NO. 17034	GROUP: 50 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO. 17043	GROUP: 50 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: CONTENT ABNORMAL YELLOWISH-CLEAR MUCOID MATERIAL	P
ANIMAL NO. 17047	GROUP: 50 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO. 17000	GROUP: 75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: ADHESION INVOLVING DIAPHRAGM, SPLEEN, BODY WALL, AND OMENTUM	P
ANIMAL NO. 17014	GROUP: 75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO. 17016	GROUP: 75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO. 17019	GROUP: 75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO. 17021	GROUP: 75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: DILATED PELVIS RIGHT; CLEAR FLUID FILLED	1

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 8

ANIMAL NO.	(CONTINUED)	LUNGS	SCHEDULED EUTHANASIA	GRADE
17021	GROUP: 75 MG/KG/DAY	LUNGS	GROSS: DARK RED FOCI ALL LOBES; MULTIPLE; PINPOINT TO 0.2 CM	P
17022	GROUP: 75 MG/KG/DAY THYMUS	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: FOCI BOTH LOBES, SEVERAL, UP TO 0.2 CM DIAMETER, RED	P
17025	GROUP: 75 MG/KG/DAY TESTES	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: DISCOLORED BILATERAL, PURPLE	P
	TESTES		GROSS: SMALL	P
	THYMUS		GROSS: BILATERAL, BOTH 2.0 X 0.9 X 0.6 CM	P
			GROSS: FOCI BOTH LOBES, MULTIPLE, UP TO 0.1 CM DIAMETER, RED	P
17027	GROUP: 75 MG/KG/DAY LUNGS	MALE	SCHEDULED EUTHANASIA 9/21/98 STUDY DAY 49 GROSS: DARK RED FOCI ALL LOBES; MULTIPLE; PINPOINT TO 0.2 CM	P
192	GROUP: 0 MG/KG/DAY LUNGS	FEMALE	SCHEDULED EUTHANASIA 10/3/98 LACTATION DAY 21 GROSS: FOCI	P
	UTERINE HORNS		GROSS: ALL LOBES; MULTIPLE; UP TO 0.1 CM DIAMETER; TAN; SOME FIRM 9, 8	P
196	GROUP: 0 MG/KG/DAY UTERINE HORNS	FEMALE	SCHEDULED EUTHANASIA 10/2/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 7, 10	P
206	GROUP: 0 MG/KG/DAY UTERINE HORNS	FEMALE	SCHEDULED EUTHANASIA 10/3/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 11, 5	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 9

ANIMAL NO.	219	221	231	233	237	188	195
GROUP:	0 MG/KG/DAY	0 MG/KG/DAY	0 MG/KG/DAY	0 MG/KG/DAY	0 MG/KG/DAY	10 MG/KG/DAY	10 MG/KG/DAY
SEX:	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE	FEMALE
ORGAN:	LUNGS	UTERINE HORNS	UTERINE HORNS	LUNGS	UTERINE HORNS	UTERINE HORNS	UTERINE HORNS
SCHEDULED EUTHANASIA	10/ 8/98	10/ 3/98	10/ 3/98	10/ 4/98	10/ 2/98	10/ 5/98	10/ 3/98
LACTATION DAY	21	21	21	21	21	21	21
GROSS:	FOCI	FOCI	FOCI	FOCI	FOCI	FOCI	FOCI
DESCRIPTION:	ALL LOBES; MULTIPLE; PINPOINT UP TO 0.3 CM IN DIAMETER; TAN; SOME APPEAR CYSTIC	UTERINE HORNS	UTERINE HORNS	UTERINE HORNS	RIGHT APICAL LOBE AND LEFT LOBE; TWO; EACH APPROXIMATELY 0.1 CM DIAMETER; TAN; SLIGHTLY RAISED	UTERINE HORNS	UTERINE HORNS
SCARS:	4, 9	8, 9	13, 6	7, 9	6, 10	0, 6	5, 12
GRADE	P	P	P	P	P	P	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO. : 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 10

ANIMAL NO.	GROUP:	MG/KG/DAY	SEX	UTERINE HORNS	SCHEDULED EUTHANASIA	LACTATION DAY	GRADE
224	GROUP:	10	FEMALE	UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 4/98	P
					GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
						6, 12	
229	GROUP:	10	FEMALE a	LIVER	SCHEDULED EUTHANASIA	9/13/98	P
				LUNGS	GROSS: PALE		
				STOMACH	GROSS: ALL LOBES		
				THYROID	GROSS: MOTTLED		
				UTERINE HORNS	GROSS: ALL LOBES; RED, TAN, AND PINK		
					GROSS: CONTENT ABNORMAL		
					GROSS: TISSUE MATERIAL MIXED WITH INGESTA		
					GROSS: PALE		
					GROSS: BILATERAL		
					GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
						6, 10	
234	GROUP:	10	FEMALE	UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 2/98	P
					GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
						12, 2	
236	GROUP:	10	FEMALE	SMALL INTESTINE	SCHEDULED EUTHANASIA	10/ 4/98	P
				UTERINE HORNS	GROSS: CONTENT ABNORMAL		
					GROSS: ILEUM: RED MUCOID MATERIAL MIXED WITH DIGESTA		
					GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
						7, 10	
238	GROUP:	10	FEMALE	UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 1/98	P
					GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
						7, 8	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

a EUTHANIZED DUE TO TOTAL LITTER LOSS.

APPENDIX S

ANIMAL NO.	GROUP:	DOSE:	SEX:	PARAMETER:	DATE:	GRADE
	SCHEDULED EUTHANASIA					
243	10 MG/KG/DAY	FEMALE	UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 3/98 LACTATION DAY 21	P
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
			EXT. APPEARANCE	GROSS: HAIRCOAT - HAIRLOSS		P
				LEFT FORELIMB		
198	20 MG/KG/DAY	FEMALE	UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 2/98 LACTATION DAY 21	P
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
205	20 MG/KG/DAY	FEMALE	UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 3/98 LACTATION DAY 21	P
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
			EXT. APPEARANCE	GROSS: HAIRCOAT - HAIRLOSS		P
				FORELIMBS		
208	20 MG/KG/DAY	FEMALE	LIVER	SCHEDULED EUTHANASIA	10/ 1/98 LACTATION DAY 21	P
				GROSS: TAN AREA(S)		
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
			UTERINE HORNS	GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
				GROSS: HAIRCOAT - HAIRLOSS		P
				FORELIMBS		
218	20 MG/KG/DAY	FEMALE	LUNGS	SCHEDULED EUTHANASIA	10/ 3/98 LACTATION DAY 21	P
				GROSS: MOTTLED		
				GROSS: ALL LOBES; DARK RED AND RED		P
				GROSS: FOCI		P
				GROSS: ALL LOBES; MULTIPLE; PINPOINT; BOTH TAN AND BLACK		P
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
239	20 MG/KG/DAY	FEMALE	LUNGS	SCHEDULED EUTHANASIA	10/ 1/98 LACTATION DAY 21	P
				GROSS: FOCI		
				GROSS: ALL LOBES; MULTIPLE; UP TO 0.2 CM IN DIAMETER; TAN		

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX S  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

PAGE 12

ANIMAL NO.	(CONTINUED)	UTERINE HORNS	SCHEDULED EUTHANASIA	GRADE
239		UTERINE HORNS EXT. APPEARANCE	GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 5, 11 GROSS: HAIRCOAT - HAIRLOSS FOREPAWS	P P
241	GROUP: 20 MG/KG/DAY	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA 10/ 3/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 0, 9	P
242	GROUP: 20 MG/KG/DAY	FEMALE UTERINE HORNS EXT. APPEARANCE	SCHEDULED EUTHANASIA 10/ 1/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 5, 11 GROSS: HAIRCOAT - HAIRLOSS THORACIC AREA, AROUND FORELIMBS AND HINDLIMBS	P P
200	GROUP: 30 MG/KG/DAY	FEMALE SMALL INTESTINE SMALL INTESTINE LUNGS UTERINE HORNS	SCHEDULED EUTHANASIA 10/ 4/98 LACTATION DAY 21 GROSS: CONTENT ABNORMAL ILEUM; RED MUCOID MATERIAL MIXED WITH DIGESTA PORTIONS OF JEJUNUM GROSS: MOTTLED ALL LOBES; DARK RED AND RED GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 8, 9	P P P P
204	GROUP: 30 MG/KG/DAY	FEMALE a UTERINE HORNS GENERAL COMMENT	SCHEDULED EUTHANASIA 9/16/98 GESTATION DAY 25 GROSS: RETAINED FETUS(ES) - (LEFT, RIGHT) 0, 1; MALE FETUS APPEARS MORPHOLOGICALLY NORMAL EXTERNALLY GROSS: GESTATION DAY 25 - FO	P P
207	GROUP: 30 MG/KG/DAY	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA 10/ 3/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 7, 7	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT  
a EUTHANIZED ON POST-BREEDING DAY 25 (FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER EVIDENCE OF MATING WAS DETECTED).

APPENDIX S  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

ANIMAL NO.	GROUP:	MG/KG/DAY	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA	10/ 2/98 LACTATION DAY 21	GRADE
212	GROUP:	30	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 7, 11	10/ 2/98 LACTATION DAY 21	P
217	GROUP:	30	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 7, 9	10/ 3/98 LACTATION DAY 21	P
222	GROUP:	30	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 9, 6 GROSS: RESORPTION(S) (LEFT, RIGHT) 0, 1	10/ 7/98 LACTATION DAY 21	P
230	GROUP:	30	FEMALE UTERINE HORNS EXT. APPEARANCE	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 6, 7 GROSS: HAIRCOAT - HAIRLOSS FORELIMBS	10/ 3/98 LACTATION DAY 21	P
240	GROUP:	30	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 6, 9	10/ 2/98 LACTATION DAY 21	P
194	GROUP:	50	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 6, 9	10/ 2/98 LACTATION DAY 21	P
199	GROUP:	50	FEMALE SKIN UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: SCABBING LEFT HINDLIMB GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 6, 7	10/ 3/98 LACTATION DAY 21	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX S  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

PAGE 14

ANIMAL NO.	199 (CONTINUED)	EXT. APPEARANCE	GROSS: HAIRCOAT - HAIRLOSS FORELIMBS AND LEFT HINDLIMB	GRADE
ANIMAL NO.	202	GROUP: 50 MG/KG/DAY UTERINE HORNS	SCHEDULED EUTHANASIA 10/ 2/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 10, 8	P
ANIMAL NO.	215	GROUP: 50 MG/KG/DAY UTERINE HORNS	SCHEDULED EUTHANASIA 10/ 2/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 6, 10	P
ANIMAL NO.	216	GROUP: 50 MG/KG/DAY SMALL INTESTINE	SCHEDULED EUTHANASIA 10/ 4/98 LACTATION DAY 21 GROSS: CONTENT ABNORMAL DUODENUM AND JEJUNUM, YELLOW MUCOID MATERIAL MIXED WITH DIGESTA; ILEUM, RED MUCOID MATERIAL MIXED WITH DIGESTA 10, 4	P
ANIMAL NO.	226	GROUP: 50 MG/KG/DAY LUNGS	SCHEDULED EUTHANASIA 10/ 5/98 LACTATION DAY 21 GROSS: NODULE(S) LEFT LOBE: ONE: 0.2 CM DIAMETER; GRAY; FIRM 8, 8	P
ANIMAL NO.	227	GROUP: 50 MG/KG/DAY UTERINE HORNS	SCHEDULED EUTHANASIA 9/26/98 STUDY DAY 54 GROSS: NONGRAVID -- AMMONIUM SULFIDE NEGATIVE	P
ANIMAL NO.	232	GROUP: 50 MG/KG/DAY UTERINE HORNS	SCHEDULED EUTHANASIA 10/ 5/98 LACTATION DAY 21 GROSS: IMPLANTATION SCARS (LEFT, RIGHT) 6, 10	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT  
a EUTHANIZED ON POST-BREEDING PERIOD DAY 25 (HAD NO EVIDENCE OF MATING, FAILED TO DELIVER AND WAS EUTHANIZED 25 DAYS AFTER COMPLETION OF THE MATING PERIOD).

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 15

ANIMAL NO.	GROUP	75 MG/KG/DAY LUNGS	FEMALE	SCHEDULED EUTHANASIA	10/ 4/98 LACTATION DAY 21	GRADE
197	GROUP:		FEMALE	SCHEDULED EUTHANASIA	10/ 4/98 LACTATION DAY 21	P
			UTERINE HORNS	GROSS: FOCI		
				GROSS: MULTIPLE; UP TO 0.2 CM DIAMETER; TAN		
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
				8, 7		
210	GROUP:		FEMALE	SCHEDULED EUTHANASIA	10/ 4/98 LACTATION DAY 21	P
			UTERINE HORNS	GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		
				5, 12		
213	GROUP:		FEMALE <sup>a</sup>	SCHEDULED EUTHANASIA	9/14/98 LACTATION DAY 2	P
			THYROID	GROSS: PALE		
			UTERINE HORNS	BILATERAL		
				GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
			EXT. APPEARANCE	8, 7		
				GROSS: HAIRCOAT - DARK MATERIAL		P
				AROUND EYES, MOUTH AND FORELIMBS, REDDISH-BROWN		
			EXT. APPEARANCE	GROSS: HAIRCOAT - WET MATTING		P
				UROGENITAL AREA, DARK YELLOW; ANOGENITAL AREA, DARK GREEN		
220	GROUP:		FEMALE	SCHEDULED EUTHANASIA	10/ 3/98 LACTATION DAY 21	P
			KIDNEYS	GROSS: TAN AREA(S)		
				RIGHT, CORTICAL SURFACE; THREE; 0.1 CM TO 0.3 CM DIAMETER;		
				RAISED; EXTENDING INTO CORTEX		
			UTERINE HORNS	GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
				9, 8		
			ABDOMINAL CAVITY	GROSS: ADHESION		P
				INVOLVING LEFT KIDNEY AND ADIPOSE TISSUE; CORTICAL SURFACE		
				OF KIDNEY IN AREA OF ADHESION IS DEPRESSED		
228	GROUP:		FEMALE	SCHEDULED EUTHANASIA	10/ 3/98 LACTATION DAY 21	P
			LUNGS	GROSS: MOTTLED		
				ALL LOBES; RED AND DARK RED		

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

<sup>a</sup> EUTHANIZED DUE TO TOTAL LITTER LOSS.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO GROSS NECROPSY OBSERVATIONS

APPENDIX S

PAGE 16

ANIMAL NO.	228 (CONTINUED)	LUNGS	GROSS: FOCI	MOST LOBES; FEW; PINPOINT TO 0.1 CM DIAMETER; DARK RED	GRADE
		UTERINE HORNS	GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
			9, 8		P
ANIMAL NO.	235 GROUP: 75 MG/KG/DAY	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT)	10/ 2/98 LACTATION DAY 21	P
			5, 7		
ANIMAL NO.	244 GROUP: 75 MG/KG/DAY	FEMALE UTERINE HORNS	SCHEDULED EUTHANASIA GROSS: IMPLANTATION SCARS (LEFT, RIGHT)	10/ 3/98 LACTATION DAY 21	P
			6, 11		
ANIMAL NO.	245 GROUP: 75 MG/KG/DAY	FEMALE a LIVER	SCHEDULED EUTHANASIA GROSS: PALE	9/13/98 LACTATION DAY 1	P
		LIVER	ALL LOBES GROSS: ACCENTUATED LOBULAR MARKINGS		P
		LUNGS	ALL LOBES GROSS: PALE		P
		STOMACH	ALL LOBES GROSS: CONTENT ABNORMAL		P
		THYROID	TISSUE MATERIAL MIXED WITH REDDISH-BROWN SOLID MATERIAL		P
		UTERINE HORNS	GROSS: PALE BILATERAL GROSS: IMPLANTATION SCARS (LEFT, RIGHT)		P
			1, 7		

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

a EUTHANIZED DUE TO TOTAL LITTER LOSS.



SLI Study No. 3472.3

APPENDIX T

Individual F0 Implantation and  
Post-Implantation Loss Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX T  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP 1: 0 MG/KG/DAY

PREGNANCY STATUS	IMPLANTATION SCAR COUNT	NUMBER OF LIVE PUPS (DAY 0)	POST-IMPLANTATION LOSS
192 G	17	17	0
196 G	17	16	1
206 G	16	16	0
219 G	13	13	0
221 G	17	17	0
231 G	19	17	2
233 G	16	16	0
237 G	16	16	0
MEAN	16.4	16.0	0.4
S. D.	1.7	1.3	0.7
N	8	8	8

G = GRAVID  
 NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPIERA, INC.

APPENDIX T  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP 2: 10 MG/RG/DAY

PREGNANCY STATUS	IMPLANTATION SCAR COUNT	NUMBER OF LIVE PUPS (DAY 0)	POST-IMPLANTATION LOSS
188 G	6	6	0
195 G	17	16	1
224 G	18	18	0
229 G	16	0	16
234 G	14	14	0
236 G	17	15	2
238 G	15	14	1
243 G	18	17	1
MEAN	15.1	12.5	2.6
S. D.	3.9	6.2	5.4
N	8	8	8

G = GRAVID  
 NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX T  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP 3: 20 MG/RG/DAY

PREGNANCY STATUS	IMPLANTATION SCAR COUNT	NUMBER OF LIVE PUPS (DAY 0)	POST-IMPLANTATION LOSS
177 G	15	14	1
198 G	16	15	1
205 G	16	15	1
208 G	13	13	0
218 G	17	12	5
239 G	16	16	0
241 G	9	7	2
242 G	16	14	2
MEAN	14.8	13.3	1.5
S. D.	2.6	2.8	1.6
N	8	8	8

G = GRAVID  
 NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX T  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP 4: 30 MG/KG/DAY

PREGNANCY STATUS	IMPLANTATION SCAR COUNT	NUMBER OF LIVE PUPS (DAY 0)	POST-IMPLANTATION LOSS
200 G	17	12	5
204 G	a	a	a
207 G	14	12	2
212 G	18	16	2
217 G	16	15	1
222 G	15	10	5
230 G	13	13	0
240 G	15	14	1
MEAN	15.4	13.1	2.3
S. D.	1.7	2.0	2.0
N	7	7	7

G = GRAVID

NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.  
 a NO IMPLANTATION SCARS WERE RECORDED, ONE MALE FETUS WAS RETAINED IN UTERO.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX T  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP 5: 50 MG/RG/DAY

PREGNANCY STATUS	IMPLANTATION SCAR COUNT	NUMBER OF LIVE PUPS (DAY 0)	POST-IMPLANTATION LOSS
194 G	15	9	6
199 G	13	12	1
202 G	18	16	2
215 G	16	12	4
216 G	14	13	1
226 G	16	12	4
232 G	16	15	1
MEAN	15.4	12.7	2.7
S. D.	1.6	2.3	2.0
N	7	7	7

G = GRAVID

NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX T  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL FO IMPLANTATION AND POST-IMPLANTATION LOSS DATA

GROUP 6: 75 MG/RG/DAY

PREGNANCY STATUS	IMPLANTATION SCAR COUNT	NUMBER OF LIVE PUPS (DAY 0)	POST-IMPLANTATION LOSS
197 G	15	9	6
210 G	17	14	3
213 G	15	9	6
220 G	17	14	3
228 G	17	12	5
235 G	12	11	1
244 G	17	11	6
245 G	8	0	8
MEAN	14.8	10.0	4.8
S. D.	3.2	4.5	2.3
N	8	8	8

G = GRAVID  
 NOTE: IMPLANTATION SCAR COUNT MINUS THE NUMBER OF LIVE PUPS (DAY 0) EQUALS POST-IMPLANTATION LOSS.

