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Final Report

Study Title	Sodium Trifluoroacetate: Extended One Generation Reproductive Toxicity Study in the Han Wistar Rat by Dietary Administration
Study Director	[redacted] BSc (Hons)
Test Facility	[redacted]
[redacted] Study Number	8439567
Co-Sponsors	Bayer AG Crop Science Division Alfred-Nobel-Straße 50 40789 Monheim Germany Rhodia Operations 25, rue de Clichy Paris 75009 France
Sponsor Reference Number	TXFO0056
Report Issue Date	11 March 2022
Page Number	1 of 1466

TABLE OF CONTENTS

COMPLIANCE WITH GOOD LABORATORY PRACTICE

The study described in this report was conducted in compliance with the following Good Laboratory Practice standards and I consider the data generated to be valid.

- The UK Good Laboratory Practice Regulations (Statutory Instrument 1999 No. 3106, as amended by Statutory Instrument 2004 No. 994).
- OECD Principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM(98)17.
- EC Commission Directive 2001/10/EC

These principles are compatible with Good Laboratory Practice regulations specified by regulatory authorities throughout the European Community, the United States (EPA and FDA), Japan (MHLW, MAFF and METI), and other countries that are signatories to the OECD Mutual Acceptance of Data Agreement [AMEND AS NECESSARY].

[redacted]

[redacted] BSc (Hons)
Study Director
[redacted]

11 March 2022
Date

QUALITY ASSURANCE STATEMENT

Sodium Trifluoroacetate: Extended One Generation Reproductive Toxicity Study in the Han Wistar Rat by Dietary Administration

This study has been reviewed by the Quality Assurance Unit of [redacted] and the report accurately reflects the raw data. The following study-specific inspections were conducted and findings reported to the Study Director (SD) and associated management.

Critical procedures performed routinely in an operational area may be audited as part of a process inspection programme. This can be in addition to phases scheduled on an individual study basis. Selected process inspections conducted and considered applicable to this study are included in the following.

In addition to the inspection programme detailed in the following, a facility inspection programme is also operated. Details of this programme, which covers all areas of the facility annually (at a minimum), are set out in standard operating procedures.

Audit Number	Audit Dates Start	End	Phase	Date Reported to SD and SD Management
AUD-016780	14 Oct 2020	14 Oct 2020	Protocol/Study Plan Review	14 Oct 2020
AUD-017729	20 Oct 2020	20 Oct 2020	Protocol/Study Plan Amendment No. 1 Review	20 Oct 2020
AUD-016863	14 Dec 2020	23 Dec 2020	Study Direction	23 Dec 2020
AUD-016865	23 Mar 2021	26 Mar 2021	Study Direction	26 Mar 2021
AUD-057608	28 Jun 2021	28 Jun 2021	Protocol/Study Plan Amendment No. 2 Review	28 Jun 2021
AUD-016875	02 Jul 2021	02 Jul 2021	Draft Report and Data Review-IPT	02 Jul 2021
AUD-016870	07 Jul 2021	09 Jul 2021	Draft Report and Data Review-RAS	09 Jul 2021
AUD-016874	08 Jul 2021	08 Jul 2021	Draft Report and Data Review-TSH	08 Jul 2021
AUD-060238	15 Jul 2021	15 Jul 2021	Protocol/Study Plan Amendment No.3 Review	15 Jul 2021
AUD-063303	03 Aug 2021	03 Aug 2021	Protocol/Study Plan Amendment No.4 Review	03 Aug 2021
AUD-016869	07 Sep 2021	13 Sep 2021	Draft Report and Data Review	13 Sep 2021
AUD-016873	18 Oct 2021	19 Oct 2021	Draft Report and Data Review – T4	19 Oct 2021
AUD-093650	18 Feb 2022	18 Feb 2022	Revised Draft Report Review	18 Feb 2022
AUD-097247	09 Mar 2022	09 Mar 2022	Final Report Review	09 Mar 2022

Process

Audit Number	Department	Phase	Audit Dates Start	End	Date Reported to Management
AUD-006501	Dose Formulations	Test item and material management	27 Aug 2020	17 Oct 2020	17 Oct 2020
AUD-019603	Dose Formulations	Preparation of liquid Vehicles/ weighing of control diet/ material management	08 Dec 2020	08 Dec 2020	08 Dec 2020
AUD-019614	Dose Formulations	Preparation of liquid Vehicles/ weighing of control diet/ material management	11 Feb 2021	13 Feb 2021	23 Feb 2021
AUD-025696	Dose Formulations	Preparation of liquid Vehicles/ weighing of control diet/ material management	11 Dec 2020	11 Dec 2020	30 Dec 2020
AUD-002613	Animal Operations	Animal Receipt and Study Set Up	17 Aug 2020	18 Sep 2020	18 Sep 2020
AUD-002849	Animal Operations	Animal Data Collection	06 Aug 2020	13 Aug 2020	13 Aug 2020
AUD-002854	Animal Operations	Animal Data Collection	09 Sep 2020	09 Sep 2020	09 Sep 2020
AUD-002855	Animal Operations	Animal Data Collection	28 Oct 2020	28 Oct 2020	28 Oct 2020
AUD-002856	Animal Operations	Animal Data Collection	25 Nov 2020	25 Nov 2020	26 Nov 2020
AUD-002857	Animal Operations	Animal Data Collection	14 Dec 2020	14 Dec 2020	14 Dec 2020