SLI Study No. 3472.3

APPENDIX U

Individual F1 Pup Viability



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX U  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP VIABILITY

PAGE 1

GROUP 1: 0 MG/KG/DAY

DAM NO.	NO. DEAD DAY 0			NO. VIABLE DAY 0			DAY 1		BEFORE SELECTION DAY 4		AFTER SELECTION DAY 4		DAY 7		DAY 14		DAY 21		
	M	F	U	M	F	%	M	F	M	F	M	F	M	F	M	F	M	F	
192	0	0	0	9/	9	100	8/	8	100	17	9	7	4	4	4	4	4	4	4
196	0	1	0	8/	8	100	8/	9	89	16	8	7	4	4	4	4	4	4	4
206	0	0	0	9/	9	100	7/	7	100	16	9	7	4	4	4	4	4	4	4
219	0	0	0	5/	5	100	8/	8	100	13	5	8	4	4	4	3	4	3	4
221	0	0	0	9/	9	100	8/	8	100	17	9	8	4	4	4	4	4	4	4
231	0	0	0	6/	6	100	11/	11	100	17	6	11	4	4	4	4	4	4	4
233	0	0	0	8/	8	100	8/	8	100	16	8	8	4	4	4	4	4	4	4
237	0	0	0	11/	11	100	5/	5	100	16	11	5	4	4	4	3	4	4	3
TOTAL	0	1	0	65/	65	63/	64	128	65	61	65	61	32	32	31	31	31	31	31

M = MALE, F = FEMALE, U = UNDETERMINED

NOTE: NUMBER DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX U  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP VIABILITY

PAGE 2

GROUP 2: 10 MG/KG/DAY

DAM NO.	NO. DEAD DAY 0			NO. VIABLE DAY 0			NO. SELECTION DAY 1			NO. SELECTION DAY 4			NO. SELECTION DAY 7			NO. SELECTION DAY 14			NO. SELECTION DAY 21			
	M	F	U	M	F	%	M	F	TOTAL	M	F	%	M	F	TOTAL	M	F	%	M	F	TOTAL	
188	0	0	0	2	2	100	4	4	100	6	2	4	2	4	4	2	4	4	2	4	4	
195	0	0	0	8	8	100	8	8	100	16	8	8	4	4	4	4	4	4	4	4	4	
224	0	0	0	8	8	100	10	10	100	18	8	10	4	4	4	4	4	4	4	4	4	
229	5	3	2	0	5	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	
234	0	0	0	7	7	100	7	7	100	14	7	7	4	4	4	4	4	4	4	4	4	
236	1	1	0	8	9	89	7	8	88	15	8	7	4	4	4	4	4	4	4	4	4	
238	0	0	0	4	4	100	10	10	100	14	4	10	4	4	4	4	4	4	4	4	4	
243	0	0	0	9	9	100	8	8	100	17	9	8	4	4	4	4	4	4	4	4	4	
TOTAL	6	4	2	46	52	54	58	100	46	54	46	54	26	28	28	26	28	28	26	28	26	28

M = MALE, F = FEMALE, U = UNDETERMINED  
 NOTE: NUMBER DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.

GROUP 3: 20 MG/KG/DAY

DAM NO.	NO. DEAD DAY 0			NO. VIABLE DAY 0			NO. SELECTION DAY 1			NO. SELECTION DAY 4			NO. SELECTION DAY 7			NO. SELECTION DAY 14			NO. SELECTION DAY 21		
	M	F	U	M	F	%	M	F	TOTAL	M	F	%	M	F	TOTAL	M	F	%	M	F	TOTAL
177	0	1	0	5/	5	100	9/10	90	14	5	9	90	4	4	8	4	4	80	0	0	0
198	0	0	0	8/	8	100	7/7	100	15	8	7	88	4	4	8	4	4	80	4	4	8
205	0	1	0	8/	8	100	7/8	88	15	8	7	88	4	4	8	4	4	80	4	4	8
208	0	0	0	6/	6	100	7/7	100	13	6	7	100	4	4	8	4	4	80	4	4	8
218	2	3	0	4/	6	67	8/11	73	12	4	7	73	4	4	8	4	4	80	4	4	8
239	0	0	0	9/	9	100	7/7	100	16	9	7	100	4	4	8	4	4	80	4	4	8
241	1	0	0	2/	3	67	5/5	100	7	2	5	100	2	5	7	2	5	71	2	5	7
242	2	0	0	7/	9	78	7/7	100	14	7	7	100	4	4	8	4	4	80	4	4	8
TOTAL	5	5	0	49/	54	57/	62	106	106	49	56	48	55	30	33	26	29	26	29	26	29

M = MALE, F = FEMALE, U = UNDETERMINED  
 NOTE: NUMBER DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX U  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP VIABILITY

GROUP 4: 30 MG/KG/DAY

DAM NO.	NO. DEAD DAY 0			NO. VIABLE DAY 0			TOTAL			BEFORE SELECTION DAY 4			AFTER SELECTION DAY 4			DAY 7			DAY 14			DAY 21		
	M	F	U	M	F	%	M	F	%	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
200	1	0	0	7/8	88	5/5	100	12	7	5	4	4	4	4	4	4	4	4	4	4	4	4	4	
207	2	0	0	8/10	80	4/4	100	12	8	4	4	4	4	4	4	4	4	4	4	4	4	4	4	
212	0	0	0	6/6	100	10/10	100	16	6	10	4	4	4	4	4	4	4	4	4	4	4	4	4	
217	1	0	0	5/6	83	10/10	100	15	5	10	4	4	4	4	4	4	4	4	4	4	4	4	4	
222	2	3	0	6/8	75	4/7	57	10	6	4	5	4	4	4	4	4	4	4	4	4	4	4	4	
230	0	0	0	6/6	100	7/7	100	13	6	7	4	4	4	4	4	4	4	4	4	4	4	4	4	
240	0	1	0	7/7	100	7/8	88	14	7	7	4	4	4	4	4	4	4	4	4	4	4	4	4	
TOTAL	6	4	0	45/51	51	47/51	51	92	45	47	44	47	28	28	28	28	28	28	28	28	28	28	28	28

M = MALE, F = FEMALE, U = UNDETERMINED  
 NOTE: NUMBER DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX U  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP VIABILITY

GROUP 5: 50 MG/KG/DAY

DAM NO.	NO. DEAD DAY 0			NO. VIABLE DAY 0			TOTAL			BEFORE SELECTION DAY 4			AFTER SELECTION DAY 4			DAY 7			DAY 14			DAY 21		
	M	F	U	M	F	%	M	F	%	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
194	1	2	0	3/	4	75	6/	8	75	9	3	6	3	5	3	5	3	5	3	5	3	5	3	5
199	0	0	0	2/	2	100	10/	10	100	12	2	9	2	9	2	6	2	6	2	6	2	6	2	6
202	0	0	0	7/	7	100	9/	9	100	16	7	9	7	9	4	4	4	4	4	4	4	4	4	4
215	1	0	0	4/	5	80	8/	8	100	12	4	8	4	8	4	4	4	4	4	4	4	4	4	4
216	0	0	0	7/	7	100	6/	6	100	13	7	6	7	6	4	4	4	4	4	4	4	4	4	4
226	0	0	0	6/	6	100	6/	6	100	12	6	6	6	6	4	4	4	4	4	4	4	4	4	4
232	0	0	0	5/	5	100	10/	10	100	15	5	10	5	10	4	4	4	4	4	4	4	4	4	4
TOTAL	2	2	0	34/	36	55/	57	89	34	54	34	54	25	31	25	31	25	31	25	31	25	31	25	31

M = MALE, F = FEMALE, U = UNDETERMINED  
 NOTE: NUMBER DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX U  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP VIABILITY

GROUP 6: 75 MG/KG/DAY

DAM NO.	NO. DEAD DAY 0			NO. VIABLE DAY 0			BEFORE SELECTION DAY 4			AFTER SELECTION DAY 4			DAY 7			DAY 14			DAY 21			
	M	F	U	M	F	%	M	F	%	M	F	%	M	F	%	M	F	%	M	F	%	
197	1	0	0	5/6	83	4/4	100	9	5	4	4	4	4	4	4	4	4	4	4	4	4	
210	2	0	0	11/13	85	3/3	100	14	11	3	5	3	5	3	5	3	5	3	5	3	5	
213	2	2	0	7/9	78	2/4	50	9	4	1	0	0	0	0	0	0	0	0	0	0	0	
220	0	2	0	6/6	100	8/10	80	14	6	8	4	4	4	4	4	4	4	4	4	4	4	
228	3	2	0	5/8	63	7/9	78	12	5	7	4	4	4	4	4	4	4	4	4	4	4	
235	0	0	0	8/8	100	3/3	100	11	8	3	5	3	5	3	5	3	5	3	5	3	5	
244	1	2	0	6/7	86	5/7	71	11	6	5	4	4	4	4	4	4	4	4	4	4	4	
245	3	2	1	0/3	0	0/2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
TOTAL	12	10	1	48/60	60	32/42	42	80	45	31	41	30	26	22	26	22	26	22	26	22	26	22

M = MALE, F = FEMALE, U = UNDETERMINED  
 NOTE: NUMBER DEAD = TOTAL PUPS FOUND DEAD, MISSING AND/OR CANNIBALIZED.

SLI Study No. 3472.3

APPENDIX V

Individual F1 Pup Observations during Lactation  
(Positive Findings)

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

APPENDIX V

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
192	2	M	CULLED ON SCHEDULED DAY	4
	4	M	CULLED ON SCHEDULED DAY	4
	5	M	SUBCUTANEOUS HEMORRHAGE(S) LEFT LATERAL HEAD	0
	7	M	CULLED ON SCHEDULED DAY	4
	8	M	CULLED ON SCHEDULED DAY	4
	10	F	CULLED ON SCHEDULED DAY COOL TO THE TOUCH PALE IN COLOR	0
			SUBCUTANEOUS HEMORRHAGE(S)	0
			ABDOMINAL REGION, RIGHT LATERAL HEAD	
			MISSING - PRESUMED CANNIBALIZED	1
		11	F	TAIL TIP ABSENT
196			SUBCUTANEOUS HEMORRHAGE(S) TAIL TIP	0
	12	F	CULLED ON SCHEDULED DAY	4
	13	F	CULLED ON SCHEDULED DAY	4
	15	F	CULLED ON SCHEDULED DAY	4
	1	F	FOUND DEAD	0
	2	M	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
	3	M	CULLED ON SCHEDULED DAY SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	4
	6	M	CULLED ON SCHEDULED DAY	4
	8	M	CULLED ON SCHEDULED DAY CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	(POSITIVE FINDINGS)	LACTATION DAY	
196	10	F	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA		0	
			SCAB(S)		0	
			TAIL TIP		0	
			TAIL TIP ABSENT		4	
			SCAB(S)		4	
			TAIL TIP		4	
			CULLED ON SCHEDULED DAY		4	
			TAIL TIP ABSENT		4	
		11	F	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA		0
			SCAB(S)		4	
206	12	F	VENTRAL THORACIC SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA		0	
			COOL TO THE TOUCH		4	
			CULLED ON SCHEDULED DAY		4	
		13	F	SUBCUTANEOUS HEMORRHAGE(S) ABDOMINAL REGION, LEFT HINDLIMB		0
			MISSING - PRESUMED CANNIBALIZED		1	
		15	F	CULLED ON SCHEDULED DAY		4
		1	M	CULLED ON SCHEDULED DAY		4
		4	M	CULLED ON SCHEDULED DAY		4
		5	M	CULLED ON SCHEDULED DAY		4
		6	M	CULLED ON SCHEDULED DAY		4
	9	M	PURPLE IN COLOR CULLED ON SCHEDULED DAY		0	
					4	

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
206	10	F	CULLED ON SCHEDULED DAY	4
	14	F	CULLED ON SCHEDULED DAY	4
	16	F	CULLED ON SCHEDULED DAY	4
219	1	M	SUBCUTANEOUS HEMORRHAGE(S) LEFT LATERAL HEAD	0
	4	M	CULLED ON SCHEDULED DAY	4
	5	M	SMALL IN SIZE COOL TO THE TOUCH CONSTRICTED AREA(S) M/D AND DISTAL TAIL	0
			FOUND DEAD	7
	6	F	CONSTRICTED AREA(S) M/D TAIL	10
			CONSTRICTED AREA(S) M/D-LATERAL TAIL	7
			CONSTRICTED AREA(S) M/D TAIL	14
			CONSTRICTED AREA(S) M/D TAIL	21
			SUBCUTANEOUS HEMORRHAGE(S) LEFT LATERAL AND VENTRAL HEAD	0
			CULLED ON SCHEDULED DAY	4
221	10	F	CULLED ON SCHEDULED DAY	4
	11	F	CULLED ON SCHEDULED DAY	4
	13	F	CULLED ON SCHEDULED DAY	4
	1	M	CULLED ON SCHEDULED DAY	4
	3	M	CULLED ON SCHEDULED DAY	4
	4	M	CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

PAGE 4

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
221	8	M	CULLED ON SCHEDULED DAY	4
	9	M	CULLED ON SCHEDULED DAY	4
	10	F	CULLED ON SCHEDULED DAY	4
	14	F	CULLED ON SCHEDULED DAY	4
	15	F	CULLED ON SCHEDULED DAY	4
	17	F	CULLED ON SCHEDULED DAY	4
	231	1	M	HAIRLOSS
2		M	SLIGHT	4
3		M	CULLED ON SCHEDULED DAY	14
4		M	HAIRLOSS	14
5		M	SLIGHT	14
6		M	HAIRLOSS	14
7		F	CULLED ON SCHEDULED DAY	4
8		F	SLIGHT	14
9		F	CULLED ON SCHEDULED DAY	4
10		F	CULLED ON SCHEDULED DAY	14
11		F	HAIRLOSS	4
12		F	SLIGHT	14
13		F	CULLED ON SCHEDULED DAY	4
14		F	CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
231	15	F	CULLED ON SCHEDULED DAY	4
	16	F	HAIRLOSS	14
	17	F	SLIGHT CULLED ON SCHEDULED DAY	4
233	1	M	CULLED ON SCHEDULED DAY	4
	2	M	CULLED ON SCHEDULED DAY	4
	5	M	CULLED ON SCHEDULED DAY	4
	6	M	SCAB(S)	4
			RIGHT HINDLIMB	
	8	F	CULLED ON SCHEDULED DAY SUBCUTANEOUS HEMORRHAGE(S) TAIL TIP	4 0
237			SCAB(S)	4
			TAIL TIP	7
			SCAB(S)	
			TAIL TIP	
			TAIL TIP	
	10	F	CULLED ON SCHEDULED DAY	4
	11	F	CULLED ON SCHEDULED DAY	4
	12	F	SCAB(S)	4
			RIGHT HINDLIMB	
	14	F	CULLED ON SCHEDULED DAY	4
15	F	CULLED ON SCHEDULED DAY	4	
237	1	M	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
			CULLED ON SCHEDULED DAY	4
	2	M	CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 1: 0 MG/KG/DAY

(POSITIVE FINDINGS)

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
237	3	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	8	M	CULLED ON SCHEDULED DAY	4
	9	M	CONSTRICTED AREA(S) DISTAL TAIL	7
			CONSTRICTED AREA(S)	14
			DISTAL TAIL	21
			CONSTRICTED AREA(S) DISTAL TAIL	
			DISTAL TAIL	
	10	M	CULLED ON SCHEDULED DAY	4
	11	M	CULLED ON SCHEDULED DAY	4
	12	F	CULLED ON SCHEDULED DAY	4
	13	F	CANNIBALIZED	7

APPEARED OTHERWISE NORMAL

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 2: 10 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY	
195	1	M	SUBCUTANEOUS HEMORRHAGE(S) TAIL	0	
	2	M	CULLED ON SCHEDULED DAY SUBCUTANEOUS HEMORRHAGE(S) RIGHT LATERAL HEAD	4	
	3	M	LACERATION(S) ABDOMINAL REGION	0	
	5	M	CULLED ON SCHEDULED DAY	4	
	7	M	CULLED ON SCHEDULED DAY	4	
	9	F	CULLED ON SCHEDULED DAY	4	
	12	F	CULLED ON SCHEDULED DAY	4	
	14	F	CULLED ON SCHEDULED DAY	4	
	15	F	CULLED ON SCHEDULED DAY	4	
	224	1	M	CULLED ON SCHEDULED DAY	4
		2	M	CULLED ON SCHEDULED DAY	4
		3	M	CULLED ON SCHEDULED DAY	4
		8	M	CULLED ON SCHEDULED DAY	4
		9	F	CULLED ON SCHEDULED DAY	4
		11	F	CULLED ON SCHEDULED DAY	4
12		F	CULLED ON SCHEDULED DAY	4	
13		F	CULLED ON SCHEDULED DAY	4	
15		F	CULLED ON SCHEDULED DAY	4	
16		F	CULLED ON SCHEDULED DAY	4	
229		1	M	CANNIBALIZED APPEARS NORMAL	0