AUD-002858	Animal Operations	Dosing Procedures	08 Sep 2020	08 Sep 2020	09 Sep 2020
AUD-002860	Animal Operations	Dosing Procedures	28 Oct 2020	28 Oct 2020	28 Oct 2020
AUD-002861	Animal Operations	Dosing Procedures	16 Nov 2020	16 Nov 2020	20 Nov 2020
AUD-002862	Animal Operations	Dosing Procedures	24 Dec 2020	24 Dec 2020	24 Dec 2020
AUD-002864	Animal Operations	Husbandry	16 Oct 2020	26 Nov 2020	26 Nov 2020
AUD-002865	Animal Operations	Sample Collection and Handling	06 Oct 2020	06 Oct 2020	09 Oct 2020
AUD-023830	Animal Operations	Dosing Procedures	21 Jan 2021	22 Jan 2021	28 Jan 2021
AUD-023831	Animal Operations	Dosing Procedures	24 Feb 2021	25 Feb 2021	25 Feb 2021
AUD-023832	Animal Operations	Dosing Procedures	31 Mar 2021	31 Mar 2021	31 Mar 2021
AUD-023833	Animal Operations	Dosing Procedures	09 Apr 2021	09 Apr 2021	12 Apr 2021
AUD-023842	Animal Operations	Animal Data Collection	21 Jan 2021	22 Jan 2021	28 Jan 2021
AUD-023843	Animal Operations	Animal Data Collection	24 Feb 2021	25 Feb 2021	25 Feb 2021
AUD-023844	Animal Operations	Animal Data Collection	18 Mar 2021	18 Mar 2021	19 Mar 2021
AUD-023845	Animal Operations	Animal Data Collection	27 Apr 2021	27 Apr 2021	29 Apr 2021
AUD-023854	Animal Operations	Sample Collection and Processing	25 Feb 2021	25 Feb 2021	25 Feb 2021
AUD-023857	Animal Operations	Terminal Procedures	17 Mar 2021	17 Mar 2021	19 Mar 2021
AUD-023860	Animal Operations	Husbandry	04 Jan 2021	14 Jan 2021	14 Jan 2021
AUD-023861	Animal Operations	Husbandry	09 Apr 2021	16 Apr 2021	16 Apr 2021
AUD-004044	Residue Analytical Services	Analytical Procedures and Data Processing	19 Oct 2020	19 Oct 2020	20 Oct 2020
AUD-004045	Residue Analytical Services	Sample Fortification, Extraction and Clean-up	19 Oct 2020	19 Oct 2020	20 Oct 2020
AUD-004046	Residue Analytical Services	Sample Management and Tracking	14 Oct 2020	19 Oct 2020	20 Oct 2020
AUD-004050	Residue Analytical Services	Test/Reference Item Management and Standard Preparation	30 Oct 2020	30 Oct 2020	30 Oct 2020
AUD-024037	Residue Analytical Services	Sample Management and Tracking	21 Apr 2021	21 Apr 2021	22 Apr 2021
AUD-024045	Residue Analytical Services	Sample Fortification, Extraction and Clean-up	20 Jan 2021	28 Jan 2021	29 Jan 2021
AUD-024046	Residue Analytical Services	Sample Fortification, Extraction and Clean-up	21 Apr 2021	21 Apr 2021	22 Apr 2021
AUD-024053	Residue Analytical Services	Analytical Procedures and Data Processing	24 Mar 2021	24 Mar 2021	30 Mar 2021
AUD-022530	Clinical Pathology Services	Clinical Pathology General Procedures	18 Nov 2020	18 Nov 2020	23 Nov 2020
AUD-024223	Clinical Pathology Services	Clinical Pathology General Procedures	24 Mar 2021	29 Mar 2021	29 Mar 2021
AUD-024224	Clinical Pathology Services	Clinical Pathology General Procedures	19 Apr 2021	20 Apr 2021	07 Jun 2021
AUD-023977	Histology	Histology Process	12 Jan 2021	26 Jan 2021	27 Jan 2021
AUD-023978	Histology	Histology Process	30 Apr 2021	07 May 2021	07 May 2021
AUD-007593	Pathology	Pathology Procedures	12 Nov 2020	12 Nov 2020	12 Nov 2020
AUD-025268	Pathology	Pathology Procedures	23 Feb 2021	23 Feb 2021	23 Feb 2021
AUD-023999	Study Direction - DART	Study Direction	04 Mar 2021	04 Mar 2021	04 Mar 2021
AUD-002161	Bioanalytical Small Molecule	Analysis and data processing	12 Jan 2021	12 Jan 2021	12 Jan 2021
AUD-023153	Bioanalytical Small Molecule	Standard, QC & Sample preparation	11 Feb 2021	16 Feb 2021	16 Feb 2021
AUD-023155	Bioanalytical Small Molecule	Standard, QC & Sample preparation	22 Jul 2021	22 Jul 2021	22 Jul 2021

AUD-023388	Bioanalytical Small Molecule	Analysis and data processing	24 Jun 2021	24 Jun 2021	24 Jun 2021
AUD-025832	Immunology and Immunotoxicology	I&I Procedures	25 Mar 2021	30 Mar 2021	30 Mar 2021
AUD-086374	Archives	Archiving Procedures	28 Jan 2022	03 Feb 2022	03 Feb 2022

[redacted]

11 March 2022
Date

Quality Assurance Unit

[redacted]

STUDY CONTACTS

Co-Sponsors	Bayer AG Crop Science Division Alfred-Nobel-Stra□e 50 40789 Monheim Germany Rhodia Operations 25, rue de Clichy Paris 75009 France
Study Monitors	[redacted] [redacted] Solvay Industrial Function - HSE
Test Facilities (Primary Location)	[redacted] Eye [redacted]
(Clinical Pathology, Thyroid Hormone Analysis, Spleen Cell Immunophenotyping, Light Microscopy)	[redacted]
Contributing Scientists Toxicologist	[redacted]
Formulation Analysis	[redacted]
Thyroid Hormone Analysis - TSH	[redacted]
Thyroid Hormone Analysis - T4	[redacted]
Spleen Cell Immunophenotyping	[redacted]
Pathology	[redacted]
Internal Pathology Peer Review	[redacted]

1. SUMMARY

The purpose of this study was to assess the influence of Sodium Trifluoroacetate (an industrial chemical) on reproductive performance when administered continuously via the diet to Han Wistar rats. Cohorts of F1 animals were used to assess the potential for systemic toxicity, and potential effects on the sexual maturation and estrous cycles.

In the F0 generation, three groups of 25 male and 25 female rats received Sodium Trifluoroacetate at dietary concentrations of 120, 600 or 3000 ppm orally, via the diet before pairing and gestation. During the lactation phase up to termination, females received reduced dietary concentrations of 60, 300 or 1500 ppm. Males were treated for ten weeks before pairing, up to necropsy after litters were weaned. Females were treated for ten weeks before pairing, throughout pairing up to necropsy on Day 28 of lactation. In the F1 generation, 20 males and 20 females were treated from Day 21 to nominal Day 35 of age at dietary concentrations of 60, 300 or 1500 ppm and from Day 35 of age to their scheduled termination at dietary concentrations of 120, 600 or 3000 ppm via the diet (relevant to each cohort). A similarly constituted Control groups received untreated basal diet.

For the F0 generation data were recorded on clinical observations, body weight, food consumption, estrous cycles, mating performance and fertility, gestation length and parturition observations and reproductive performance. Clinical pathology (hematology and blood chemistry) and thyroid-related hormones, sperm assessment, organ weight, macroscopic pathology and microscopic pathology investigations were performed.

For F1 offspring, clinical condition, litter size and survival, sex ratio, body weight, ano-genital distance, organ weights and macropathology were assessed. Nipple counts were performed on male offspring on Day 13 of age. Serum samples that were collected from selected offspring on Day 22 of age were analyzed for thyroid-related hormones.