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 2: 10 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
229	2	M	CANNIBALIZED	0
			APPEARS NORMAL	
	3	M	CANNIBALIZED	0
			APPEARS NORMAL	
	4	M	CANNIBALIZED	0
			APPEARS NORMAL	
	5	M	CANNIBALIZED	0
			APPEARS NORMAL	
	6	F	CANNIBALIZED	0
			APPEARS NORMAL	
234	7	F	CANNIBALIZED	0
			APPEARS NORMAL	
	8	F	CANNIBALIZED	0
			APPEARS NORMAL	
	9	a	CANNIBALIZED	0
			APPEARS NORMAL	
	10	a	CANNIBALIZED	0
			APPEARS NORMAL	
	1	M	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
	2	M	CULLED ON SCHEDULED DAY	4
	3	M	CULLED ON SCHEDULED DAY	4
	10	F	CULLED ON SCHEDULED DAY	4
	11	F	CULLED ON SCHEDULED DAY	4
13	F	CULLED ON SCHEDULED DAY	4	

a SEX OF PUP COULD NOT BE DETERMINED DUE TO CANNIBALIZATION.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

APPENDIX V

PAGE 9

GROUP 2: 10 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY	
236	1	M	FOUND DEAD	0	
	2	F	FOUND DEAD	0	
	4	M	CULLED ON SCHEDULED DAY	4	
	5	M	CULLED ON SCHEDULED DAY	4	
	9	M	CULLED ON SCHEDULED DAY	4	
	10	M	CULLED ON SCHEDULED DAY	4	
	11	F	CULLED ON SCHEDULED DAY	4	
	12	F	CULLED ON SCHEDULED DAY	4	
	13	F	SCAB(S)	4	
			LEFT FORELIMB		
			CULLED ON SCHEDULED DAY	4	
	238	5	F	CULLED ON SCHEDULED DAY	4
		6	F	CULLED ON SCHEDULED DAY	4
7		F	CULLED ON SCHEDULED DAY	4	
8		F	SCAB(S)	4	
			LEFT PINNA		
			CULLED ON SCHEDULED DAY	4	
			SCAB(S)	4	
			DORSAL HEAD		
243	14	F	CULLED ON SCHEDULED DAY	4	
	1	M	CULLED ON SCHEDULED DAY	4	
	2	M	CULLED ON SCHEDULED DAY	4	
	5	M	SUBCUTANEOUS HEMORRHAGE(S) NOSE	0	
			CULLED ON SCHEDULED DAY	4	



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 2: 10 MG/KG/DAY

(POSITIVE FINDINGS)

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
243	6	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	11	F	CULLED ON SCHEDULED DAY	4
	13	F	CULLED ON SCHEDULED DAY	4
	14	F	SUBCUTANEOUS HEMORRHAGE(S) TAIL TIP	0
	15	F	CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 3: 20 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
177	1	F	FOUND DEAD	0
	3	M	CULLED ON SCHEDULED DAY	4
	7	F	CULLED ON SCHEDULED DAY	4
	8	F	CULLED ON SCHEDULED DAY	4
	9	F	SCAB(S)	4
			AROUND MOUTH	
	12	F	CULLED ON SCHEDULED DAY	4
	13	F	CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
198	1	M	CULLED ON SCHEDULED DAY	4
	2	M	CULLED ON SCHEDULED DAY	4
	3	M	CULLED ON SCHEDULED DAY	4
	8	M	CULLED ON SCHEDULED DAY	4
	11	F	CULLED ON SCHEDULED DAY	4
	12	F	CULLED ON SCHEDULED DAY	4
	14	F	CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
205	1	F	FOUND DEAD	0
	2	M	LACERATION(S)	0
			RIGHT HINDLIMB	
	3	M	CULLED ON SCHEDULED DAY	4
	5	M	CULLED ON SCHEDULED DAY	4
	6	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	10	F	LACERATION(S)	0
			FACIAL AREA	
			CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

APPENDIX V

GROUP 3: 20 MG/KG/DAY

(POSITIVE FINDINGS)

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
205	15	F	CULLED ON SCHEDULED DAY	4
	16	F	CULLED ON SCHEDULED DAY	4
208	2	M	CULLED ON SCHEDULED DAY	4
	5	M	CULLED ON SCHEDULED DAY	4
	7	F	CULLED ON SCHEDULED DAY	4
	9	F	SUBCUTANEOUS HEMORRHAGE(S) AROUND MOUTH	0
	12	F	CULLED ON SCHEDULED DAY	4
218	13	F	CULLED ON SCHEDULED DAY	4
	1	M	FOUND DEAD	0
	2	M	FOUND DEAD	0
	3	F	FOUND DEAD	0
	4	F	FOUND DEAD	0
	5	F	FOUND DEAD	0
	7	M	SUBCUTANEOUS HEMORRHAGE(S) DORSAL HEAD	4
218			SUBCUTANEOUS HEMORRHAGE(S) ABDOMINAL REGION	7
	10	F	CULLED ON SCHEDULED DAY	4
	11	F	CULLED ON SCHEDULED DAY	4
	12	F	SUBCUTANEOUS HEMORRHAGE(S) LEFT PINNA	4
218	15	F	CULLED ON SCHEDULED DAY	4
	16	F	PURPLE IN COLOR	0
			COOL TO THE TOUCH FOUND DEAD	0
			FOUND DEAD	1

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 3: 20 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
218	17	F	SMALL IN SIZE	0
239	1	M	CULLED ON SCHEDULED DAY	4
	3	M	CULLED ON SCHEDULED DAY	4
	4	M	CULLED ON SCHEDULED DAY	4
	5	M	CULLED ON SCHEDULED DAY	4
	6	M	CULLED ON SCHEDULED DAY	4
	12	F	SUBCUTANEOUS HEMORRHAGE(S) TAIL TIP	0
241	13	F	CULLED ON SCHEDULED DAY	4
	14	F	CULLED ON SCHEDULED DAY	4
	15	F	CULLED ON SCHEDULED DAY	4
	4	F	FOUND DEAD SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
242	1	M	FOUND DEAD	0
	2	M	FOUND DEAD	0
	3	M	HAIRLOSS SLIGHT	14
			HAIRLOSS	21
			SLIGHT	14
			SLIGHT	21
			SLIGHT	2
	5	M	MISSING - PRESUMED CANNIBALIZED	

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 3: 20 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
242	6	M	HAIRLOSS	14
			SLIGHT	
			HAIRLOSS	21
	7	M	SLIGHT	
	8	M	CULLED ON SCHEDULED DAY	4
	9	M	CULLED ON SCHEDULED DAY	4
			HAIRLOSS	14
			SLIGHT	
			HAIRLOSS	21
	10	F	SLIGHT	
	11	F	CULLED ON SCHEDULED DAY	4
			HAIRLOSS	14
			SLIGHT	
			HAIRLOSS	21
	12	F	SLIGHT	
		PALE IN COLOR	0	
		SMALL IN SIZE	0	
		COOL TO THE TOUCH	0	
13	F	MISSING - PRESUMED CANNIBALIZED	2	
		HAIRLOSS	14	
		SLIGHT		
		HAIRLOSS	21	
14	F	SLIGHT		
		HAIRLOSS	14	
		SLIGHT		
		HAIRLOSS	21	
15	F	SLIGHT		
		HAIRLOSS	14	
		SLIGHT		

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX V  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 3: 20 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
242	15	F	HAIRLOSS	21
	16	F	SLIGHT CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

PAGE 16

GROUP 4: 30 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
200	1	M	FOUND DEAD	0
	2	M	CULLED ON SCHEDULED DAY	4
	3	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
207	13	F	CULLED ON SCHEDULED DAY	4
	1	M	FOUND DEAD	0
	2	M	FOUND DEAD	0
	4	M	CULLED ON SCHEDULED DAY	4
212	5	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	8	M	SUBCUTANEOUS HEMORRHAGE(S) NOSE	0
	9	M	SUBCUTANEOUS HEMORRHAGE(S) NOSE	0
217	10	M	CULLED ON SCHEDULED DAY	4
	4	M	CULLED ON SCHEDULED DAY	4
	6	M	CULLED ON SCHEDULED DAY	4
	7	F	CULLED ON SCHEDULED DAY	4
	10	F	CULLED ON SCHEDULED DAY	4
	13	F	CULLED ON SCHEDULED DAY	4
	14	F	CULLED ON SCHEDULED DAY	4
	15	F	CULLED ON SCHEDULED DAY	4
	16	F	CULLED ON SCHEDULED DAY	4
	1	M	FOUND DEAD	0
	6	M	CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 4: 30 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	(POSITIVE FINDINGS)	LACTATION DAY	
217	7	F	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA		0	
	8	F	CULLED ON SCHEDULED DAY		4	
		F	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA		0	
	9	F	CULLED ON SCHEDULED DAY		4	
	10	F	CULLED ON SCHEDULED DAY		4	
	11	F	CULLED ON SCHEDULED DAY		4	
	12	F	CULLED ON SCHEDULED DAY		4	
	13	F	CULLED ON SCHEDULED DAY		4	
	222	1	M	FOUND DEAD		0
		2	M	FOUND DEAD		0
		3	F	FOUND DEAD		0
		4	F	FOUND DEAD		0
		5	F	FOUND DEAD		0
7		M	CULLED ON SCHEDULED DAY		4	
8		M	PURPLE IN COLOR		0	
13		F	MISSING - PRESUMED CANNIBALIZED		2	
		F	BENT TAIL		21	
		F	MID-TAIL		0	
14		F	SUBCUTANEOUS HEMORRHAGE(S) AROUND MOUTH		0	
230		2	M	CULLED ON SCHEDULED DAY		4
		3	M	CULLED ON SCHEDULED DAY		4
	9	F	CULLED ON SCHEDULED DAY		4	
	10	F	CULLED ON SCHEDULED DAY		4	



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 4: 30 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
230	13	F	CULLED ON SCHEDULED DAY	4
240	1	F	FOUND DEAD	0
	2	M	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
	3	M	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
	4	M	CULLED ON SCHEDULED DAY SUBCUTANEOUS HEMORRHAGE(S) RIGHT HINDLIMB	4
	5	M	SCAB(S) TAIL TIP	0
	6	M	CULLED ON SCHEDULED DAY	4
	8	M	CULLED ON SCHEDULED DAY	4
	9	F	LACERATION(S) DORSAL HEAD AND THORACIC SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
	10	F	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
	11	F	CULLED ON SCHEDULED DAY SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	4
	13	F	CULLED ON SCHEDULED DAY	4
	15	F	CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 5: 50 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
194	1	M	FOUND DEAD	0
			APPARENT EXTERNAL MALFORMATIONS	
	2	F	FOUND DEAD	0
			APPARENT EXTERNAL MALFORMATIONS	
	3	F	FOUND DEAD	0
	7	F	LACERATION(S) LEFT LATERAL HEAD	0
			LACERATION(S) LEFT LATERAL ABDOMINAL	4
			SCAB(S) LEFT LATERAL HEAD	4
			SCAB(S) LEFT LATERAL ABDOMINAL	7
			SCAB(S) LEFT LATERAL ABDOMINAL	14
199	10	F	SCAB(S) LEFT LATERAL ABDOMINAL CULLED ON SCHEDULED DAY	21
			SCAB(S) LEFT LATERAL ABDOMINAL	4
	1	M	SCAB(S) LEFT LATERAL ABDOMINAL	7
			SCAB(S) LEFT LATERAL ABDOMINAL	14
	3	F	CULLED ON SCHEDULED DAY	4
	4	F	MISSING - PRESUMED CANNIBALIZED	1
	5	F	SCAB(S) LEFT CORNER OF MOUTH CULLED ON SCHEDULED DAY	14
	6	F	CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 5: 50 MG/KG/DAY

(POSITIVE FINDINGS)

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
199	11	F	CULLED ON SCHEDULED DAY	4
	3	M	CULLED ON SCHEDULED DAY	4
202	5	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	8	F	CULLED ON SCHEDULED DAY	4
	12	F	CULLED ON SCHEDULED DAY	4
	14	F	CULLED ON SCHEDULED DAY	4
	15	F	CULLED ON SCHEDULED DAY	4
	16	F	CULLED ON SCHEDULED DAY	4
	1	M	PALE IN COLOR	0
215			GASPING	0
			FOUND DEAD	0
	6	F	CULLED ON SCHEDULED DAY	4
	7	F	CULLED ON SCHEDULED DAY	4
	8	F	CULLED ON SCHEDULED DAY	4
	13	F	CULLED ON SCHEDULED DAY	4
	1	M	SUBCUTANEOUS HEMORRHAGE(S) FACIAL AREA	0
216	4	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	8	F	SCAB(S) FACIAL AREA	0
			CULLED ON SCHEDULED DAY	4
	12	F	CULLED ON SCHEDULED DAY	4

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 5: 50 MG/KG/DAY

(POSITIVE FINDINGS)

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
226	2	M	CULLED ON SCHEDULED DAY	4
	5	M	CULLED ON SCHEDULED DAY	4
	7	F	CULLED ON SCHEDULED DAY	4
	12	F	CULLED ON SCHEDULED DAY	4
232	3	M	CULLED ON SCHEDULED DAY	4
	6	F	SUBCUTANEOUS HEMORRHAGE(S) ABDOMINAL REGION	0
	7	F	CULLED ON SCHEDULED DAY	4
			SCAB(S)	4
	8	F	ANTERIOR DORSAL CULLED ON SCHEDULED DAY	4
			SUBCUTANEOUS HEMORRHAGE(S) AROUND MOUTH	0
			CULLED ON SCHEDULED DAY	4
	9	F	CULLED ON SCHEDULED DAY	4
CULLED ON SCHEDULED DAY			4	
CULLED ON SCHEDULED DAY			4	
12	F	CULLED ON SCHEDULED DAY	4	

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 6: 75 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
197	1	M	FOUND DEAD	0
	2	M	SUBCUTANEOUS HEMORRHAGE(S) LEFT HINDLIMB, RIGHT HINDLIMB CULLED ON SCHEDULED DAY	4
	3	M	SMALL IN SIZE	0
	7	F	SUBCUTANEOUS HEMORRHAGE(S) LEFT LATERAL HEAD, FACIAL AREA	0
	1	M	FOUND DEAD	0
	2	M	FOUND DEAD	0
	5	M	SUBCUTANEOUS HEMORRHAGE(S) RIGHT FORELIMB, RIGHT HINDLIMB, TAIL LACERATION(S) RIGHT FORELIMB	4
210	8	M	CULLED ON SCHEDULED DAY	4
	9	M	CULLED ON SCHEDULED DAY	4
	11	M	CULLED ON SCHEDULED DAY	4
	12	M	CULLED ON SCHEDULED DAY	4
	13	M	CULLED ON SCHEDULED DAY	4
	14	F	SCAB(S) ABDOMINAL REGION	4
	1	M	FOUND DEAD	0
	2	M	FOUND DEAD	0
	3	F	FOUND DEAD	0
	4	F	FOUND DEAD	0
	5	M	COOL TO THE TOUCH	0

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX V  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 6: 75 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
213	5	M	FOUND DEAD	1
	6	M	COOL TO THE TOUCH	0
			FOUND DEAD	1
	7	M	COOL TO THE TOUCH	0
			FOUND DEAD	2
	8	M	COOL TO THE TOUCH	0
			FOUND DEAD	2
	9	M	COOL TO THE TOUCH	0
			FOUND DEAD	2
	10	M	COOL TO THE TOUCH	0
			FOUND DEAD	1
	11	M	COOL TO THE TOUCH	0
			FOUND DEAD	2
220	12	F	COOL TO THE TOUCH	0
			FOUND DEAD	2
	13	F	COOL TO THE TOUCH	0
			FOUND DEAD	1
	1	F	FOUND DEAD	0
	2	F	FOUND DEAD	0
	4	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	9	F	CULLED ON SCHEDULED DAY	4
	10	F	CULLED ON SCHEDULED DAY	4
228	13	F	CULLED ON SCHEDULED DAY	4
	16	F	CULLED ON SCHEDULED DAY	4
	1	M	FOUND DEAD	0

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX V  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

GROUP 6: 75 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
228	2	M	FOUND DEAD	0
	3	M	FOUND DEAD	0
	4	F	FOUND DEAD	0
	5	F	FOUND DEAD	0
	6	M	CULLED ON SCHEDULED DAY	4
	9	M	APPARENT UMBILICAL HERNIA	14
	11	F	GASPING	0
			CULLED ON SCHEDULED DAY	4
	12	F	PALE IN COLOR	0
			CULLED ON SCHEDULED DAY	4
		14	F	CULLED ON SCHEDULED DAY
235	6	M	CULLED ON SCHEDULED DAY	4
	7	M	CULLED ON SCHEDULED DAY	4
	8	M	CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
244	1	M	CANNIBALIZED	0
			APPEARS NORMAL	
	2	F	FOUND DEAD	0
	3	F	FOUND DEAD	0
	4	M	CULLED ON SCHEDULED DAY	4
	9	M	CULLED ON SCHEDULED DAY	4
	10	F	CULLED ON SCHEDULED DAY	4
			CULLED ON SCHEDULED DAY	4
	1	M	FOUND DEAD	0
	2	M	CANNIBALIZED	0
245			APPEARS NORMAL	
	3	F	FOUND DEAD	0
			FOUND DEAD	0

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX V  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP OBSERVATIONS DURING LACTATION

PAGE 25

GROUP 6: 75 MG/KG/DAY

DAM NO.	PUP NO.	SEX	PUP GROSS OBSERVATION	LACTATION DAY
245	4	F	CANNIBALIZED APPEARS NORMAL	0
	5	a	CANNIBALIZED APPEARS NORMAL	0
	6	M	GASPING COOL TO THE TOUCH FOUND DEAD	0 0 0

a SEX OF PUP COULD NOT BE DETERMINED DUE TO CANNIBALIZATION.