At weaning the F1 generation was split into two cohorts:

For F1 Cohort 1A, data were recorded on clinical condition, body weight, food consumption, sexual maturation and estrous cycles. Clinical pathology (hematology, blood chemistry and urinalysis) and thyroid-related hormones, sperm assessment, ovarian follicle and corpora lutea counts, organ weight, macroscopic pathology, full microscopic pathology and immunophenotyping investigations were performed.

For F1 Cohort 1B, data was recorded on clinical condition, body weight, food consumption, sexual maturation and estrous cycles. Organ weight and macroscopic pathology investigations were performed.

Results

Circulating levels of thyroid stimulating hormone in F0 males, F0 females, F1 offspring on Day 22 of age and selected F1 Cohort 1A animals at scheduled termination did not reveal any treatment-related differences.

Mean serum T4 concentrations in F0 males at 3000 ppm and females receiving 3000/1500 ppm were low when compared with Controls ($p<0.01$). At 1500 ppm mean serum T4 concentrations for F1 male and female offspring on Day 22 of age were low when compared with Controls ($p<0.01$), with most individual values below the lowest value in the concurrent Controls. Mean serum T4 concentrations in F1A males at 600 or 3000 ppm were low when compared with Controls ($p<0.01$), with most individual values below the lowest value in the concurrent Controls.

Immunophenotyping parameters (percentages and cells/spleen) across the different treatment groups for F1 males and females in Cohort 1A showed no differences that could be related to dietary administration of Sodium Trifluoroacetate.

F0 responses

The mean achieved dose levels over the ten-week pre-pairing treatment period at 120, 600 and 3000 ppm were 9.71, 49.2 and 248 mg/kg/day for males and 10.26, 53.9 and 265 mg/kg/day for females, respectively.

During gestation mean achieved dose levels were 8.65, 44.3 and 223 mg/kg/day for females receiving 120, 600 and 3000 ppm and during lactation the mean achieved dose levels were 9.85, 47.5 and 233 mg/kg/day for females receiving 60, 300 and 1500 ppm, respectively.

There was no mortality and there was no effect on general condition.

There were slight effects on body weight for males at 600 or 3000 ppm and females at 3000/1500 ppm during the course of the F0 generation, but they were slight and were not considered adverse.

Food consumption for males and females before pairing and for females during gestation was unaffected by treatment. During lactation food consumption at 3000/1500 ppm was low from LD4 to LD20; consumption at 120/60 ppm or 600/300 ppm was similar to Controls.

Estrous cycles, pre-coital interval, mating performance, fertility, gestation length, gestation index were unaffected by administration of Sodium Trifluoroacetate at dietary concentrations up to and including 3000 ppm.

Males at 3000 ppm and females at 3000/1500 ppm showed slightly low hemoglobin and low mean cell hemoglobin ($p<0.05$). Females at 3000/1500 ppm also showed low hematocrit and low mean cell hemoglobin concentration. At 3000 ppm males showed low monocyte counts and short activated partial thromboplastin time and at 3000/1500 ppm females showed high platelet counts.

Alkaline phosphatase activity for males at 600 or 3000 ppm was elevated when compared to Controls.

Males and females at all dose levels showed low plasma glucose levels and low levels of non-esterified fatty acids; males at all dose levels also showed low triglyceride concentrations.

Other differences included:

- bilirubin concentrations were slightly low for females at all dose levels
- sodium concentrations were high for males at 3000 ppm
- potassium concentrations were high for females at 3000/1500 ppm
- calcium concentrations were low for males at 3000 ppm
- A/G ratio was high for males at 600 or 3000 ppm and females at 3000/1500 ppm

At 3000 ppm there was a statistically significant decreases in cauda weights and total sperm count with a non-statistical decrease in cauda epididymal sperm number per gram however these values were within the historical control data (HCD) range whilst mean Control values exceeded HCD.

Body weight relative kidney weights and liver weights were high for males at 3000 ppm and females at 3000/1500 ppm; males at 600 ppm also had high bodyweight relative kidney weight , when compared with Controls.

There were no test-item related macroscopic findings in the F0 adult animals.

There was a test item-related increased incidence of minimal gland dilatation in the stomachs of the females given 600/300 ppm and 3000/1500 ppm; this finding was present in the fundic portion of the glandular stomach.

F1 litter responses

The general condition of offspring, litter size, offspring survival, sex ratio and ano-genital distance were unaffected by parental treatment.

No nipples/areola were observed for male offspring assessed on Day 13 of age.

Offspring body weight on Day 1 of age and subsequent weight gain up to Day 4 of age showed no effects of parental treatment. From Day 4 to Day 14 of age male and female offspring at 3000/1500 ppm showed statistically significantly low body weight gain and overall body weight gain from Day 1 of age up to weaning on Day 21 of age at 3000/1500 ppm was low.

Organ weights for unselected offspring on Day 22 of age showed no test item related differences.

Macroscopic examination of offspring that either died prematurely, were culled on Day 4 of age or terminated on Day 22 of age did not reveal any findings that could be related to administration of Sodium Trifluoroacetate.

F1 responses

The mean achieved dose levels were 9.37, 47.3 and 242 mg/kg/day for males, and were 9.83, 49.4 and 248 mg/kg/day for females, at 120/60, 600/300 and 3000/1500 ppm respectively.

There was no mortality and there was no effect on general condition.

At 3000/1500 ppm the mean bodyweight for selected F1 males and females was low from weaning on Day 21 of age up to scheduled termination at approximately 13 weeks of age; males at this dietary concentration also showed low overall body weight gain.

Overall, there was no adverse effect on food consumption during treatment of the F1 generation.

The age and body weight at attainment of balano preputial separation or vaginal opening were unaffected by treatment.

Males at 3000/1500 ppm and females at 600/300 or 3000/1500 ppm showed low hematocrit and hemoglobin count. Lymphocyte and monocyte counts were slightly low in males at 3000/1500 ppm ($p<0.05$); this was not evident for females at this dose level. Females at 600/300 or 3000/1500 ppm had slightly high platelet counts ($p<0.05$); there was no evidence of a dose response, and it was not evident in males.

Males at 3000/1500 ppm had slightly high alkaline phosphatase, high aspartate amino-transferase activity and high alanine amino-transferase activity; slightly high alanine amino-transferase activity was also apparent in females at this dose level. Bilirubin plasma concentrations were statistically significantly low in males at 600/300 or 3000/1500 ppm and females at 3000/1500 ppm. Glucose plasma concentrations were statistically significantly low for both males and females at all dose levels and cholesterol concentrations were slightly low in males at 600/300 or 3000/1500 ppm.