SLI Study No. 3472.3

APPENDIX W

Individual F1 Pup Weights during Lactation

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 1  
 DAY 1

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
192	6.0	5.7	6.5	6.0	6.1	6.5	6.4	5.8	6.3	6.4	D	6.2	6.2	5.4	5.5	5.4	5.9	5.7						
196	6.8	D	6.9	7.4	6.6	7.2	7.3	6.9	6.8	7.0	6.2	6.5	6.9	D	6.7	7.0	6.1	6.4						
206	6.9	7.2	7.8	7.5	7.7	6.8	6.8	6.5	7.6	7.1	6.7	6.1	6.4	5.3	7.3	6.7	6.5							
219	6.8	7.6	6.8	7.1	7.3	5.3	6.7	6.2	7.1	6.7	6.6	7.3	6.6	6.8										
221	6.0	6.1	6.2	6.1	6.3	6.5	6.6	6.4	5.7	6.6	5.8	6.2	6.0	5.8	5.2	5.6	6.1	5.1						
231	6.8	6.7	6.9	8.1	6.7	6.7	7.0	7.1	6.3	6.9	6.7	6.5	6.5	6.1	7.4	6.8	6.6	7.2						
233	6.8	7.0	6.8	6.8	7.1	7.1	6.7	6.9	6.6	6.8	7.2	6.6	6.5	7.1	6.9	6.5	6.4							
237	6.3	7.7	6.0	5.6	6.2	6.9	7.0	6.3	5.9	6.2	6.2	6.7	6.2	6.2	5.7	5.7	6.2							
MEAN																								
S.D.																								
N																								

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 2: 10 MG/RG/DAY

PAGE 2  
 DAY 1

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
188	9.7	10.3	8.8	9.4	9.7	9.6	10.3																	
195	6.6	6.7	6.9	6.2	6.5	7.9	6.9	7.0	7.8	6.7	6.4	6.3	6.8	6.4	5.8	5.9	6.0							
224	6.3	5.9	7.3	6.8	6.7	6.5	6.6	6.8	6.1	5.7	6.0	6.8	6.7	6.3	5.3	5.5	6.1	6.0	5.8					
234	7.1	7.4	7.1	7.6	7.6	7.0	7.4	7.4	7.4	6.9	6.4	6.2	6.9	7.4	6.9									
236	7.7	D	D	7.3	8.3	7.2	7.3	7.4	8.2	8.0	7.8	8.1	7.5	7.7	7.4	8.2	7.6	7.0						
238	6.2	6.6	6.4	6.5	5.9	6.0	6.2	6.3	6.3	6.2	6.5	6.0	6.2	5.7	6.2									
243	6.6	6.7	6.8	6.9	6.7	6.5	6.9	6.1	6.5	6.7	6.2	6.6	7.0	6.7	6.7	6.2	6.0	6.2						
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 3: 20 MG/RG/DAY

PAGE 3  
 DAY 1

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
177	6.8	D	6.7	7.7	7.0	7.0	6.7	7.6	6.7	6.8	6.7	6.9	6.6	6.4	6.7	6.2								
198	6.8	7.4	6.2	6.8	7.4	6.9	6.4	7.0	7.1	6.8	7.0	6.0	6.5	6.8	7.3	6.3								
205	5.9	D	5.9	5.7	6.1	6.6	6.0	5.3	5.8	5.6	6.6	5.3	5.9	6.2	5.6	6.3	5.6							
208	7.1	7.2	7.9	8.0	7.3	6.5	7.5	7.2	6.5	6.8	7.4	7.1	6.8	6.4										
218	4.9	D	D	D	D	D	5.1	3.8	5.8	5.3	5.1	5.5	5.2	4.3	5.4	5.5	D	3.2						
239	6.8	7.5	8.0	6.1	5.8	7.0	7.4	7.0	6.1	7.1	6.6	7.0	6.7	6.4	6.0	7.0	6.8							
241	6.3	D	5.9	6.5	5.9	6.5	6.1	7.3	5.8															
242	6.2	D	D	6.0	5.9	5.8	6.0	5.7	7.2	7.4	6.9	6.5	3.8	7.0	6.0	6.3	6.8							
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 4: 30 MG/RG/DAY

PAGE 4  
 DAY 1

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
200	7.6	D	7.7	6.8	7.9	7.8	7.2	7.9	7.9	8.0	8.1	7.5	6.9	7.1										
207	7.5	D	7.7	7.1	7.3	8.3	8.0	7.6	7.2	7.8	7.4	7.4	7.3	7.4	6.9									
212	6.6	6.4	6.3	7.1	7.0	7.3	7.0	6.5	6.4	6.5	5.6	7.6	6.7	7.1	5.8	6.5	6.3							
217	6.3	D	7.0	6.4	6.4	6.8	6.8	6.2	6.0	6.8	6.4	6.0	5.4	6.3	7.2	4.8	6.1							
222	6.9	D	D	D	D	D	7.5	6.8	5.6	6.9	7.7	7.5	6.7	6.7	7.3	6.6								
230	7.3	7.5	7.7	7.9	7.6	7.6	7.0	7.2	7.1	6.4	7.3	7.3	7.3	7.3										
240	7.1	D	6.6	7.3	7.5	7.4	7.9	6.9	7.3	7.2	6.3	6.4	6.8	7.0	7.0	7.4								
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 5  
 DAY 1

GROUP 5: 50 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
194	7.1	D	7.3	D	6.7	7.8	7.8	7.0	6.0	7.2	6.1	7.6	7.5											
199	7.4	7.3	7.9	6.2	D	7.4	7.9	7.5	7.1	7.6	7.1	7.2	7.8											
202	6.8	6.7	6.7	6.6	7.2	6.9	7.3	6.7	6.7	6.2	7.2	6.2	6.4	6.7	6.5	6.8	7.5							
215	6.8	D	7.0	7.1	6.8	6.5	6.6	6.5	6.5	7.0	6.4	6.7	7.3	7.4										
216	7.7	7.9	8.4	6.8	8.4	8.0	8.2	8.4	6.9	8.1	7.5	7.1	7.7	7.0										
226	7.0	8.1	7.1	7.2	7.4	6.9	6.8	6.3	6.6	6.5	7.5	6.9	7.0											
232	7.3	7.7	8.3	7.6	7.7	7.4	6.0	7.4	6.9	7.3	7.2	7.0	7.2	7.5	7.6	7.3								
MEAN	7.2																							
S. D.	0.33																							
N	7																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 6: 75 MG/RG/DAY

PAGE 6  
 DAY 1

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
197	6.6	D	7.3	4.7	7.4	7.5	6.9	5.4	6.7	6.5	7.0													
210	7.8	D	D	8.4	7.4	8.6	7.8	8.4	8.7	8.1	7.7	6.3	8.1	6.8	8.2	7.8	7.3							
213	5.8	D	D	D	D	D	D	5.5	6.1	5.7	D	5.7	6.0	D										
220	7.1	D	D	7.5	7.8	7.2	7.1	7.1	7.6	6.9	6.5	6.8	6.9	7.0	7.8	6.9	6.4							
228	5.5	D	D	D	D	D	D	5.5	6.0	6.5	5.1	4.7	4.8	6.4	6.5	4.6	4.9	5.5						
235	7.3	7.6	7.9	7.5	7.7	6.6	7.3	7.5	7.2	7.1	6.7	6.7												
244	6.4	D	D	D	6.4	7.0	6.1	5.9	7.0	6.9	6.6	6.3	5.8	6.2	5.8									
245	NA	D	D	D	D	D	D																	
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP NA = NOT APPLICABLE

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 1: 0 MG/KG/DAY

PAGE 7  
 DAY 4

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
	MEAN																								
192	8.3	7.5	9.2	7.7	8.6	8.7	8.6	7.4	8.7	9.5	D	7.5	9.1	7.7	7.8	7.5	8.1	8.9							
196	9.6	D	9.5	10.5	9.9	10.6	11.1	9.4	9.3	9.7	8.4	9.4	9.1	D	9.0	9.2	9.1	9.0							
206	10.0	10.4	10.9	10.7	11.0	8.8	10.0	10.2	10.8	10.0	10.1	8.8	10.2	8.6	9.8	9.7	9.4								
219	9.0	9.7	8.9	9.3	9.7	6.6	9.2	8.2	9.4	9.1	9.3	10.0	8.6	9.4											
221	8.9	9.2	9.5	10.2	9.7	9.1	10.1	9.8	8.5	9.5	8.8	9.1	8.1	8.3	7.5	8.1	9.0	7.3							
231	9.4	9.3	9.8	10.4	9.4	8.5	10.0	9.7	8.5	8.9	8.3	9.1	9.2	9.0	10.3	9.8	9.1	10.1							
233	9.5	9.5	9.5	9.9	10.2	9.9	9.5	9.1	8.9	10.3	9.7	9.5	9.4	9.0	9.9	8.6	9.2								
237	9.2	10.5	8.7	7.9	9.7	9.6	9.6	9.1	8.8	8.9	9.3	9.4	9.5	9.3	9.0	7.9	9.6								
MEAN		9.2																							
S.D.		0.52																							
N		8																							

D = DEAD PUP



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 2: 10 MG/RG/DAY

PAGE 8  
 DAY 4

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
188	14.6	15.2	13.4	14.2	14.5	14.6	15.4																	
195	9.0	9.2	9.4	8.7	9.2	10.1	9.2	9.8	10.3	9.1	8.1	8.3	9.0	9.0	7.7	8.1	8.0							
224	8.6	8.2	9.9	9.1	9.2	9.5	9.3	9.5	8.4	8.2	8.9	8.1	8.9	9.1	5.9	8.5	8.1	7.9	8.3					
234	11.0	11.1	10.6	11.4	12.2	10.8	10.9	11.7	11.0	11.1	10.5	10.1	10.8	11.2	10.6									
236	11.0	D	10.6	11.5	10.7	10.9	11.4	11.1	11.1	10.6	11.8	10.8	10.9	11.1	11.1	10.8	10.6							
238	9.0	9.5	9.6	7.8	9.2	8.8	8.3	9.1	9.0	9.3	9.1	9.0	8.7	9.3										
243	9.4	10.2	9.6	10.4	10.2	9.2	10.0	8.4	9.6	10.0	8.8	9.8	9.2	9.9	9.2	9.4	7.7	8.6						
	MEAN	10.4																						
	S. D.	2.10																						
	N	7																						

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 3: 20 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
177	9.4	D	9.4	9.8	9.6	10.0	9.5	10.8	9.3	9.6	9.1	9.4	8.4	9.3	8.5	8.6								
198	9.4	10.0	8.9	9.6	9.5	10.5	8.9	10.1	9.6	8.9	9.8	8.5	8.9	9.5	9.5	8.9								
205	8.2	D	8.7	8.3	8.3	8.7	8.6	8.0	8.5	7.7	8.7	7.0	7.8	9.0	7.7	8.5	7.3							
208	10.3		9.9	11.4	11.0	10.3	8.7	10.8	10.6	9.8	10.0	11.1	10.3	10.0	9.5									
218	8.1	D	D	D	D	D	8.4	6.7	9.4	8.8	8.3	8.9	8.4	6.5	9.1	9.0	D	5.2						
239	9.0		9.8	10.5	8.6	7.2	9.3	10.2	9.6	8.5	8.8	8.7	8.4	6.5	9.1	9.0	D	5.2						
241	10.4	D	9.1	10.9	10.1	10.8	10.3	11.6	10.2															
242	10.1	D	D	9.2	9.5	D	9.6	8.2	11.4	11.0	10.8	9.8	D	11.1	9.6	9.9	10.8							
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 10  
 DAY 4

GROUP 4: 30 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
200	11.3	D	11.9	10.2	11.3	11.3	10.8	11.9	11.7	11.5	12.1	11.5	10.6	10.7										
207	10.9	D	D	11.0	10.4	11.2	11.3	11.5	11.2	11.2	10.2	11.0	11.2	10.9	10.1									
212	9.2	9.4	8.4	9.7	9.8	10.6	9.2	9.1	8.8	8.8	8.0	10.3	9.3	9.7	8.0	9.2	8.6							
217	8.3	D	10.0	8.7	8.2	9.1	8.3	7.9	6.4	9.0	8.7	8.0	7.6	8.7	9.0	7.2	8.2							
222	8.7	D	D	D	D	D	8.7	8.8	D	7.5	9.4	9.5	8.4	7.7	9.3	8.6								
230	10.2	10.4	10.2	11.1	10.4	10.6	9.1	10.3	10.2	9.2	10.3	9.8	10.3	10.1										
240	10.2	D	9.3	10.8	10.9	11.2	10.9	10.0	10.3	11.0	8.5	9.5	9.6	9.7	10.7	10.4								
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 5: 50 MG/RG/DAY  
 PAGE 11  
 DAY 4

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
194	9.8	D	D	D	8.7	10.3	11.0	9.8	8.1	10.3	8.2	10.8	10.7											
199	10.5	10.7	11.1	8.8	D	10.7	11.2	10.8	10.2	10.9	10.1	10.2	10.4											
202	9.8	9.0	9.7	8.9	10.4	9.6	10.2	14.1	9.9	8.7	9.8	8.7	9.7	9.7	9.8	8.8	10.4							
215	10.4	D	10.9	10.8	10.2	10.0	10.0	10.3	10.1	10.7	10.1	9.9	10.5	11.1										
216	11.0	10.5	12.5	10.1	11.3	11.0	11.4	11.7	10.1	11.2	11.1	10.4	10.9	10.1										
226	9.0	10.5	9.1	8.4	9.5	8.4	8.9	8.4	8.2	8.2	9.5	9.0	9.4											
232	10.8	11.4	11.9	11.1	11.2	11.2	9.2	10.9	10.3	10.6	10.2	9.8	10.9	10.8	11.0	10.8								
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 6: 75 MG/RG/DAY  
 PAGE 12  
 DAY 4

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
197	9.8	D	11.0	7.5	10.9	10.3	10.1	8.0	9.7	9.8	10.6													
210	11.8	D	12.5	11.0	12.4	11.7	12.4	12.8	12.0	12.0	9.5	12.2	10.5	12.5	11.6	11.5								
220	9.9	D	9.7	9.9	10.1	10.1	10.8	10.4	10.3	9.1	9.8	9.0	9.6	10.9	10.7	8.5								
228	8.4	D	D	D	D	D	9.1	9.0	9.6	7.9	7.4	7.6	7.2	9.2	9.4	7.3	7.3	9.4						
235	10.5	10.9	11.4	10.8	11.2	9.6	10.5	10.3	10.8	10.1	10.1	9.7												
244	10.1	D	D	10.0	11.2	9.9	9.9	9.1	10.9	11.0	10.1	10.1	9.7	10.0	9.3									
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 13  
 DAY 7

GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
192	13.8	12.4	C	13.6	C	C	14.5	C	C	15.9	D	13.5	C	C	12.9	C	12.7	14.5						
196	15.5	D	C	15.8	16.4	C	14.4	C	16.1	C	15.3	C	D	15.4	C	15.2	15.0							
206	17.3	C	19.4	18.4	C	C	17.4	18.5	C	15.3	C	15.9	17.8	14.7	C	16.6	C							
219	14.7	16.6	15.4	16.2	C	9.0	15.8	14.7	C	15.3	C	C	14.7	C										
221	15.0	C	16.0	C	C	14.8	16.1	15.9	C	C	C	15.3	13.3	13.8	C	C	14.7	C						
231	15.2	14.5	C	16.9	15.3	14.1	C	15.9	C	14.7	C	15.3	C	C	C	C	15.2	C						
233	15.8	C	C	16.4	17.2	C	C	15.3	14.7	17.1	C	C	15.6	14.9	C	C	14.9							
237	14.9	C	C	C	15.7	15.4	15.9	C	C	13.7	C	C	C	D	14.4	13.2	15.8							
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 14  
 DAY 7

GROUP 2: 10 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
188	21.4	22.2	20.1	20.7	21.6	21.2	22.6																	
195	15.3	C	16.7	C	15.7	C	16.3	C	17.2	C	14.0	14.3	C	15.0	C	C	13.5							
224	15.1	C	C	C	16.8	16.7	16.5	16.1	C	C	15.8	C	C	C	10.7	C	C	13.3	14.6					
234	18.4	C	C	C	20.4	17.7	18.2	19.2	18.9	18.3	C	C	17.6	C	16.9									
236	18.4	D	D	17.9	C	C	18.0	18.7	19.2	C	C	C	C	18.5	18.7	18.6	17.8	C						
238	15.0	15.8	15.2	16.4	13.0	C	C	C	C	14.7	15.6	C	15.1	14.4	C									
243	15.9	C	C	17.9	17.0	C	C	C	16.2	17.3	14.4	C	15.8	C	C	C	14.0	14.5						
MEAN	17.1																							
S. D.	2.41																							
N	7																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 3: 20 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
177	15.9	D	16.2	C	16.5	17.3	15.5	C	C	C	15.9	16.1	C	C	15.1	14.6								
198	15.7	C	C	C	15.9	17.0	13.8	17.0	C	14.9	15.9	C	C	15.7	C	15.3								
205	13.2	D	14.4	C	14.3	C	C	C	13.9	13.0	C	10.7	12.9	14.5	12.2	C								
208	17.8	16.9	C	18.8	18.0	C	18.8	C	16.6	16.5	18.9	17.8	C											
218	13.0	D	D	D	D	D	14.4	10.8	15.8	14.5	C	C	14.4	10.3	15.6	C	D	8.0						
239	14.8	C	17.6	C	C	C	15.8	14.5	14.4	14.1	14.0	14.1	C	C	14.0									
241	15.7	D	14.2	16.2	15.5	16.2	15.5	17.3	15.2															
242	15.8	D	14.2	15.3	D	15.5	C	C	17.0	C	15.0	D	18.1	15.3	15.6	C								
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP C = CULLED PUP



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

GROUP 4: 30 MG/RG/DAY

-----  
 DAM NO. PUP NO. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23  
 MEAN  
 -----