Non-esterified fatty acid and triglyceride concentrations for males at all dose levels were low; females at 3000/1500 ppm had significantly low non esterified fatty acid concentrations.

Sodium plasma concentrations were statistically significantly high for males at all dose levels and calcium plasma concentrations were slightly low for males at 3000/1500 ppm. Potassium plasma concentrations were statistically significantly high in females at all dose levels.

Total protein concentrations in males and females at 3000/1500 ppm were slightly low.

Albumin concentrations in males at 600/300 ppm and 3000/1500 ppm were high, with albumin to globulin ratios for males at 3000/1500 ppm and females at 600/300 or 3000/1500 ppm.

Urinary total sodium and protein levels were slightly high in males at 600/300 or 3000/1500 ppm. Total potassium concentrations were low and total sodium concentrations slightly high for females at 3000/1500 ppm

Estrous cycles, ovarian follicle and corpora lutea counts were unaffected by treatment.

Sperm analysis showed an effect on testis weight and abnormal head (flat head) with treatment of Sodium Trifluoroacetate at 3000/1500 ppm.

Mean body weight relative liver weights were high in the Cohort 1A males and females that received 1500/3000 ppm.

Mean absolute testes weight was low in both Cohort 1A and 1B males that received 1500/3000 ppm.

There were no test-item related macroscopic findings in the F1 generation (Cohort 1A and 1B).

There was a test item-related increased incidence of minimal to slight glandular dilatation in the fundic portion of the glandular stomach and a high incidence of minimal to slight decreased secretion in the fundic mucous neck cells of females given 1500/3000 ppm.

Conclusion
Dietary administration of Sodium Trifluoroacetate to Han Wistar rats at dietary concentrations of 120, 600 or 3000 ppm reduced to 60, 300 or 1500 pm for F0 females during lactation and F1 offspring up to nominal Day 28 of age was well tolerated.

There were test item-related microscopic findings in the glandular stomachs of the F0 females and F1 Cohort 1A females with an increased incidence of minimal to slight gland dilatation. The F1 cohort 1A females also exhibited a high incidence of minimal to slight decreased secretion in the mucous neck cells located in the fundic region of the glandular stomach. These finding were considered non-adverse at the severity seen in this study.

Reproductive performance (encompassing mating performance, fertility and offspring development) showed no adverse effects of treatment.

It is therefore concluded that 3000/1500ppm (approximating to 242-265 mg/kg/day) was the no observed adverse effect level for both reproductive performance/offspring development and for general systemic toxicity.

2. GENERAL STUDY INFORMATION

2.1 Purpose

The purpose of this study was to assess the influence of Sodium Trifluoroacetate (an industrial chemical) on reproductive performance when administered continuously via the diet to Han Wistar rats. Cohorts of F1 animals was used to assess the potential for systemic toxicity, and potential effects on the sexual maturation and estrus cycles.

2.1.1 Animal Model

The rat was chosen as the test species because of the requirement for a rodent species by regulatory agencies. The Han Wistar (RccHan™;WIST) strain was used because of the historical control data available at this laboratory.

2.2 Route of Administration

The dietary route of administration was chosen to simulate the conditions of possible human exposure.

2.3 Rationale for Dietary Concentration Selection

The dose levels 120, 600 and 3000 ppm, approximating to 10, 50 and 250 mg/kg/day were selected in conjunction with the Sponsor based on the dose-range-finding study ([redacted] study no. 8437241), plasma TK-data, as well as further repeat dose toxicity studies conducted with the test compound.

In the dose-range finder study body weight gains were dose-related statistically significantly reduced during the first days of gestation at all dose levels. At 3400 ppm (229 mg/kg/day) body weights were reduced by 38% although there was no effect on food consumption at this dose. Liver weights were dose-related increased in F0 and liver weight were statistically significantly high in F1 animals. These findings correlate with observation in the 90-day rat study (Report no: SA 06080) where histopathological liver findings were observed (hypertrophy and necrotic foci). In addition, glucose and bilirubin vales were statistically significantly decreased, and urinary volume was increased at 100 mg/kg/day and above.

In addition, analysis of plasma samples taken in the dose range finding study (Study No. 8437241) demonstrated very high plasma concentrations up to 485 mg/L in F0 high-dose females and up to 394 mg/L in F1 offspring at PND 21. Evaluation of the plasma analysis data for the different time points indicated a sub-proportional increase of plasma concentrations with increasing dose levels of Sodium Trifluoroacetate. Based on calculated AUC values for the timepoint Gestation Day 17 using a statistical data driven approach sub-proportionality started between 1500 to 2100 ppm. For Lactation Day 11 sub-proportionality started between 1200 to 3000 ppm.

To account/compensate for the higher food intake during lactation and in the early post-weaning phase, dietary levels were reduced to 60, 300 and 1500 ppm during lactation and for F1 offspring from PND 21 to PND 35.

2.4 Study Schedule

2.4.1 Duration of Treatment

F0 animals For ten weeks before pairing until termination after litters were weaned.

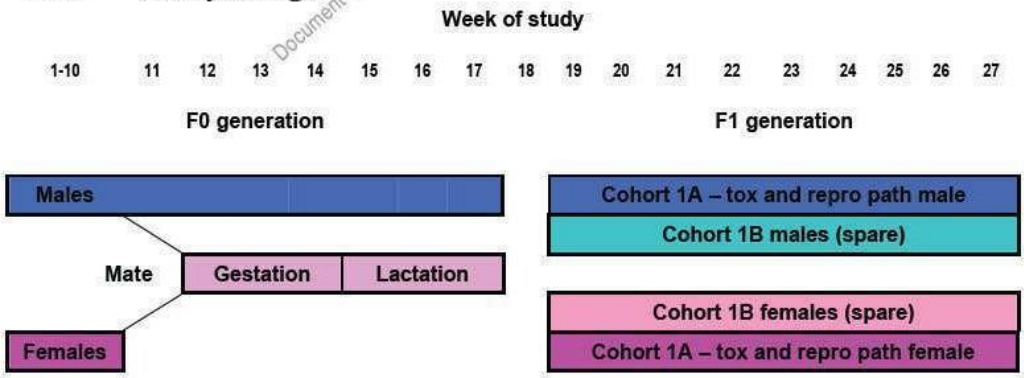
F1 animals Direct treatment from mid-lactation as offspring start to consume treated diet; offspring had potential for indirect exposure in utero and through the milk during lactation.

Unselected F1 offspring	:	Retention of brain, spleen, thymus and mammary tissue and organ weights - no direct treatment, killed on Day 22 of age
Cohort 1A	:	General toxicity and pathology of the tissues of the male and female reproductive systems - treated from weaning to 13 weeks of age.
Cohort 1B	:	Spare cohort - treated from weaning to 14 weeks of age.

2.4.2 Time Schedule

Study initiation (Study Plan signed by Study Director)	09 October 2020
Experimental start date (Animal arrival)	14 October 2020
Treatment of F0 animals commenced	20 October 2020
F0 necropsy	
Males	22 to 25 February 2021
Females	17 February to 02 March 2021
F1 generation commenced	19 February 2021
F1 generation necropsy	
Cohort 1A	26 to 29 April 2021
Cohort 1B	04 to 07 May 2021
Experimental completion date (Pathology)	03 September 2021

2.4.3 Study Design



2.5 Animal Welfare

The study was conducted in accordance with the applicable sections of the United Kingdom Animals (Scientific Procedures) Act 1986, Amendment Regulations 2012 (the Act).

2.6 Regulatory Testing Guidelines

The study was designed to meet the requirements of the following guideline:

- Organisation for Economic Co-operation and Development Testing of Chemicals Guideline No. 443: (Adopted 25 June 2018).

The study was conducted in accordance with the requirements of current, internationally recognized Good Laboratory Practice Standards.

2.7 Major Computerized Systems

The computer systems used to acquire and quantify data for this main report include:

System name*	System function
ClinAxys II	Used for in-life data collection.
Hamilton Thorne IVOS Computer Assisted Sperm Analyzer (CASA)	Used for Sperm analysis.
Liberate Global	In-house system used for reporting in-life, necropsy, pathology and statistics.
Quasar	In-house statistical analysis package.
StarTox	In-house statistical analysis package.
StatXact 3 statistical analysis package	Used for mating data.
Veeva Quality Management System (QMS)	Electronic communication system.
Xybion Pristima	Used for in-life, necropsy and pathology data collection and pharmacy test item management.

* All version numbers of the systems are maintained by [redacted]

The computer systems used to acquire and quantify data reported as part of a contributory report are detailed in the relevant attachment.

2.8 Quality Assurance

Details of the Quality Assurance inspections and audits undertaken at [redacted] are presented on the Quality Assurance Statement.

3. METHODS

3.1 Test Item and Supporting Information

Information supplied by the Sponsor regarding the test item is contained in the test item data sheet, which is retained in study records, and the Certificate of Analysis, which is presented in Attachment 14.1.

The following information is given in summary:

Test item:	Sodium Trifluoroacetate
Test item identity (including alternative names):	Trifluoroacetate (TFA)
CAS number:	2923-18-4
Intended use/type:	Industrial chemical / Metabolite
Appearance:	White solid
Storage conditions:	At ambient temperature (15 to 25°C)
Supplier:	Sponsor
Batch number:	2019052304
Expiry date:	23 May 2021 (two years after date of manufacture)
Purity:	99.9%
Supplier's responsibilities:	Characterization of the test item and the documentation of the methods of synthesis, fabrication or derivation and stability.
Archive sample:	A 0.5 g representative sample was taken from each batch of test item. This sample was placed in a well closed glass container and stored in the archives under the same conditions as the bulk material.

3.2 Test Item Preparation and Analysis

3.2.1 Formulation

Main Phase (F0 males up to termination, F0 females before pairing and during gestation, and selected F1 animals from nominal Day 35 of age)

Group	Treatment	Formulated concentration (ppm)
1	Basal diet	0
2	Sodium Trifluoracetate	120
3	Sodium Trifluoracetate	600
4	Sodium Trifluoracetate	3000

Lactation Phase (F0 females during lactation up to termination and F1 offspring from Day 21 up to nominal Day 35 of age)

Group	Treatment	Formulated concentration (ppm)
1	Basal diet	0
2	Sodium Trifluoracetate	60
3	Sodium Trifluoracetate	300
4	Sodium Trifluoracetate	1500

Correction factor	None.
Diet	SDS VRF1 Certified, powdered diet.
Method of preparation	The test substance was incorporated into the diet to provide the required concentrations by initial preparation of a premix. The amount of test substance required for the premix was added to an equal amount of plain diet and stirred. An amount of plain diet equal to the weight of the mixture was added and the mixture was stirred again until visibly homogenous. The doubling up process was repeated until approximately half the premix diet was added. At this stage the mixture was ground with a mechanical grinder. The mixture was made up to the weight of the premix with plain diet. The premix was then mixed using a turbula mixer for 200 cycles. This premix was diluted with further quantities of plain diet using the doubling up process to prepare the test mixes. Each formulation was mixed using a Turbula mixer for 200 cycles.
Frequency of preparation	Weekly.
Storage of formulation	At ambient temperature (15 to 25°C).
Test item accounting	Detailed records of compound usage were maintained. The amount of test item necessary to prepare the formulations and the amount actually used were determined on each occasion. The difference between these amounts was checked before the formulations were dispensed.

3.2.2 Formulation Analysis

Stability and homogeneity	Before commencement of treatment, the suitability of the proposed mixing procedures was determined and stability and homogeneity at a concentration of 50 to 10000 ppm was determined as part of another study ([redacted] Study no. LK56VW). It was demonstrated stable for 22 days at ambient temperature (15 to 25°C).
Achieved concentration	Samples of each formulation prepared for administration in Week 1 (F0 generation), last week of lactation (F0/F1 generation and last week (F1 generation) of treatment were analyzed for achieved concentration of the test item.
Analysis	The method of analysis and results are presented in Attachment 14.2.

3.3 Animal Information

3.3.1 Animals

Strain/Species	[redacted] WIST rat.
Supplier	[redacted]
Number of animals ordered	106 males and 106 females. Spare animals were removed from the study room after treatment commenced.
Duration of acclimatization	Six days before commencement of treatment.
Age of the F0 animals at the start of treatment	28 to 34 days old.
Weight range of the F0 animals at the start of treatment	Males 70 to 107 g. Females 66 to 87 g.

3.3.2 Allocation to Treatment Groups - F0 Generation

Allocation	On arrival by non-selective allocation to cages. Animals showing signs of ill health were excluded. Animals at the extreme of the weight range were not selected if alternatives were available. At commencement of the study the body weight of animals did not exceed ±20% of the mean for each sex.