200	18.5	D	C	18.9	18.4	18.2	C	19.1	18.6	19.2	18.4	16.9	C									
207	16.9	D	D	16.4	C	17.3	C	16.9	16.9	C	17.0	17.3	17.2	15.8								
212	15.3	15.1	13.2	16.3	C	17.2	C	14.5	14.5	C	17.0	14.3	C	C	C							
217	13.5	D	16.1	14.2	13.3	15.0	C	C	10.8	C	C	C	C	14.4	11.6	12.3						
222	12.8	D	D	D	D	11.7	C	D	11.7	12.1	14.7	13.6	12.0	13.7	13.0							
230	15.6	16.3	C	C	15.7	16.2	14.6	15.9	15.7	C	C	15.0	15.4	C								
240	16.4	D	15.3	C	16.9	17.1	C	16.8	C	17.3	C	14.8	15.6	C	17.2	C						

MEAN 15.6  
 S. D. 1.96  
 N 7

-----  
 D = DEAD PUP C = CULLED PUP  
 -----

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 17  
 DAY 7

GROUP 5: 50 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
194	14.1	D	D	D	12.9	14.1	15.6	13.4	11.7	14.7	C	14.8	15.4											
199	16.2	15.0	17.3	C	D	16.2	C	16.8	16.2	17.0	15.3	C	16.0											
202	15.9	15.4	16.1	C	17.8	C	16.7	C	C	14.4	17.0	14.0	C	16.1	C	C	C							
215	16.2	D	16.8	17.0	16.2	15.1	C	C	C	16.5	15.4	16.0	16.8	C										
216	17.4	C	19.4	16.2	C	18.0	17.4	C	C	17.8	17.6	16.6	C	16.4										
226	12.7	14.1	C	13.2	13.5	C	11.4	C	11.7	11.6	13.3	12.4	C											
232	17.1	17.8	18.0	C	17.3	18.1	C	C	C	C	15.6	C	C	16.5	16.6	17.2								

MEAN 15.7  
 S. D. 1.68  
 N 7

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 6: 75 MG/RG/DAY  
 PAGE 18  
 DAY 7

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
197	14.4	D	C	11.0	16.3	15.1	15.6	12.3	14.3	15.0	15.9													
210	19.0	D	D	20.0	18.4	C	18.1	20.0	C	C	18.6	C	C	C	20.4	18.6	17.6							
220	16.0	D	D	15.9	C	15.5	15.9	C	16.6	C	C	15.5	14.7	C	17.0	17.2	C							
228	14.2	D	D	D	D	D	C	15.2	16.6	13.2	11.8	C	C	C	15.6	C	12.6	12.7	15.8					
235	16.4	17.1	18.2	17.6	17.7	14.6	C	C	C	15.6	15.5	15.1												
244	16.3	D	D	D	C	17.8	16.8	15.1	17.2	C	C	16.7	15.4	16.8	14.9									

MEAN 16.1  
 S.D. 1.73  
 N 6

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 1: 0 MG/KG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
192	30.0	28.7	C	29.1	C	C	30.8	C	C	33.5	D	30.2	C	C	27.8	C	29.1	30.7						
196	32.1	D	C	C	32.5	33.7	C	31.0	C	33.0	C	33.0	C	D	32.6	C	30.6	30.7						
206	35.2	C	38.3	36.9	C	C	34.0	37.1	C	C	33.1	36.1	30.9	C	35.3	C								
219	31.1	33.7	30.7	32.1	C	D	31.1	28.4	C	31.3	C	C	30.6	C										
221	31.3	C	33.1	C	C	31.7	32.4	32.3	C	C	C	31.4	28.2	30.2	C	C	30.9	C						
231	31.8	31.2	C	34.1	32.7	30.5	C	33.5	C	C	29.4	C	30.4	C	C	C	32.2	C						
233	32.1	C	C	32.9	34.0	C	C	32.0	30.8	34.0	C	C	31.2	31.7	C	C	30.2	C						
237	31.7	C	C	C	32.9	33.5	31.9	C	C	29.5	C	C	C	D	29.9	30.5	33.4							
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 2: 10 MG/RG/DAY  
 PAGE 20  
 DAY 14

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
188	38.5	C	34.5	C	37.7	37.8	38.0	39.2																
195	33.5	C	34.5	C	34.2	C	35.3	C	35.9	C	31.6	32.7	C	33.0	C	C	30.8							
224	32.0	C	C	C	32.6	35.4	33.6	34.3	C	C	32.5	C	C	C	25.7	C	C	30.0	32.2					
234	34.6	C	C	C	37.2	33.3	34.3	36.2	35.5	32.9	C	C	34.3	C	32.7									
236	36.5	D	D	D	36.1	C	C	35.8	37.6	36.9	C	C	C	35.7	37.9	36.1	36.2	C						
238	28.6	C	C	C	30.2	25.8	C	C	C	28.5	29.5	C	29.3	27.3	C									
243	31.9	C	C	C	33.9	33.5	C	C	C	31.1	33.3	29.5	C	32.1	C	C	29.8	31.6						
MEAN	33.7																							
S. D.	3.26																							
N	7																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 3: 20 MG/RG/DAY  
 PAGE 21  
 DAY 14

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
198	34.3	C	C	C	34.8	35.9	32.9	36.3	C	32.9	34.6	C	C	32.6	C	34.0								
205	29.2	D	30.3	C	30.5	C	C	C	29.2	29.0	C	25.0	29.2	31.4	28.6	C	C							
208	37.0	35.5	C	38.1	36.8	C	38.2	C	36.1	36.0	38.0	37.6	C											
218	28.0	D	D	D	D	D	30.3	25.3	31.3	30.7	C	C	29.8	24.0	32.0	C	D	20.7						
239	29.3	C	33.5	C	C	C	C	30.7	28.7	28.4	28.8	27.5	29.0	C	C	C	28.0							
241	30.1	D	28.4	31.5	30.7	29.9	30.0	30.9	29.4															
242	30.5	D	28.5	31.5	D	30.5	C	C	31.8	C	28.2	D	32.7	30.1	31.0	C								
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 22  
 DAY 14

GROUP 4: 30 MG/RG/DAY

DAM NO. PUP NO. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23  
 MEAN

200	35.0	D	C	35.9	35.2	35.3	C	35.9	34.7	35.4	33.9	33.7	C									
207	32.1	D	D	32.7	C	32.7	C	32.6	32.1	C	31.0	31.7	32.2	31.5								
212	32.8	32.0	29.7	34.1	C	35.4	C	32.2	31.8	C	34.7	32.5	C	C	C							
217	27.7	D	31.4	28.4	28.0	29.9	C	23.6	C	C	C	C	C	29.6	24.8	26.1						
222	30.9	D	D	D	D	29.4	C	D	29.9	29.7	33.6	32.2	29.2	32.1	30.7							
230	30.9	32.3	C	C	31.2	32.6	30.3	31.1	30.5	C	C	29.0	30.0	C								
240	30.8	D	27.9	C	32.7	32.7	C	31.9	C	31.3	C	28.6	28.9	C	32.6	C						

MEAN 31.5  
 S. D. 2.23  
 N 7

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 23  
 DAY 14

GROUP 5: 50 MG/KG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
194	27.1	D	D	D	24.2	27.0	29.0	25.8	24.3	27.3	C	29.4	29.6											
199	31.9	30.1	32.9	C	D	32.0	C	32.4	32.6	32.4	32.0	C	31.0											
202	31.8	31.7	31.0	C	34.8	C	32.2	C	C	29.8	33.6	28.5	C	33.0	C	C	C							
215	30.2	D	30.0	32.2	30.1	28.8	C	C	C	30.1	29.3	29.8	31.3	C										
216	35.1	C	37.7	34.3	C	36.0	34.9	C	C	35.3	36.0	33.4	C	33.5										
226	27.7	30.5	C	28.3	29.0	C	26.2	C	26.5	26.1	28.3	26.9	C											
232	34.7	35.0	36.7	C	36.5	35.8	C	C	C	C	32.9	C	C	32.5	33.6	34.5								
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP C = CULLED PUP



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 6: 75 MG/RG/DAY  
 PAGE 24  
 DAY 14

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
197	27.7	D	C	23.6	29.3	28.6	29.4	25.3	27.5	28.2	29.8													
210	36.2	D	D	38.3	35.3	C	34.3	37.4	C	C	35.5	C	C	C	C	38.2	35.9	34.3						
220	31.2	D	D	32.0	C	30.4	29.2	C	31.9	C	C	31.3	28.7	C	33.2	32.7	C							
228	29.8	D	D	D	D	D	C	30.0	32.9	29.1	27.3	C	C	31.7	C	27.4	27.6	32.3						
235	32.1	33.5	34.7	34.1	34.8	28.8	C	C	C	30.7	29.7	30.4												
244	31.1	D	D	D	C	33.3	31.7	30.0	33.4	C	C	30.6	29.1	29.9	30.6									

MEAN 31.4  
 S.D. 2.82  
 N 6

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 1: 0 MG/KG/DAY

PAGE 25  
 DAY 21

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
192	49.8	C	48.4	C	C	51.2	C	C	55.4	D	50.0	C	C	46.9	C	48.3	50.7							
196	50.8	D	C	52.0	52.4	C	48.8	C	51.7	C	52.1	C	D	51.9	C	48.3	49.5							
206	54.0	C	58.2	54.4	C	C	56.1	54.8	C	50.2	C	C	50.1	C										
219	49.8	54.6	47.4	50.4	C	D	49.1	46.9	C	50.2	C	C	50.1	C										
221	52.7	C	56.5	C	C	54.0	52.9	51.0	C	C	54.2	48.3	50.0	C	C	54.9	C							
231	50.1	C	53.5	51.8	50.1	C	52.5	C	46.7	C	48.4	C	C	47.6	C									
233	54.3	C	53.7	57.4	C	C	54.9	51.8	58.0	C	53.1	53.3	C	C	52.2									
237	50.2	C	C	52.8	52.0	51.3	C	C	46.9	C	C	D	46.6	48.9	52.6									
	MEAN																							
	S.D.																							
	N																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 26  
 DAY 21

GROUP 2: 10 MG/RG/DAY

DAM NO. PUP NO. 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23  
 MEAN

188	64.8	66.6	64.9	63.7	63.9	64.0	65.8															
195	53.0	C	56.2	C	54.4	C	54.2	C	57.3	C	47.9	50.9	C	54.0	C	C	49.3					
224	50.8	C	C	C	53.2	55.9	54.3	57.1	C	C	55.2	C	C	C	41.8	C	C	46.9	41.8			
234	55.4	C	C	C	59.8	52.9	54.3	58.9	56.4	51.8	C	C	55.9	C	53.3							
236	61.5	D	D	61.5	C	61.4	65.3	63.8	C	C	C	C	59.9	60.6	59.7	59.6	C					
238	48.4	51.7	49.7	49.4	43.2	C	C	C	C	48.8	51.5	C	47.9	44.8	C							
243	51.9	C	C	53.7	55.0	C	C	C	50.0	55.2	49.2	C	53.1	C	C	C	47.9	51.4				

MEAN 55.1  
 S. D. 5.96  
 N 7

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)  
 GROUP 3: 20 MG/RG/DAY

PAGE 27  
 DAY 21

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
198	54.3	C	C	C	54.7	58.1	49.7	58.5	C	55.2	53.0	C	C	53.7	C	51.5								
205	47.0	D	48.2	C	47.5	C	C	C	47.5	47.4	C	42.7	46.7	50.5	45.8	C	C							
208	59.2	54.7	C	62.2	57.2	C	60.4	C	58.0	60.2	61.1	59.8	C											
218	45.0	D	D	D	D	D	49.6	39.8	51.9	49.1	C	C	49.2	38.0	48.7	C	D	33.9						
239	49.6	C	55.9	C	C	C	C	52.2	48.3	49.2	48.7	45.1	50.2	C	C	46.8								
241	50.0	D	47.3	51.9	49.8	50.9	51.3	51.1	47.8															
242	50.4	D	D	48.4	51.3	D	49.8	C	C	53.8	C	47.0	D	55.1	48.3	49.7	C							
MEAN	50.8																							
S. D.	4.71																							
N	7																							

D = DEAD PUP C = CULLED PUP

APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 28  
 DAY 21

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

GROUP 4: 30 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
200	58.2	D	C	C	61.5	57.3	59.9	C	60.0	58.3	57.0	57.2	54.2	C										
207	52.1	D	D	C	53.7	C	52.4	C	51.3	53.3	C	51.0	50.7	51.4	53.0									
212	53.9	52.8	47.8	57.2	C	58.4	C	C	53.5	52.0	C	55.9	53.9	C	C	C								
217	44.9	D	50.1	47.6	47.2	48.2	C	C	37.8	C	C	C	C	C	48.8	37.9	41.6							
222	48.7	D	D	D	D	48.7	C	D	47.1	48.6	51.2	49.4	46.9	49.5	48.0									
230	52.8	54.0	C	C	52.0	55.0	48.4	53.1	52.7	C	C	52.2	55.0	C										
240	46.7	D	41.3	C	51.0	49.1	C	46.1	C	47.9	C	43.3	44.6	C	50.4	C								
	MEAN																							
	S. D.																							
	N																							

D = DEAD PUP C = CULLED PUP

SLI STUDY NO. : 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 29  
 DAY 21

GROUP 5: 50 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	MEAN																							
194	40.7	D	D	D	40.6	23.4	48.0	39.8	38.5	47.3	C	39.9	47.9											
199	51.1	48.4	54.5	C	D	51.2	C	48.8	49.7	53.9	50.6	C	51.8											
202	50.0	48.7	45.7	C	55.3	C	52.4	C	C	48.9	53.2	44.8	C	50.7	C	C	C							
215	48.8	D	48.5	51.6	49.0	48.1	C	C	C	46.6	48.9	48.5	49.5	C										
216	57.5	C	62.4	55.8	C	61.0	56.7	C	C	58.2	57.3	54.5	C	54.4										
226	43.9	48.6	C	45.2	46.5	C	38.3	C	43.1	41.9	43.7	44.0	C											
232	59.2	61.5	64.4	C	61.5	60.4	C	C	C	56.2	C	C	53.6	56.2	60.1									
	MEAN	50.2																						
	S. D.	6.67																						
	N	7																						

D = DEAD PUP C = CULLED PUP

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.  
 APPENDIX W  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP WEIGHTS DURING LACTATION (GRAMS)

PAGE 30  
 DAY 21

GROUP 6: 75 MG/RG/DAY

DAM NO.	PUP NO.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	
	MEAN																								
197	42.6	D	C	36.0	47.0	45.1	44.1	38.1	41.5	42.9	46.3														
210	57.6	D	D	61.0	57.8	C	57.0	61.9	C	C	56.1	C	C	C	C	59.2	53.8	54.0							
220	51.8	D	D	52.0	C	52.9	49.4	C	53.1	C	C	53.0	46.1	C	53.3	54.6	C								
228	44.9	D	D	D	D	D	C	45.5	47.8	44.8	41.2	C	C	48.9	C	40.8	42.9	47.3							
235	49.9	51.7	54.0	52.9	55.8	43.5	C	C	C	48.1	45.6	47.5													
244	51.9	D	D	D	C	58.4	54.5	51.2	56.3	C	C	50.0	48.5	47.6	49.0										

MEAN 49.8  
 S.D. 5.39  
 N 6

D = DEAD PUP C = CULLED PUP

(376)

SLI Study No. 3472.3

APPENDIX X

Individual F1 Pup Gross Necropsy Observations



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX X  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

PAGE 1

ANIMAL NO.	219-05	GROUP:	0 MG/KG/DAY EYES	MALE	FOUND DEAD	9/27/98	LACTATION DAY 10	GRADE
					GROSS: MICROPHthalmia			P
			KIDNEYS		GROSS: RENAL PAPILLA(E) NOT DEVELOPED			P
			URETERS		GROSS: DISTENDED			P
			EXT. APPEARANCE		GROSS: TAIL - CONSTRICTION			P
					MEDIAL PORTION, WITH SKIN SCABBING, DISTAL TAIL DISCOLORED PURPLE			
ANIMAL NO.	236-01	GROUP:	10 MG/KG/DAY STOMACH	MALE	FOUND DEAD	9/13/98	LACTATION DAY 0	P
					GROSS: MILK NOT PRESENT			
ANIMAL NO.	242-01	GROUP:	20 MG/KG/DAY LUNGS	MALE	FOUND DEAD	9/10/98	LACTATION DAY 0	P
					GROSS: ATELECTASIS			
					ALL LOBES			
					GROSS: MILK NOT PRESENT			P
ANIMAL NO.	242-02	GROUP:	20 MG/KG/DAY LUNGS	MALE	FOUND DEAD	9/10/98	LACTATION DAY 0	P
					GROSS: ATELECTASIS			
					ALL LOBES			
					GROSS: MILK NOT PRESENT			P
ANIMAL NO.	218-01	GROUP:	20 MG/KG/DAY LUNGS	MALE a	FOUND DEAD	9/12/98	LACTATION DAY 0	P
					GROSS: ATELECTASIS			
					ALL LOBES			
					GROSS: TISSUE(S) TOO AUTOLYZED TO EXAMINE			P
					INVOLVING ABDOMINAL AND URINARY/REPRODUCTIVE ORGANS			
ANIMAL NO.	218-02	GROUP:	20 MG/KG/DAY STOMACH	MALE	FOUND DEAD	9/12/98	LACTATION DAY 0	P
					GROSS: MILK NOT PRESENT			

a SEX COULD NOT BE VERIFIED AT NECROPSY DUE TO AUTOLYSIS.  
GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

APPENDIX X

ANIMAL NO.	GROUP:	MG/KG/DAY	SEX	FOUND DEAD	GRADE
241-01	20	MG/KG/DAY LUNGS	MALE	FOUND DEAD 9/12/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
		STOMACH		GROSS: MILK NOT PRESENT	P
177-01	20	MG/KG/DAY LUNGS	MALE	FOUND DEAD 9/13/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
		STOMACH		GROSS: MILK NOT PRESENT	P
207-01	30	MG/KG/DAY LUNGS	MALE	FOUND DEAD 9/12/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
		STOMACH URETERS		GROSS: MILK NOT PRESENT GROSS: DISTENDED LEFT	P 1
207-02	30	MG/KG/DAY LUNGS	MALE	FOUND DEAD 9/12/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
		STOMACH		GROSS: MILK NOT PRESENT	P
217-01	30	MG/KG/DAY LUNGS	MALE	FOUND DEAD 9/12/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
		STOMACH		GROSS: MILK NOT PRESENT	P
200-01	30	MG/KG/DAY LUNGS	MALE	FOUND DEAD 9/13/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
		STOMACH GENERAL COMMENT		GROSS: MILK NOT PRESENT GROSS: TISSUE(S) TOO AUTOLYZED TO EXAMINE INVOLVING INTESTINES, KIDNEYS AND URETERS	P P