3.3.3 Selection of Offspring to Form F1 Generation

Selection	Nominally Day 21 of age.
Allocation - formal start of F1 generation	Nominally Day 28 of age (28±2 days of age)
Method	Where possible, two males and two females were selected from each selected litter (if more were required, up to three males and three females were selected from each selected litter) and allocated to each of the two cohorts. (See Attachment 14.7). Selected animals were microchipped on Day 18 to 21 of age and separated from littermates on Day 21 of age. Up to two male and two female F1 offspring per group were retained as spares, to provide potential replacement in the event of any mortality. These spares had body weights and clinical signs recorded weekly and were terminated after commencement of the F1 generation.

3.3.4 Identification

Identification of animals	Unique for each F0 animal and selected F1 offspring within study. All pre-weaning offspring were numbered individually within each litter on Day 1 of age.
Method	Microchip (F0 generation and selected F1 generation). Toe tattoo (pre-weaning offspring).
Identification of cages	Each cage label was color-coded according to group and was numbered uniquely with cage and study number, as well as the identity of the occupant(s).

3.4 Animal Care and Husbandry

3.4.1 Environmental Control

Animal facility	Limited access - to minimize entry of external biological and chemical agents and to minimize the transference of such agents between rooms.
Air supply	Filtered fresh air which was passed to atmosphere and not recirculated.
Temperature and relative humidity	Monitored and maintained within the range of 20-24°C and 40-70%. Although conditions were occasionally outside the indicated ranges, these deviations were minor and/or of short duration and were not considered to have influenced the health of the animals and/or the outcome of the study (See Section 4).

Lighting	Artificial lighting, 12 hours light: 12 hours dark.
Electricity supply	Public supply with automatic stand-by generators.

3.4.2 Animal Accommodation

Cages	Cages comprised of a polycarbonate body with a stainless steel mesh lid; changed at appropriate intervals. Solid (polycarbonate) bottom cages were used throughout the study except during pairing. Grid bottomed cages were used during pairing. These were suspended above absorbent paper which was changed daily.
Cage distribution	The cages were distributed on the racking to equalize, as far as possible, environmental influences amongst the groups.
Bedding	Solid bottom cages contained softwood based bark-free fiber bedding, which was changed at appropriate intervals each week.

Number of animals per cage

Study period	Number of animals/cage		Cage material	Cage flooring
	Male	Female		
Pre-pairing (acclimatization and after selection)*	Up to 4	Up to 4	Polycarbonate	Solid polycarbonate
Pairing	1 : 1		Polycarbonate/ Stainless steel	Stainless steel grid
Males to termination	Up to 4	-	Polycarbonate	Solid polycarbonate
Females after mating (from Day 0 after mating)	-	1	Polycarbonate	Solid polycarbonate
Females during littering (from Day 20 after mating)	-	1 + litter	Polycarbonate	Solid polycarbonate
Females to termination (after weaning)	-	Up to 4	Polycarbonate	Solid polycarbonate
Offspring maturation (from weaning until selection)	Litter		Polycarbonate	Solid polycarbonate

*Except when F1 Cohort 1A animals were separated into single housing overnight prior to urine collection (Section 3.6.11).

3.4.3 Environmental Enrichment

Aspen wood based product	A soft white untreated wood block; provided to each cage throughout the study (except for F0 females during lactation and when F1 Cohort 1A animals were separated into single housing overnight during urine collection) and replaced when necessary.
Plastic shelter	Provided to each cage throughout the study (except for

	F0 animals when paired for mating and lactation and when F1 Cohort 1A animals were separated into single housing overnight during urine collection) and replaced at the same time as the cages.
Paper shavings	From Day 20 after mating and throughout lactation, approximately two handfuls of paper shavings were provided to each cage as nesting material; this nesting material was changed at the same frequency as the cage bedding.

3.4.4 Diet Supply

Diet	SDS VRF1 Certified powdered diet. The diet contained no added antibiotic or other chemotherapeutic or prophylactic agent.
Availability	Non-restricted (diet was removed overnight before blood sampling for hematology, blood chemistry and thyroid hormones and during the period of urine collection).

3.4.5 Water Supply

Supply	Potable water from the public supply via polycarbonate bottles with sipper tubes. Bottles were changed at appropriate intervals.
Availability	Non-restricted (except during urine collection).

3.4.6 Supplier Certificates of Analysis

Certificates of analysis for the diet were scrutinized and approved before any batch of diet was released for use. Certificates of analysis were routinely provided by the water supplier.

Certificates of analysis were also received from the suppliers of the softwood based bark-free fiber bedding and Aspen wood based product.

No specific contaminants were known that may have interfered with or prejudiced the outcome of the study and therefore no special assays were performed.

3.5 Dose Administration

3.5.1 Identity of Treatment Groups

The study consisted of one control and three treated groups identified as follows:

F0 generation

Group	Treatment	Dose (ppm)#		Number of animals		Animal numbers	
		Main phase	Lactation phase	Male	Female	Male	Female
1	Control	0	0	25	25	1-25	201-225
2	Sodium Trifluoracetate	120	60	25	25	26-50	226-250
3	Sodium Trifluoracetate	600	300	25	25	51-75	251-275
4	Sodium Trifluoracetate	3000	1500	25	25	76-100	276-300

Expressed in terms of material as supplied

F1 generation

Cohort	Group	Treatment	Dose (ppm)#		Number of animals		Animal numbers	
			Day 21 to nominal Day 35 of age	From nominal Day 35 of age	Male	Female	Male	Female
1A	1	Control	0	0	20	20	401-420	601-620
	2	Sodium Trifluoracetate	60	120	20	20	421-440	621-640
	3	Sodium Trifluoracetate	300	600	20	20	441-460	641-660
	4	Sodium Trifluoracetate	1500	3000	20	20	461-480	661-680
1B	1	Control	0	0	20	20	481-500	681-700
	2	Sodium Trifluoracetate	60	120	20	20	501-520	701-720
	3	Sodium Trifluoracetate	300	600	20	20	521-540	721-740
	4	Sodium Trifluoracetate	1500	3000	20	20	541-560	741-760

Expressed in terms of material as supplied

3.5.2 Administration

Route — Oral, via the diet.

Treated at — Constant dietary concentrations (ppm) for each group.

Primary (main phase) dose levels of 120, 600 and 3000 ppm dose levels were reduced to 60, 300 and 1500 ppm during the F0 lactation phase (up to termination of the F0 females and up to nominal Day 35 of age of the selected F1 animals).

Control (Group 1) — Untreated diet of the same batch.

Frequency — Continuously.

Diet — A record of the usage of the diets was maintained on all occasions when food consumption was measured. This was performed using the initial weight of the diet container and an on-line data check on completion of the feeding procedure to ensure that all cages were fed the correct amount of diet. No significant discrepancy was found.

3.6 Serial Observations

3.6.1 Clinical Observations - F0 and F1 Generation

Animals were inspected visually at least twice daily for evidence of ill-health or reaction to treatment. Cages were inspected daily for evidence of animal ill-health amongst the occupant(s). Any deviation from normal was recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate.

During the acclimatization period, observations of the animals and their cages were recorded at least once per day.

Clinical Signs
A detailed physical examination was performed on each animal to monitor general health according to the following schedule:

F0 males	Once each week.
F0 females	Once each week until mating detected. Days 0, 5, 12, 18 and 20 after mating and Days 1, 7, 14 and 21 of lactation.
F1 selected animals	Once each week.

3.6.2 Body Weight - F0 and F1 Generation
The weight of animals was recorded as follows:

F0 males	Day that treatment commenced. Each week. Before necropsy.
F0 females	Day that treatment commenced. Each week until mating detected. Days 0, 7, 14 and 20 after mating. Days 1, 4, 7, 14, 18, 21 and 28 of lactation. Before necropsy
F1 selected animals	Day 21 and 25 of age and then weekly from nominal four weeks of age (at the formal start of the F1 generation). Before necropsy.

3.6.3 Food Consumption - F0 and F1 Generation
The weight of food supplied to each cage, that remaining and an estimate of any spilled was recorded as follows:

F0 males	Each week until paired for mating.
F0 females	Each week until paired for mating. Days 0-6, 7-13, and 14-19 after mating. Days 1-3, 4-6, 7-13, 14-17 and 18-20 of lactation.
F1 selected animals	Each week from nominal four weeks of age.

From these records the mean weekly or daily consumption per animal (g/animal/week or g/animal/day) was calculated for each relevant phase.

3.6.4 Estrous Cycle Monitoring - F0 Generation

Dry and wet smears were taken as follows:

Dry smears	For 15 days before pairing, using cotton swabs.
Wet smears	Daily after pairing until evidence of mating confirmed, using pipette lavage. For four days before scheduled termination (nominally Days 25 to 28 post partum). Females that failed to litter or mate were retained and smeared for four days starting on the day on which the first batch of 'true' Day 25 post partum females started smearing, and were then killed with that first batch of females.

3.6.5 Mating Procedure - F0 Generation

F0 pairing commenced	After ten weeks of treatment.
Male/female ratio	1:1 from within the same treatment groups (sibling pairing was not permitted).
Duration of pairing	Up to two weeks.
Daily checks for evidence of mating	Ejected copulation plugs in cage tray and sperm in the vaginal smear.
Day 0 of gestation	When positive evidence of mating was detected.
Male/female separation	Day when mating evidence was detected.
Pre-coital interval	Calculated for each female as the time between first pairing and evidence of mating.

3.6.6 Parturition Observations and Gestation Length - F0 Generation

Duration of gestation	Time that elapsed between mating and commencement of parturition.
Parturition observations	From Day 20 after mating animals were checked three times daily for evidence of parturition. The progress and completion of parturition was monitored; numbers of live and dead offspring were recorded and any difficulties observed were noted.

3.6.7 Records Made During Littering Phase - F0 Generation

The records maintained were as follows:

Clinical observations	Observed approximately 24 hours after birth (Day 1 of age) and then daily for evidence of ill-health or reaction to treatment. On Day 1 of age, all offspring received a qualitative assessment of body temperature, state of activity and reaction to handling.
Litter size	Daily records were maintained of mortality and consequent changes in litter size from Days 1-21 of age. On Day 4 of age, litters containing more than ten offspring were reduced to ten by random culling, leaving, whenever possible, five male and five female offspring in each litter.
Sex ratio of each litter	Recorded on Days 1, 4 (before and after culling) and on Day 21 of age.
Individual offspring body weights	Recorded on Days 1, 4 (before culling), 7, 14 and 21 of age. Selected F1 generation: Days 25 of age. Unselected F1 offspring: Day 22 of age.
Weaning of offspring	The dam was removed from the litter cage and offspring were weaned on Day 21 of age.
Ano-genital distance	Day 1 of age - all offspring (See Section 4).
Nipple/areolae count	Day 13 of age - male offspring (See Section 4).

3.6.8 Sexual Maturation - F1 Generation - Cohorts 1A and 1B

Males	Sexual maturation was assessed by daily examination from Day 38 of age until balano-preputial separation occurred. Body weight was recorded on the day of completion of separation.
Females	Sexual maturation was assessed by daily examination from Day 25 of age until vaginal opening occurred. Body weight was recorded on the day of vaginal opening (See section 4). For Cohort 1A: a wet smear was taken daily from the day of vaginal opening until first estrus was detected.

3.6.9 Hematology, Peripheral Blood - F0 and F1 Cohort 1A Generation

Blood samples were collected after overnight withdrawal of food. Sampling for F1 Cohort 1A was performed on the morning after overnight collection of urine. These animals were, therefore, also deprived of water overnight but had access to water for a minimum period of one hour prior to the commencement of blood sampling procedures. Samples were collected at the following occasions:

Occasion	Generation	Animals
Termination	F0 Adults	Ten male and ten female animals per group
	F1 Cohort 1A	Ten male and ten female animals per group

Animals were held under light general anesthesia induced by isoflurane. Blood samples (nominally 0.5 mL) were withdrawn from the sublingual vein, collected into tubes containing EDTA anticoagulant and examined for the following characteristics using a Bayer Advia 120 analyzer:

- Hematocrit (Hct)*
- Hemoglobin concentration (Hb)
- Erythrocyte count (RBC)
- Mean cell hemoglobin (MCH)*
- Mean cell hemoglobin concentration (MCHC)*
- Mean cell volume (MCV)
- Total leucocyte count (WBC)
- Differential leucocyte count:
  - Neutrophils (N)
  - Lymphocytes (L)
  - Eosinophils (E)
  - Basophils (B)
  - Monocytes (M)
  - Large unstained cells (LUC)
- Platelet count (Plt)

* Derived values calculated in ClinAxys

Blood film (prepared for all samples) - Romanowsky stain, examined for abnormalities by light microscopy, in the case of flags from the Advia 120 analyzer. Confirmation or a written description from the blood film was made where appropriate.

Additional blood samples (nominally 0.5 mL) were taken into tubes containing citrate anticoagulant and examined using a Stago STA Compact Max analyzer and appropriate reagent in respect of:

- Prothrombin time (PT) - using IL PT Fibrinogen reagent.
- Activated partial thromboplastin time (APTT) - using IL APTT reagent.