GROSS GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- MARKED, P- PRESENT

SLI STUDY NO. : 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

APPENDIX X

ANIMAL NO.	GROUP:	MG/KG/DAY	SEX	FOUND DEAD	GRADE
222-01	30	LUNGS	MALE	FOUND DEAD 9/16/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES GROSS: MILK NOT PRESENT	P
222-02	30	LUNGS	MALE	FOUND DEAD 9/16/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES GROSS: MILK NOT PRESENT	P
194-01	50	STOMACH	MALE	FOUND DEAD 9/11/98 LACTATION DAY 0 GROSS: UNABLE TO DETERMINE SEX NO SEX ORGANS PRESENT GROSS: BRAIN - UNABLE TO EXAMINE APPARENTLY CANNIBALIZED GROSS: SHORTENED TORSO ABDOMINAL VISCERA, AXIAL SKELETON AND PELVIC GIRDLE UNDEVELOPED, ANAL ATRESIA, THORACIC VISCERA HYPOPLASTIC, TAIL EXISTS AS A SMALL FLESHY BUD - NO CAUDAL VERTEBRAE; EXENCEPHALY; OPEN EYELID - RIGHT; ANOPHTHALMIA - LEFT	P
215-01	50	STOMACH URETERS	MALE	FOUND DEAD 9/11/98 LACTATION DAY 0 GROSS: MILK NOT PRESENT GROSS: DISTENDED BILATERAL	P 2
213-01	75	LUNGS	MALE	FOUND DEAD 9/12/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES GROSS: MILK NOT PRESENT	P
		STOMACH		GROSS: MILK NOT PRESENT	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX X  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

ANIMAL NO.	GROUP:	75 MG/KG/DAY	MALE	FOUND DEAD	9/12/98 LACTATION DAY 0	GRADE
213-02		LUNGS		FOUND DEAD GROSS: ATELECTASIS ALL LOBES		P
		STOMACH		GROSS: MILK NOT PRESENT		P
228-01		75 MG/KG/DAY KIDNEYS	MALE	FOUND DEAD GROSS: RENAL PAPILLA(E) NOT DEVELOPED LEFT	9/13/98 LACTATION DAY 0	P
		LUNGS		GROSS: ATELECTASIS ALL LOBES		P
		STOMACH URETERS		GROSS: MILK NOT PRESENT GROSS: DISTENDED LEFT, MODERATE; RIGHT, SLIGHT		P P
228-02		75 MG/KG/DAY LUNGS	MALE	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98 LACTATION DAY 0	P
		STOMACH		GROSS: MILK NOT PRESENT		P
228-03		75 MG/KG/DAY LUNGS	MALE	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98 LACTATION DAY 0	P
		STOMACH		GROSS: MILK NOT PRESENT		P
245-01		75 MG/KG/DAY GENERAL COMMENT	MALE a	FOUND DEAD GROSS: TISSUE(S) TOO AUTOLYZED TO EXAMINE INVOLVING ABDOMINAL AND URINARY/REPRODUCTIVE ORGANS	9/13/98 LACTATION DAY 0	P
245-06		75 MG/KG/DAY KIDNEYS	MALE	FOUND DEAD GROSS: RENAL PAPILLA(E) NOT DEVELOPED BILATERAL	9/13/98 LACTATION DAY 0	P

a SEX COULD NOT BE VERIFIED AT NECROPSY DUE TO AUTOLYSIS.  
 GROSS GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- MARKED, P- PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX X  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

ANIMAL NO.	245-06 (CONTINUED)	STOMACH URETERS	FOUND DEAD	GRADE
ANIMAL NO. 245-06	GROUP: 75 MG/KG/DAY	MALE	GROSS: MILK NOT PRESENT GROSS: DISTENDED BILATERAL	P 1
ANIMAL NO. 213-05	GROUP: 75 MG/KG/DAY	MALE	FOUND DEAD 9/13/98 LACTATION DAY 1 GROSS: MILK NOT PRESENT	P
ANIMAL NO. 213-06	GROUP: 75 MG/KG/DAY	MALE	FOUND DEAD 9/13/98 LACTATION DAY 1 GROSS: MILK NOT PRESENT	P
ANIMAL NO. 213-10	GROUP: 75 MG/KG/DAY	MALE	FOUND DEAD 9/13/98 LACTATION DAY 1 GROSS: MILK NOT PRESENT	P
ANIMAL NO. 210-01	GROUP: 75 MG/KG/DAY	MALE a	FOUND DEAD 9/13/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
ANIMAL NO. 210-02	GROUP: 75 MG/KG/DAY	MALE a	FOUND DEAD 9/13/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
ANIMAL NO. 197-01	GROUP: 75 MG/KG/DAY	MALE	FOUND DEAD 9/13/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES	P
ANIMAL NO. 213-07	GROUP: 75 MG/KG/DAY	MALE	FOUND DEAD 9/14/98 LACTATION DAY 2 GROSS: MILK NOT PRESENT	P

a SEX COULD NOT BE VERIFIED AT NECROPSY DUE TO AUTOLYSIS.  
 GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

APPENDIX X

ANIMAL NO.	213-08	213-09	213-11	196-01	236-02	218-03	218-04
GROUP:	75	75	75	0	10	20	20
MG/KG/DAY							
SEX	MALE	MALE	MALE	FEMALE	FEMALE	FEMALE a	FEMALE a
ORGAN	KIDNEYS	LIVER	STOMACH	LUNGS	STOMACH	LUNGS	LUNGS
FOUND DEAD	9/14/98	9/14/98	9/14/98	9/11/98	9/13/98	9/12/98	9/12/98
LACTATION DAY	2	2	2	0	0	0	0
GROSS:	RENAL PAPILLA(E) NOT DEVELOPED RIGHT	PALE ALL LOBES	MILK NOT PRESENT	ATELECTASIS ALL LOBES	MILK NOT PRESENT	ATELECTASIS ALL LOBES	ATELECTASIS ALL LOBES
GRADE	P	P	P	P	P	P	P

a SEX COULD NOT BE VERIFIED AT NECROPSY DUE TO AUTOLYSIS.  
 GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX X  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

PAGE 7

ANIMAL NO.	218-04 (CONTINUED)	GENERAL COMMENT	FOUND DEAD	GRADE
ANIMAL NO.	218-05	GROUP: 20 MG/KG/DAY FEMALE STOMACH	GROSS: TISSUE(S) TOO AUTOLYZED TO EXAMINE INVOLVING ABDOMINAL AND URINARY/REPRODUCTIVE ORGANS  FOUND DEAD 9/12/98 LACTATION DAY 0 GROSS: NO SIGNIFICANT CHANGES OBSERVED GROSS: a	P
ANIMAL NO.	205-01	GROUP: 20 MG/KG/DAY FEMALE LUNGS STOMACH	GROSS: ATELECTASIS ALL LOBES GROSS: MILK NOT PRESENT	P
ANIMAL NO.	218-16	GROUP: 20 MG/KG/DAY FEMALE b TRACHEA	FOUND DEAD 9/13/98 LACTATION DAY 1 GROSS: CONTENT ABNORMAL CLEAR FOAMY FLUID GROSS: TISSUE(S) TOO AUTOLYZED TO EXAMINE INVOLVING ABDOMINAL AND URINARY/REPRODUCTIVE ORGANS	P
ANIMAL NO.	240-01	GROUP: 30 MG/KG/DAY FEMALE SKIN STOMACH	FOUND DEAD 9/11/98 LACTATION DAY 0 GROSS: SUBCUTANEOUS EDEMA AROUND NECK AND HINDLIMBS GROSS: MILK NOT PRESENT	P
ANIMAL NO.	222-03	GROUP: 30 MG/KG/DAY FEMALE STOMACH	FOUND DEAD 9/16/98 LACTATION DAY 0 GROSS: MILK NOT PRESENT	P
ANIMAL NO.	222-04	GROUP: 30 MG/KG/DAY FEMALE LUNGS STOMACH	FOUND DEAD 9/16/98 LACTATION DAY 0 GROSS: ATELECTASIS ALL LOBES GROSS: MILK NOT PRESENT	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT  
a THE PRESENCE OR ABSENCE OF MILK WAS INADVERTENTLY NOT RECORDED AT NECROPSY.  
b SEX COULD NOT BE VERIFIED AT NECROPSY DUE TO AUTOLYSIS.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

APPENDIX X

ANIMAL NO.	222-05	GROUP:	30	MG/KG/DAY	FEMALE	FOUND DEAD	9/16/98	LACTATION DAY 0	GRADE
				LUNGS		GROSS: ATELECTASIS			P
				STOMACH		GROSS: MILK NOT PRESENT			P
				URETERS		GROSS: DISTENDED			1
						BILATERAL			
ANIMAL NO.	194-02	GROUP:	50	MG/KG/DAY	FEMALE	FOUND DEAD	9/11/98	LACTATION DAY 0	P
				EYES		GROSS: ANOPHTHALMIA			
				KIDNEYS		GROSS: RENAL PAPILLA(E)		INCOMPLETELY DEVELOPED	P
				LIVER		GROSS: PALE			P
				LUNGS		GROSS: ATELECTASIS			P
				STOMACH		GROSS: MILK NOT PRESENT			P
				URETERS		GROSS: DISTENDED			2
				GENERAL COMMENT		GROSS: BILATERAL			P
				HEAD		GROSS: BRAIN - UNABLE TO EXAMINE			P
				HEAD		GROSS: APPARENTLY CANNIBALIZED			P
						GROSS: RHINOCEPHALY			P
ANIMAL NO.	194-03	GROUP:	50	MG/KG/DAY	FEMALE	FOUND DEAD	9/11/98	LACTATION DAY 0	P
				STOMACH		GROSS: MILK NOT PRESENT			
ANIMAL NO.	213-03	GROUP:	75	MG/KG/DAY	FEMALE	FOUND DEAD	9/12/98	LACTATION DAY 0	P
				LUNGS		GROSS: ATELECTASIS			
				STOMACH		GROSS: ALL LOBES			P
				URETERS		GROSS: MILK NOT PRESENT			P
						GROSS: DISTENDED			1
						LEFT			

GROSS GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- MARKED, P- PRESENT



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

APPENDIX X

ANIMAL NO.	GROUP:	MG/KG/DAY	SEX	ORGAN	FOUND DEAD	LACTATION DAY	GRADE
213-04	75	75	FEMALE	LUNGS	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/12/98	P
				STOMACH	GROSS: MILK NOT PRESENT		P
220-01	75	75	FEMALE	HEART	FOUND DEAD GROSS: TRANSPOSITION OF GREAT VESSELS PULMONARY ARISES FROM LEFT VENTRICLE, AORTA FROM RIGHT VENTRICLE WITH RETROESOPHAGEAL RIGHT SUBCLAVIAN; INTERRUPTED AORTIC ARCH; INTERVENTRICULAR SEPTAL DEFECT	9/12/98	P
				LUNGS	GROSS: ATELECTASIS ALL LOBES		P
				STOMACH	GROSS: MILK NOT PRESENT		P
220-02	75	75	FEMALE	LUNGS	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/12/98	P
				STOMACH	GROSS: MILK NOT PRESENT		P
244-02	75	75	FEMALE	LUNGS	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98	P
				STOMACH	GROSS: MILK NOT PRESENT		P
244-03	75	75	FEMALE	LUNGS	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98	P
				STOMACH URETERS	GROSS: MILK NOT PRESENT GROSS: DISTENDED LEFT		P 1

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 PUP GROSS NECROPSY OBSERVATIONS

APPENDIX X

PAGE 10

ANIMAL NO.	GROUP:	75 MG/KG/DAY LUNGS	FEMALE	FOUND DEAD	9/13/98 LACTATION DAY 0	GRADE
228-04	GROUP:	75 MG/KG/DAY LUNGS	FEMALE	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98 LACTATION DAY 0	P
228-05	GROUP:	75 MG/KG/DAY LUNGS	FEMALE	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98 LACTATION DAY 0	P
245-03	GROUP:	75 MG/KG/DAY LUNGS	FEMALE a	FOUND DEAD GROSS: ATELECTASIS ALL LOBES	9/13/98 LACTATION DAY 0	P
213-13	GROUP:	75 MG/KG/DAY STOMACH	FEMALE	FOUND DEAD GROSS: MILK NOT PRESENT	9/13/98 LACTATION DAY 1	P
213-12	GROUP:	75 MG/KG/DAY STOMACH	FEMALE	FOUND DEAD GROSS: MILK NOT PRESENT	9/14/98 LACTATION DAY 2	P

a SEX COULD NOT BE VERIFIED AT NECROPSY DUE TO AUTOLYSIS.  
GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI Study No. 3472.3

APPENDIX Y

Individual F1 Survival and Clinical Observations  
(Positive Findings)

ANIMAL NO.	GROUP	CATEGORY	STUDY DAY	GRADE OBSERVATIONS
192-01	M 0 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
196-07	M 0 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
206-08	M 0 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
219-03	M 0 MG/KG/DAY	DEAD	29	P SCHEDULED EUTHANASIA
221-02	M 0 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
231-01	M 0 MG/KG/DAY	EYES	8	P CORNEAL OPACITY - RIGHT EYE
		EYES	15	P CORNEAL OPACITY - RIGHT EYE
		EYES	22	P CORNEAL OPACITY - RIGHT EYE
		EYES	24	P CORNEAL OPACITY - RIGHT EYE
		DEAD	24	P SCHEDULED EUTHANASIA
233-03	M 0 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
237-06	M 0 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
188-02	M 10 MG/KG/DAY	DEAD	26	P SCHEDULED EUTHANASIA
195-08	M 10 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
224-06	M 10 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
234-05	M 10 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
236-06	M 10 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
238-02	M 10 MG/KG/DAY	DEAD	22	P SCHEDULED EUTHANASIA
243-09	M 10 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
198-07	M 20 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
205-08	M 20 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
208-06	M 20 MG/KG/DAY	DEAD	22	P SCHEDULED EUTHANASIA
218-06	M 20 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
218-09	M 20 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
239-08	M 20 MG/KG/DAY	DEAD	22	P SCHEDULED EUTHANASIA
241-03	M 20 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
242-04	M 20 MG/KG/DAY	DEAD	22	P SCHEDULED EUTHANASIA
200-04	M 30 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA

GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- SEVERE, P- PRESENT

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	STUDY DAY	GRADE OBSERVATIONS
200-05	M 30 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
207-08	M 30 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
212-05	M 30 MG/KG/DAY	EXCRETA/EMESIS	22	P SOFT STOOLS
		DEAD	23	P SCHEDULED EUTHANASIA
217-04	M 30 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
222-10	M 30 MG/KG/DAY	DEAD	28	P SCHEDULED EUTHANASIA
230-06	M 30 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
240-04	M 30 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
194-05	M 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
199-02	M 50 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
202-04	M 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
215-02	M 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
215-05	M 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
216-05	M 50 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
226-06	M 50 MG/KG/DAY	BODY	26	P SCAB(S) - TAIL
		DEAD	26	P SCHEDULED EUTHANASIA
232-04	M 50 MG/KG/DAY	EYES	26	P MALPOSITIONED PUPIL - RIGHT EYE
		DEAD	26	P SCHEDULED EUTHANASIA
197-05	M 75 MG/KG/DAY	POST-DOSE OBS	16	P SALIVATION
		DEAD	25	P SCHEDULED EUTHANASIA
210-04	M 75 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
220-03	M 75 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
228-08	M 75 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
228-09	M 75 MG/KG/DAY	POST-DOSE OBS	16	P SALIVATION
		DEAD	24	P SCHEDULED EUTHANASIA
235-02	M 75 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
235-05	M 75 MG/KG/DAY	POST-DOSE OBS	16	P SALIVATION
		DEAD	23	P SCHEDULED EUTHANASIA

GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- SEVERE, P- PRESENT

( POSITIVE FINDINGS )

ANIMAL NO.	GROUP	CATEGORY	STUDY DAY	GRADE OBSERVATIONS
244-05	M	75 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
192-16	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
196-14	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
206-12	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
219-09	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
221-16	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
231-10	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
233-08	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
237-14	F	0 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
188-06	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
195-10	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
224-10	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
234-14	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
236-14	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
236-15	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
238-10	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
243-12	F	10 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
198-15	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
205-12	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
205-14	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
208-11	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
218-14	F	20 MG/KG/DAY	BODY	P SCAB(S) - TAIL
			BODY	P SCAB(S) - TAIL
			DEAD	P SCHEDULED EUTHANASIA
239-12	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
241-05	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
242-11	F	20 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA
200-12	F	30 MG/KG/DAY	DEAD	P SCHEDULED EUTHANASIA

GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- SEVERE, P- PRESENT

(POSITIVE FINDINGS)

ANIMAL NO.	GROUP	CATEGORY	STUDY DAY	GRADE OBSERVATIONS
207-13	F 30 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
212-12	F 30 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
217-16	F 30 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
222-12	F 30 MG/KG/DAY	DEAD	28	P SCHEDULED EUTHANASIA
222-13	F 30 MG/KG/DAY	DEAD	28	P SCHEDULED EUTHANASIA
230-11	F 30 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
240-11	F 30 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
194-07	F 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
194-12	F 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
199-09	F 50 MG/KG/DAY	POST-DOSE OBS	23	P SALIVATION
		DEAD	24	P SCHEDULED EUTHANASIA
202-10	F 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
215-12	F 50 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
216-11	F 50 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
226-08	F 50 MG/KG/DAY	DEAD	26	P SCHEDULED EUTHANASIA
232-10	F 50 MG/KG/DAY	DEAD	26	P SCHEDULED EUTHANASIA
197-07	F 75 MG/KG/DAY	POST-DOSE OBS	15	P SALIVATION
		POST-DOSE OBS	17	P SALIVATION
		DEAD	25	P SCHEDULED EUTHANASIA
210-14	F 75 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
210-16	F 75 MG/KG/DAY	DEAD	25	P SCHEDULED EUTHANASIA
220-14	F 75 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
228-15	F 75 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA
235-10	F 75 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
235-11	F 75 MG/KG/DAY	DEAD	23	P SCHEDULED EUTHANASIA
244-11	F 75 MG/KG/DAY	DEAD	24	P SCHEDULED EUTHANASIA

GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-SEVERE, P-PRESENT

SLI Study No. 3472.3

APPENDIX Z

Individual F1 Body Weight Data



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY

WEEK	1	2	3	4	FBW
192-01 M	50	74	124	180	196
196-07 M	53	86	135	196	203
206-08 M	57	89	140	197	211
219-03 M	a	53	90	137	186
221-02 M	61	88	145	216	230
231-01 M	53	83	147	210	231
233-03 M	58	78	135	200	227
237-06 M	53	88	147	217	226
MEAN	55	80	133	194	214
S. D.	3.8	12.1	19.0	26.1	17.3
N	7	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.  
 a BODY WEIGHT WAS NOT RECORDED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

GROUP 2: 10 MG/KG/DAY

WEEK	1	2	3	4	FBW
188-02 M	70	89	141	217	256
195-08 M	62	91	147	208	220
224-06 M	59	78	130	193	213
234-05 M	64	91	153	216	225
234-07 M	58	97	161	230	233
236-06 M	66	89	146	215	240
238-02 M	54	102	166	228	a
243-09 M	60	89	147	212	227
MEAN	62	91	149	215	231
S. D.	5.0	6.9	11.3	11.6	14.2
N	8	8	8	8	7

NOTE: FBW = FINAL BODY WEIGHT.  
 a FINAL BODY WEIGHT RECORDED ON WEEK 4 (SCHEDULED EUTHANASIA).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

GROUP 3: 20 MG/KG/DAY

WEEK	1	2	3	4	FBW
198-07 M	58	91	148	216	225
205-08 M	48	75	124	177	190
208-06 M	62	106	170	240	a
218-06 M	53	82	139	201	214
218-09 M	53	81	132	179	193
239-08 M	51	91	153	212	a
241-03 M	56	87	143	217	231
242-04 M	53	97	159	221	a
MEAN	54	89	146	208	211
S. D.	4.3	9.8	14.8	21.4	18.5
N	8	8	8	8	5

NOTE: FBW = FINAL BODY WEIGHT.  
 a FINAL BODY WEIGHT RECORDED ON WEEK 4 (SCHEDULED EUTHANASIA).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

GROUP 4: 30 MG/KG/DAY

WEEK	1	2	3	4	FBW
200-04 M	65	89	149	214	240
200-05 M	61	81	135	188	210
207-08 M	55	87	147	213	230
212-05 M	62	101	170	237	250
217-04 M	51	76	134	197	214
222-10 M	51	54	103	168	224
230-06 M	52	82	141	211	231
240-04 M	55	89	148	204	212
MEAN	57	82	141	204	226
S. D.	5.5	13.6	19.0	20.4	14.2
N	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

PAGE 5

GROUP 5: 50 MG/KG/DAY

WEEK	1	2	3	4	FBW
194-05 M	26	51	94	142	149
199-02 M	59	89	148	208	225
202-04 M	59	93	156	224	234
215-02 M	52	88	146	208	218
215-05 M	52	87	149	217	229
216-05 M	65	85	143	209	230
226-06 M	40	55	100	153	176
232-04 M	67	82	139	204	231
MEAN	53	79	134	196	212
S. D.	13.7	16.2	23.6	30.5	31.5
N	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

PAGE 6

GROUP 6: 75 MG/KG/DAY

WEEK	1	2	3	4	FBW
197-05 M	48	67	111	158	177
210-04 M	64	85	143	213	241
220-03 M	56	85	146	217	235
228-08 M	51	83	141	202	218
228-09 M	48	74	127	187	198
235-02 M	57	93	148	202	213
235-05 M	46	77	115	147	151
244-05 M	63	87	140	208	222
MEAN	54	81	134	192	207
S. D.	7.0	8.2	14.4	26.0	30.3
N	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY

WEEK	1	2	3	4	FBW
192-16 F	50	74	116	151	158
196-14 F	56	89	140	178	185
206-12 F	57	78	120	152	161
219-09 F	a	53	91	135	169
221-16 F	58	83	122	159	160
231-10 F	50	75	120	153	164
233-08 F	56	72	114	150	157
237-14 F	47	76	119	156	156
MEAN	53	75	118	154	164
S. D.	4.3	10.4	13.4	11.9	9.6
N	7	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.  
 a BODY WEIGHT WAS NOT RECORDED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

GROUP 2: 10 MG/RG/DAY

WEEK	1	2	3	4	FBW
188-06 F	72	89	136	185	197
195-10 F	50	75	118	146	156
224-10 F	61	76	124	167	179
234-14 F	58	87	131	169	175
236-14 F	64	80	124	164	175
236-15 F	62	82	127	163	174
238-10 F	53	96	141	177	a
243-12 F	58	86	129	161	168
MEAN	60	84	129	167	175
S. D.	6.8	7.0	7.3	11.5	12.3
N	8	8	8	8	7

NOTE: FBW = FINAL BODY WEIGHT.  
 a FINAL BODY WEIGHT RECORDED ON WEEK 4 (SCHEDULED EUTHANASIA).



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

PAGE 9

GROUP 3: 20 MG/RG/DAY

WEEK	1	2	3	4	FBW
198-15 F	53	80	121	155	154
205-12 F	48	71	111	147	153
205-14 F	47	71	115	155	161
208-11 F	62	97	137	165	a
218-14 F	52	75	122	159	159
239-12 F	52	92	127	157	a
241-05 F	55	82	127	162	170
242-11 F	48	88	142	180	a
MEAN	52	82	125	160	159
S. D.	4.9	9.7	10.4	9.7	6.8
N	8	8	8	8	5

NOTE: FBW = FINAL BODY WEIGHT.  
 a FINAL BODY WEIGHT RECORDED ON WEEK 4 (SCHEDULED EUTHANASIA).

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

PAGE 10

GROUP 4: 30 MG/KG/DAY

WEEK	1	2	3	4	FBW
200-12 F	58	73	115	153	159
207-13 F	56	81	132	164	174
212-12 F	56	86	134	163	168
217-16 F	45	75	124	164	173
222-12 F	50	55	98	139	172
222-13 F	48	51	89	130	163
230-11 F	54	77	122	151	158
240-11 F	48	76	118	143	148
MEAN	52	72	117	151	164
S. D.	4.7	12.3	15.7	12.7	9.1
N	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

PAGE 11

GROUP 5: 50 MG/KG/DAY

WEEK	1	2	3	4	FBW
194-07 F	43	70	112	146	152
194-12 F	51	79	108	134	137
199-09 F	58	82	129	159	162
202-10 F	56	86	136	171	168
215-12 F	51	79	127	171	173
216-11 F	60	80	129	169	178
226-08 F	46	59	100	141	158
232-10 F	59	69	107	145	154
MEAN	53	76	119	155	160
S. D.	6.3	8.8	13.2	14.8	13.1
N	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX Z  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT DATA (GRAMS)

PAGE 12

GROUP 6: 75 MG/KG/DAY

WEEK	1	2	3	4	FBW
197-07 F	41	57	88	109	120
210-14 F	64	85	138	191	204
210-16 F	57	74	122	163	171
220-14 F	57	79	129	169	178
228-15 F	42	61	101	139	148
235-10 F	48	77	114	139	144
235-11 F	50	83	129	163	160
244-11 F	51	72	107	136	145
MEAN	51	74	116	151	159
S. D.	7.9	10.0	16.7	25.3	25.6
N	8	8	8	8	8

NOTE: FBW = FINAL BODY WEIGHT.

SLI Study No. 3472.3

APPENDIX AA

Individual F1 Body Weight Gain Data

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
192-01 M	24	50	56
196-07 M	33	49	61
206-08 M	32	51	57
219-03 M	a	37	47
221-02 M	27	57	71
231-01 M	30	64	63
233-03 M	20	57	65
237-06 M	35	59	70
MEAN	29	53	61
S. D.	5.3	8.2	7.9
N	7	8	8

a BODY WEIGHT GAIN WAS NOT RECORDED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 2: 10 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
188-02 M	19	52	76
195-08 M	29	56	61
224-06 M	19	52	63
234-05 M	27	62	63
234-07 M	39	64	69
236-06 M	23	57	69
238-02 M	48	64	62
243-09 M	29	58	65
MEAN	29	58	66
S. D.	10.0	4.9	5.0
N	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

PAGE 3

GROUP 3: 20 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
198-07 M	33	57	68
205-08 M	27	49	53
208-06 M	44	64	70
218-06 M	29	57	62
218-09 M	28	51	47
239-08 M	40	62	59
241-03 M	31	56	74
242-04 M	44	62	62
MEAN	35	57	62
S. D.	7.1	5.3	8.9
N	8	8	8



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
200-04 M	24	60	65
200-05 M	20	54	53
207-08 M	32	60	66
212-05 M	39	69	67
217-04 M	25	58	63
222-10 M	3	49	65
230-06 M	30	59	70
240-04 M	34	59	56
MEAN	26	59	63
S. D.	11.1	5.7	5.7
N	8	8	8

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX AA  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 5: 50 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
194-05 M	25	43	48
199-02 M	30	59	60
202-04 M	34	63	68
215-02 M	36	58	62
215-05 M	35	62	68
216-05 M	20	58	66
226-06 M	15	45	53
232-04 M	15	57	65
MEAN	26	56	61
S. D.	8.8	7.5	7.3
N	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 6: 75 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
197-05 M	19	44	47
210-04 M	21	58	70
220-03 M	29	61	71
228-08 M	32	58	61
228-09 M	26	53	60
235-02 M	36	55	54
235-05 M	31	38	32
244-05 M	24	53	68
MEAN	27	53	58
S. D.	5.8	7.8	13.3
N	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 1: 0 MG/KG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
192-16 F	24	42	35
196-14 F	33	51	38
206-12 F	21	42	32
219-09 F	a	38	44
221-16 F	25	39	37
231-10 F	25	45	33
233-08 F	16	42	36
237-14 F	29	43	37
MEAN	25	43	37
S. D.	5.4	4.0	3.7
N	7	8	8

a BODY WEIGHT GAIN WAS NOT RECORDED.

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 2: 10 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
188-06 F	17	47	49
195-10 F	25	43	28
224-10 F	15	48	43
234-14 F	29	44	38
236-14 F	16	44	40
236-15 F	20	45	36
238-10 F	43	45	36
243-12 F	28	43	32
MEAN	24	45	38
S. D.	9.4	1.8	6.5
N	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 3: 20 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
198-15 F	27	41	34
205-12 F	23	40	36
205-14 F	24	44	40
208-11 F	35	40	28
218-14 F	23	47	37
239-12 F	40	35	30
241-05 F	27	45	35
242-11	40	54	38
MEAN	30	43	35
S. D.	7.3	5.7	4.0
N	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 4: 30 MG/RG/DAY

WEEK	1	2	3	4
200-12 F	15	42	38	38
207-13 F	25	51	32	32
212-12 F	30	48	29	29
217-16 F	30	49	40	40
222-12 F	5	43	41	41
222-13 F	3	38	41	41
230-11 F	23	45	29	29
240-11 F	28	42	25	25
MEAN	20	45	34	34
S. D.	10.9	4.3	6.4	6.4
N	8	8	8	8

SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 5: 50 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
194-07 F	27	42	34
194-12 F	28	29	26
199-09 F	24	47	30
202-10 F	30	50	35
215-12 F	28	48	44
216-11 F	20	49	40
226-08 F	13	41	41
232-10 F	10	38	38
MEAN	23	43	36
S. D.	7.5	7.1	6.0
N	8	8	8



SLI STUDY NO.: 3472.3  
 CLIENT: NIPERA, INC.

APPENDIX AA  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 BODY WEIGHT GAIN DATA (GRAMS)

GROUP 6: 75 MG/RG/DAY

WEEK	1 TO 2	2 TO 3	3 TO 4
197-07 F	16	31	21
210-14 F	21	53	53
210-16 F	17	48	41
220-14 F	22	50	40
228-15 F	19	40	38
235-10 F	29	37	25
235-11 F	33	46	34
244-11 F	21	35	29
MEAN	22	43	35
S. D.	5.9	7.9	10.2
N	8	8	8

SLI Study No. 3472.3

APPENDIX BB

Individual F1 Gross Necropsy Observations

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

APPENDIX BB

PAGE 1

GRADE

ANIMAL NO.	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	STUDY DAY	GRADE
192-01	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/25/98 STUDY DAY 24	
196-07	GROUP:	0 MG/KG/DAY LUNGS TRACHEA	MALE	SCHEDULED EUTHANASIA GROSS: MOTTLED ALL LOBES; RED AND LIGHT RED GROSS: CONTENT ABNORMAL SMALL AMOUNT OF WHITE FOAM	10/24/98 STUDY DAY 23	P
206-08	GROUP:	0 MG/KG/DAY KIDNEYS	MALE	SCHEDULED EUTHANASIA GROSS: PITTED RIGHT; CORTICAL SURFACE; FEW; PINPOINT	10/25/98 STUDY DAY 24	P
219-03	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/30/98 STUDY DAY 29	
221-02	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/25/98 STUDY DAY 24	
231-01	GROUP:	0 MG/KG/DAY EYES	MALE	SCHEDULED EUTHANASIA GROSS: OPACITY RIGHT	10/25/98 STUDY DAY 24	P
233-03	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY 25	
237-06	GROUP:	0 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	
188-02	GROUP:	10 MG/KG/DAY EXT. APPEARANCE	MALE	SCHEDULED EUTHANASIA GROSS: TAIL BENT PROXIMAL TAIL	10/27/98 STUDY DAY 26	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO. : 3472.3  
 CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

APPENDIX BB

PAGE 2

ANIMAL NO.	GROUP	DOSE (MG/KG/DAY)	SEX	ORGAN	GROUP	DOSE (MG/KG/DAY)	SEX	ORGAN	GROUP	DOSE (MG/KG/DAY)	SEX	ORGAN	GROUP	DOSE (MG/KG/DAY)	SEX	ORGAN	GRADE
195-08	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	
224-06	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	
234-05	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	
234-07	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	
236-06	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: PITTED				GROSS: PITTED				GROSS: PITTED				GROSS: PITTED	P
				LEFT: CORTICAL SURFACE; ONE; 0.1 CM DIAMETER				LEFT: CORTICAL SURFACE; ONE; 0.1 CM DIAMETER				LEFT: CORTICAL SURFACE; ONE; 0.1 CM DIAMETER				LEFT: CORTICAL SURFACE; ONE; 0.1 CM DIAMETER	P
				GRAY AREA(S)				GRAY AREA(S)				GRAY AREA(S)				GRAY AREA(S)	
				CAPSULAR SURFACE; MULTIPLE; UP TO 0.5 CM DIAMETER; SLIGHTLY RAISED				CAPSULAR SURFACE; MULTIPLE; UP TO 0.5 CM DIAMETER; SLIGHTLY RAISED				CAPSULAR SURFACE; MULTIPLE; UP TO 0.5 CM DIAMETER; SLIGHTLY RAISED				CAPSULAR SURFACE; MULTIPLE; UP TO 0.5 CM DIAMETER; SLIGHTLY RAISED	
238-02	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	
243-09	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	10	10	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	
198-07	20	20	MALE	SCHEDULED EUTHANASIA	20	20	MALE	SCHEDULED EUTHANASIA	20	20	MALE	SCHEDULED EUTHANASIA	20	20	MALE	SCHEDULED EUTHANASIA	
				GROSS: DILATED PELVIS RIGHT				GROSS: DILATED PELVIS RIGHT				GROSS: DILATED PELVIS RIGHT				GROSS: DILATED PELVIS RIGHT	2
205-08	20	20	MALE	SCHEDULED EUTHANASIA	20	20	MALE	SCHEDULED EUTHANASIA	20	20	MALE	SCHEDULED EUTHANASIA	20	20	MALE	SCHEDULED EUTHANASIA	
				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED				GROSS: NO SIGNIFICANT CHANGES OBSERVED	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

APPENDIX BB  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

ANIMAL NO.	GROUP	DOSE (MG/KG/DAY)	SEX	SCHEDULED EUTHANASIA DATE	STUDY DAY	GRADE
208-06	20	20	MALE	10/23/98	22	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
218-06	20	20	MALE	10/25/98	24	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
218-09	20	20	MALE	10/25/98	24	P
GROSS: MOTTLED ALL LOBES; DARK RED AND RED						
239-08	20	20	MALE	10/23/98	22	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
241-03	20	20	MALE	10/25/98	24	P
GROSS: GRAY AREA(S) CAPSULAR SURFACE; MULTIPLE; UP TO 0.2 CM DIAMETER; SLIGHTLY RAISED						
242-04	20	20	MALE	10/23/98	22	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
200-04	30	30	MALE	10/26/98	25	
GROSS: NO SIGNIFICANT CHANGES OBSERVED						
200-05	30	30	MALE	10/26/98	25	1
GROSS: DILATED PELVIS RIGHT						
EXT. APPEARANCE GROSS: TAIL BENT DISTAL TIP						
207-08	30	30	MALE	10/25/98	24	P
GROSS: NODULE(S) ALL LOBES; SEVERAL; UP TO 0.1 CM DIAMETER; FIRM; TAN						

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

ANIMAL NO.	207-08	(CONTINUED)	SPLEEN	SCHEDULED EUTHANASIA	GRADE
				GROSS: GRAY AREA(S) CAPSULAR SURFACE; SEVERAL; UP TO 0.3 CM DIAMETER; SLIGHTLY RAISED	P
ANIMAL NO.	212-05	GROUP: 30 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 10/24/98 STUDY DAY 23 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO.	217-04	GROUP: 30 MG/KG/DAY SPLEEN	MALE	SCHEDULED EUTHANASIA 10/25/98 STUDY DAY 24 GROSS: GRAY AREA(S) CAPSULAR SURFACE; SEVERAL; UP TO 0.1 CM DIAMETER; SLIGHTLY RAISED	P
ANIMAL NO.	222-10	GROUP: 30 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 10/29/98 STUDY DAY 28 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO.	230-06	GROUP: 30 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 10/25/98 STUDY DAY 24 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO.	240-04	GROUP: 30 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 10/24/98 STUDY DAY 23 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO.	194-05	GROUP: 50 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 10/24/98 STUDY DAY 23 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO.	199-02	GROUP: 50 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA 10/25/98 STUDY DAY 24 GROSS: NO SIGNIFICANT CHANGES OBSERVED	
ANIMAL NO.	202-04	GROUP: 50 MG/KG/DAY LUNGS	MALE	SCHEDULED EUTHANASIA 10/24/98 STUDY DAY 23 GROSS: NODULE(S) ALL LOBES; MULTIPLE; UP TO 0.4 CM DIAMETER; FIRM; TAN	P

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

APPENDIX BB

PAGE 5

ANIMAL NO.	GROUP	DOSE (MG/KG/DAY)	SEX	SCHEDULED EUTHANASIA	STUDY DAY	GRADE
215-02	50	50	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	
215-05	50	50	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	
216-05	50	50	MALE	SCHEDULED EUTHANASIA GROSS: GRAY AREA(S) CAPSULAR SURFACE; MULTIPLE; UP TO 0.1 CM DIAMETER; SLIGHTLY RAISED	10/26/98 STUDY DAY 25	P
226-06	50	50	MALE	SCHEDULED EUTHANASIA GROSS: SCABBING MEDIAL TAIL	10/27/98 STUDY DAY 26	P
232-04	50	50	MALE	SCHEDULED EUTHANASIA GROSS: NODULE(S) ALL LOBES; MULTIPLE; UP TO 0.2 CM DIAMETER; FIRM; TAN	10/27/98 STUDY DAY 26	P
197-05	75	75	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY 25	
210-04	75	75	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY 25	
220-03	75	75	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/25/98 STUDY DAY 24	
228-08	75	75	MALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/25/98 STUDY DAY 24	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX BB  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

PAGE 6

ANIMAL NO.	GROUP	75 MG/KG/DAY KIDNEYS	MALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	GRADE
228-09	GROUP:	75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY	23	1
GROSS: DILATED PELVIS BILATERAL								
235-02	GROUP:	75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY	23	
GROSS: NO SIGNIFICANT CHANGES OBSERVED								
235-05	GROUP:	75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY	23	
GROSS: NO SIGNIFICANT CHANGES OBSERVED								
244-05	GROUP:	75 MG/KG/DAY	MALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	
GROSS: NO SIGNIFICANT CHANGES OBSERVED								
192-16	GROUP:	0 MG/KG/DAY VAGINA	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	P
GROSS: CONTENT ABNORMAL SMALL AMOUNT OF WHITE MUCOID MATERIAL								
196-14	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY	23	
GROSS: NO SIGNIFICANT CHANGES OBSERVED								
206-12	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	
GROSS: NO SIGNIFICANT CHANGES OBSERVED								
219-09	GROUP:	0 MG/KG/DAY EXT. APPEARANCE MEDIASITINAL L. N.	FEMALE	SCHEDULED EUTHANASIA	10/30/98	STUDY DAY	29	P
GROSS: TAIL BENT PROXIMAL TAIL FEW REDDENED								
221-16	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	
GROSS: NO SIGNIFICANT CHANGES OBSERVED								

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT



SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

APPENDIX BB  
A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

PAGE 7

ANIMAL NO.	231-10	GROUP:	0 MG/KG/DAY SPLEEN	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	GRADE
					GROSS: GRAY AREA(S) CAPSULAR SURFACE; MULTIPLE; UP TO 0.1 CM DIAMETER; SLIGHTLY RAISED				P
ANIMAL NO.	233-08	GROUP:	0 MG/KG/DAY LUNGS	FEMALE	SCHEDULED EUTHANASIA	10/26/98	STUDY DAY	25	P
					GROSS: DARK RED RIGHT APICAL LOBE; AREA 0.5 CM DIAMETER; EXTENDS THROUGH LOBE				
			VAGINA		GROSS: CONTENT ABNORMAL				P
			EXT. APPEARANCE		GROSS: SMALL AMOUNT OF WHITE MUCOID MATERIAL TAIL BENT MEDIAL PORTION				P
ANIMAL NO.	237-14	GROUP:	0 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY	23	
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				
ANIMAL NO.	188-06	GROUP:	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/27/98	STUDY DAY	26	
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				
ANIMAL NO.	195-10	GROUP:	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY	24	
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				
ANIMAL NO.	224-10	GROUP:	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/26/98	STUDY DAY	25	
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				
ANIMAL NO.	234-14	GROUP:	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY	23	
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				
ANIMAL NO.	236-14	GROUP:	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/26/98	STUDY DAY	25	
					GROSS: NO SIGNIFICANT CHANGES OBSERVED				

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

APPENDIX BB  
 A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
 WITH NICKEL SULFATE HEXAHYDRATE  
 INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

ANIMAL NO.	GROUP:	DOSE	SEX	ORGAN	DATE	STUDY DAY	GRADE
236-15	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/26/98	STUDY DAY 25	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
238-10	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/23/98	STUDY DAY 22	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
243-12	10 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY 24	1	
GROSS: DILATED PELVIS RIGHT							
198-15	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/24/98	STUDY DAY 23	1	
GROSS: DILATED PELVIS RIGHT							
205-12	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY 24	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
205-14	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY 24	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
208-11	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/23/98	STUDY DAY 22	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
218-14	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY 24	1	
GROSS: DARK RED RIGHT APICAL LOBE							
239-12	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/23/98	STUDY DAY 22	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							
241-05	20 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/25/98	STUDY DAY 24	1	
GROSS: NO SIGNIFICANT CHANGES OBSERVED							

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

ANIMAL NO.	GROUP:	MG/KG/DAY	HEART	FEMALE	SCHEDULED EUTHANASIA	STUDY DAY	GRADE
242-11	GROUP:	20	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: APPARENT CONSTRICTION	10/23/98 STUDY DAY 22	P
200-12	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY 25	
207-13	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/25/98 STUDY DAY 24	
212-12	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	
217-16	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: DILATED PELVIS RIGHT	10/25/98 STUDY DAY 24	1
222-12	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/29/98 STUDY DAY 28	
222-13	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: TAIL BENT PROXIMAL TAIL	10/29/98 STUDY DAY 28	P
230-11	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: DILATED PELVIS BILATERAL	10/25/98 STUDY DAY 24	1
240-11	GROUP:	30	MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	

GROSS GRADE CODE: 1- SLIGHT, 2- MODERATE, 3- MARKED, P- PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

APPENDIX BB

PAGE 10

GRADE

ANIMAL NO.	GROUP	50 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/24/98 STUDY DAY	23	GRADE
194-07	GROUP:	50 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY	23	
194-12	GROUP:	50 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY	23	
199-09	GROUP:	50 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/25/98 STUDY DAY	24	
202-10	GROUP:	50 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY	23	
215-12	GROUP:	50 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY	23	
216-11	GROUP:	50 MG/KG/DAY EXT. APPEARANCE	FEMALE	SCHEDULED EUTHANASIA GROSS: HAIRCOAT - WET MATTING AROUND RIGHT EYE; CLEAR COLORLESS	10/26/98 STUDY DAY	25	P
226-08	GROUP:	50 MG/KG/DAY EXT. APPEARANCE	FEMALE	SCHEDULED EUTHANASIA GROSS: TAIL BENT PROXIMAL TAIL	10/27/98 STUDY DAY	26	P
232-10	GROUP:	50 MG/KG/DAY SPLEEN	FEMALE	SCHEDULED EUTHANASIA GROSS: GRAY AREA(S) CAPSULAR SURFACE; MULTIPLE; UP TO 0.1 CM DIAMETER; SLIGHTLY RAISED	10/27/98 STUDY DAY	26	P
197-07	GROUP:	75 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY	25	

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI STUDY NO.: 3472.3  
CLIENT: NIPERA, INC.

A ONE-GENERATION REPRODUCTION RANGE-FINDING STUDY IN RATS  
WITH NICKEL SULFATE HEXAHYDRATE  
INDIVIDUAL F1 GROSS NECROPSY OBSERVATIONS

APPENDIX BB

PAGE 11

GRADE

ANIMAL NO.	GROUP	75 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA	10/26/98 STUDY DAY 25	GRADE
210-14	GROUP:	75 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY 25	
210-16	GROUP:	75 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/26/98 STUDY DAY 25	
220-14	GROUP:	75 MG/KG/DAY LUNGS	FEMALE	SCHEDULED EUTHANASIA GROSS: MOTTLED ALL LOBES; DARK RED AND RED	10/25/98 STUDY DAY 24	P
228-15	GROUP:	75 MG/KG/DAY VAGINA	FEMALE	SCHEDULED EUTHANASIA GROSS: CONTENT ABNORMAL SMALL AMOUNT OF WHITE MUCOID MATERIAL	10/25/98 STUDY DAY 24	P
235-10	GROUP:	75 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	
235-11	GROUP:	75 MG/KG/DAY	FEMALE	SCHEDULED EUTHANASIA GROSS: NO SIGNIFICANT CHANGES OBSERVED	10/24/98 STUDY DAY 23	
244-11	GROUP:	75 MG/KG/DAY KIDNEYS	FEMALE	SCHEDULED EUTHANASIA GROSS: DILATED PELVIS RIGHT	10/25/98 STUDY DAY 24	1

GROSS GRADE CODE: 1-SLIGHT, 2-MODERATE, 3-MARKED, P-PRESENT

SLI Study No. 3472.3

APPENDIX CC

SLI Historical Control Data

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA  
FERTILITY INDICES**

STUDY NO.	PRECONITAL INTERVAL MEAN	GESTATION LENGTH MEAN	NO. WITH SUCCESSFUL COPULATION	NO. MALES PAIRED	NO. FEMALES GRAVID	COPULATION INDEX	FERTILITY INDEX
R-01	3.1	21.9	18	20	14	90	76
R-02	3.2	21.9	20	20	18	100	90
R-03	3.2	21.8	20	20	17	100	85
R-03	3.7	21.7	39	40	36	98	92
R-04	3.4	21.9	18	20	16	90	89
R-05	2.8	22.0	42	42	41	100	98
R-05	3.2	21.9	19	20	16	95	84
R-06	2.9	22.0	19	20	18	95	95
R-07	3.4	21.7	20	20	20	100	100
R-08	2.6	21.8	20	20	19	100	95
R-14	2.9	21.9	19	20	19	95	100
MEAN	3.1	21.9				96.6	91.4
RANGE	2.6 - 3.7	21.7 - 22.0				90.0 - 100.0	77.8 - 100.0

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA  
IMPLANTATION DATA AND POST-IMPLANTATION LOSS ON LACTATION DAY 0**

	MEAN IMPLANTATION SCAR COUNT	MEAN NO. LIVE PUPS	MEAN POST-IMPLANTATION LOSS
<b>F0</b>			
R-01	16.96	15.48	1.48
R-02	16.00	14.54	1.46
R-03	15.88	14.19	1.69
R-04	14.84	13.00	1.84
R-05	17.25	14.95	2.30
R-06	16.08	15.20	0.88
R-07	15.84	14.40	1.44
R-08	15.54	14.29	1.25
MEAN	16.05	14.51	1.54
RANGE	14.84-17.25	13-15.48	0.88-2.3

Note: Implantation scar count minus the number of live pups on Lactation Day 0 equals post-implantation loss.

Wednesday, February 17, 1999



**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA**  
**F1 PUP DATA DURING LACTATION**

STUDY NO.	% LIVE PUPS	% DEAD PUPS	% LITTERS WITH LIVE OFFSPRING	SEX RATIO (M/F)	SEX RATIO (M/TOTAL)	MEAN LIVE LITTER SIZE
<b>LACTATION DAY: 0</b>						
R-06	97.7	2.3	100.0	1.1	52.6	15.2
R-08	98.6	1.4	96.0	1.2	54.8	14.3
R-01	97.3	2.7	92.0	1.2	54.8	15.5
R-03	97.4	2.6	94.1	1.0	49.3	14.2
R-02	99.1	0.9	96.0	0.9	48.4	14.5
R-07	97.3	2.7	100.0	1.0	50.0	14.4
R-04	95.6	4.4	100.0	1.1	51.7	13.0
R-05	97.7	2.3	100.0	1.1	51.8	15.0
R-14	98.4	1.6	100.0	1.1	53.3	14.4
MEAN	97.7	2.3	97.6	1.1	51.9	14.5
RANGE	95.6 - 99.1	0.9 - 4.4	92.0 - 100.0	0.9 - 1.2	48.4 - 54.8	13.0 - 15.5



**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA**  
**F1 PUP SURVIVAL AND BODY WEIGHT**

STUDY NO.	PUP SURVIVAL-%	SEX RATIO (MF)	MEAN PUP WEIGHT (G)
R-01	98.6	1.2	7.5
R-02	98.9	0.9	6.6
R-03	99.6	1.0	6.5
R-04	99.1	1.1	6.8
R-06	99.2	1.1	7.5
R-07	98.3	1.0	7.4
R-08	99.4	1.2	6.7
R-14	99.4	1.1	7.3
MEAN	99.1	1.1	7.0
RANGE	98.3 - 99.6	0.9 - 1.2	6.5 - 7.5

LACTATION DAY: 01

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA**  
**F1 PUP SURVIVAL AND BODY WEIGHT**

STUDY NO.	PUP SURVIVAL-%	SEX RATIO (M/F)	MEAN PUP WEIGHT (G)
R-01	98.3	1.2	10.9
R-02	98.3	0.9	9.3
R-03	98.2	1.0	9.4
R-04	98.5	1.1	9.8
R-06	98.9	1.1	11.0
R-07	98.3	1.0	11.1
R-08	98.8	1.2	9.4
R-14	99.2	1.2	10.6
MEAN	98.6	1.1	10.2
RANGE	98.2 - 99.2	0.9 - 1.2	9.3 - 11.1

LACTATION DAY: 04 (BC)

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA  
F1 PUP SURVIVAL AND BODY WEIGHT**

STUDY NO.	PUP SURVIVAL-%	SEX RATIO (M/F)	MEAN PUP WEIGHT (G)
R-01	100.0	1.0	11.0
R-02	100.0	1.0	9.3
R-03	100.0	1.0	9.4
R-04	100.0	1.1	9.8
R-07	100.0	1.0	11.1
R-08	100.0	1.1	9.4
R-14	100.0	1.1	10.6
MEAN	100.0	1.0	10.1
RANGE	100.0-100.0	1.0-1.1	9.3-11.1

LACTATION DAY: 04 (PC)

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA**  
**F1 PUP SURVIVAL AND BODY WEIGHT**

STUDY NO.	PUP SURVIVAL-%	SEX RATIO (M/F)	MEAN PUP WEIGHT (G)
R-01	100.0	1.0	18.0
R-02	100.0	1.0	15.4
R-03	100.0	1.0	15.5
R-04	100.0	1.1	16.0
R-05	100.0	1.0	18.7
R-06	100.0	1.0	18.4
R-07	100.0	1.0	18.7
R-08	100.0	1.1	15.6
R-14	100.0	1.1	17.0
MEAN	100.0	1.0	17.0
RANGE	100.0-100.0	1.0 -1.1	15.4-18.7

LACTATION DAY: 07

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA**  
**F1 PUP SURVIVAL AND BODY WEIGHT**

STUDY NO.	PUP SURVIVAL-%	SEX RATIO (M/F)	MEAN PUP WEIGHT (G)
R-01	100.0	1.0	37.7
R-02	100.0	1.0	33.1
R-03	100.0	1.0	33.4
R-04	100.0	1.1	33.5
R-05	100.0	1.0	38.6
R-06	100.0	1.0	37.9
R-07	100.0	1.0	38.7
R-08	100.0	1.1	33.5
R-14	100.0	1.1	35.6
MEAN	100.0	1.0	35.8
RANGE	100.0-100.0	1.0 -1.1	33.1-38.7

LACTATION DAY: 14

**SPRINGBORN LABORATORIES, INC. HISTORICAL CONTROL DATA**  
**F1 PUP SURVIVAL AND BODY WEIGHT**

STUDY NO.	PUP SURVIVAL-%	SEX RATIO (M/F)	MEAN PUP WEIGHT (G)
<b>LACTATION DAY: 21</b>			
R-01	100.0	1.0	61.5
R-02	100.0	1.0	53.5
R-03	100.0	1.0	52.9
R-04	100.0	1.1	54.6
R-05	100.0	1.0	61.1
R-06	100.0	1.0	62.9
R-07	100.0	1.0	61.6
R-08	100.0	1.1	52.7
R-14	99.5	1.1	57.1
MEAN	99.9	1.0	57.5
RANGE	99.5 - 100.0	1.0 - 1.1	52.7 - 62.9



(441)

SLI Study No. 3472.3

## APPENDIX DD

### SLI Personnel Responsibilities

SLI Study No. 3472.3

### SLI PERSONNEL RESPONSIBILITIES

Joseph C. Siglin, Ph.D., DABT	Study Director/Director of Research
Bjorn A. Thorsrud, Ph.D.	Alternate Contact/Manager, Developmental and Reproductive Toxicology
Robert C. Springborn, Ph.D.	Chairman, President and CEO
Malcolm Blair, Ph.D.	Senior Vice President and Managing Director
Anita M. Bosau, RQAP-GLP	Director of Compliance Assurance
J. Dale Thurman, D.V.M., M.S., DACVP	Director of Pathology
Deanna M. Talerico, RQAP-GLP	Supervisor of Nonacute Quality Assurance
Delores P. Knippen	Supervisor of Pharmacy
Linda Unrue, B.S., LATG	Primary Technician
Steven H. Magness, B.S., LATG	Supervisor of Gross and Fetal Pathology
Cheryl A. Bellamy	Supervisor of Nonacute Report Preparation
Kathy M. Gasser	Supervisor of Archives