3.6.10 Blood Chemistry - F0 and F1 Cohort 1A Generation

Blood samples were collected after overnight withdrawal of food. Sampling for F1 Cohort 1A was performed on the morning after overnight collection of urine. These animals were, therefore, also deprived of water overnight but had access to water for a minimum period of one hour prior to the commencement of blood sampling procedures. Samples were collected at the following occasions:

Occasion	Generation	Animals
Termination	F0 Adults	Ten male and ten female animals per group
	F1 Cohort 1A	Ten male and ten female animals per group

Animals were held under light general anesthesia induced by isoflurane. Blood samples (nominally 0.7 mL) were withdrawn from the sublingual vein and collected into tubes containing lithium heparin as anticoagulant. After separation, the plasma was examined using a Roche Cobas 6000 Analyzer in respect of:

- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transpeptidase (gGT)
- Total bilirubin (Bili)
- Urea
- Creatinine (Creat)
- Glucose (Gluc)
- Total cholesterol (Chol)
- Non esterified fatty acids (NEFA)
- Triglycerides (Trig)
- Sodium (Na)
- Potassium (K)
- Chloride (Cl)
- Calcium (Ca)
- Inorganic phosphorus (Phos)
- Total protein (Total Prot)
- Albumin (Alb)

Albumin/globulin ratio (A/G Ratio) was calculated from total protein concentration and analyzed albumin concentration.

3.6.11 Urinalysis - F1 Cohort 1A Generation

Urine samples were collected after overnight withdrawal of food and water at the following occasion:

Occasion	Generation	Animals
Termination	F1 Cohort 1A	Ten male and ten female animals per group

The individual samples were examined for the following characteristics:

- Using manual methods:
  - Clarity and Color (App) - by visual assessment
  - Volume (Vol) - using a measuring cylinder
  - pH - using a pH meter
  - Specific gravity (SG) - by direct refractometry using a SG meter

- Using Multistix reagent strips interpreted using the Clinitek®500 instrument:
  - Glucose (Gluc)
  - Ketones (Keto)
  - Bile pigments (Bili)
  - Blood pigments (UBld)

- Using a Cobas 6000 Analyzer:
  - Protein - total (T-Prot) and concentration (Prot)
  - Sodium - total (T-Na) and concentration (U-Na)
  - Potassium - total (T-K) and concentration (U-K)
  - Chloride - total (T-Cl) and concentration (U-Cl)

A microscopic examination of the urine sediment was performed. An aliquot of the urine sample was centrifuged, stained with Kova stain and the resulting deposit spread on a microscope slide. The number of elements seen in nine high or low power fields (HPF or LPF) was recorded in the raw data and entered onto the database and the number seen /HPF or /LPF was derived from these data as described below.

- Epithelial cells (Epi)
- Leucocytes (WBC)
- Erythrocytes (RBC)
- Casts
- Other abnormal components (A)

The slide was also examined for abnormalities in spermatozoa and crystals.

3.6.12 Thyroid Hormone Analysis - TSH and T4

Blood samples were collected at the following occasions:

Occasion	Generation	Animals
Termination	F0 Adults	Ten male and ten female animals per group
	F1 Offspring	Ten litters per group - pooled litter sample Day 4 of age#
		Ten male and ten female animals per group on Day 22 of age (one male and one female from up to 20 litters)
	F1 Adults - Cohort 1A	Ten male and ten female animals per group

T4 only.

Animal numbers are documented in Attachment 14.3 and Attachment 14.4.

Conditions	Adults: Following overnight deprivation of food. F1 Cohort 1A: coincided with urine collection, animals were therefore deprived of water overnight but had access to water for a minimum period of one hour prior to blood sampling. Offspring: No overnight deprivation of food.
Blood sample site	Adults and offspring at Day 22 of age: Sublingual vein. Offspring Day 4 of age: Decapitation
Anesthetic	Adults and offspring at Day 22 of age: Isoflurane. Offspring Day 4 of age: not required.
Anticoagulant	None.
Tubes	Greiner Minicollect - with clot activator.
Blood volume	Adults and offspring at Day 22 of age: 1.0 mL. Offspring Day 4 of age: maximum possible
Treatment of samples	Samples were kept at ambient temperature (15 to 25°C) for a minimum of 30 minutes prior to centrifugation.
Centrifugation conditions	At 2000 *g* for ten minutes at 4°C.
Number of aliquots	Adults and offspring at Day 22 of age: Two per animal. Aliquot 1: 0.2 mL serum for T4 Aliquot 2: residual serum for TSH Offspring Day 4 of age: single aliquot for T4 analysis, all available collected.
Final storage conditions	Deep frozen (approximately -60°C to -90°C).
Fate of samples	Dispatched to the Department of Bioanalysis, [redacted]

T4 Analysis	By the Department of Bioanalysis, [redacted] Serum samples for adults and offspring at Day 22 of age were analyzed. Serum samples obtained from F1 offspring at Day 4 of age were retained frozen (-60 to -90ºC) pending future requirement for analysis. The method of analysis and results are presented in Attachment 14.3.
TSH Analysis	By the Department of Immunology and Immunotoxicity, [redacted] The method of analysis and results are presented in Attachment 14.4.

3.7 Cohort Specific in Life Investigations - F1 Generation

3.7.1 Estrous Cycle Monitoring - Cohort 1A

Dry and wet smears were taken as follows:

Wet smears (using pipette lavage)	Following onset of vaginal patency until first cornified (estrus) smear was recorded. For at least three days prior to the start of the necropsy phase and on the day of termination.
Dry smears (using cotton swabs)	For two weeks from approximately Day 75 of age.

3.7.2 Estrous Cycle Monitoring - Cohort 1B

Wet smears (using pipette lavage)	For at least three days prior to the start of the necropsy phase and on the day of termination.

3.8 Terminal Investigations

3.8.1 Time of Necropsy

F0 males	After weaning of the F1 animals, after confirmation that no further mating required.
F0 females	Day 28 post partum.
F0 females failing to produce a viable litter	Terminated with first cohort of females with live litters.
Unselected offspring	F1 litters: Culled on Day 4 and Day 22 of age.
Cohort 1A animals	At approximately 13 weeks of age.
Cohort 1B animals	At approximately 14 weeks of age.

3.8.2 Method of Kill

Animals	Animals 14 days and older: Carbon dioxide asphyxiation with subsequent exsanguination. Animals less than 14 days of age: Intraperitoneal injection of sodium pentobarbitone.
Day 4 offspring selected for blood sampling	Decapitation.
Sequence	To allow satisfactory inter-group comparison.

3.8.3 Macroscopic examination

All animals, including surplus offspring culled on Day 4 of age and Day 22 of age unselected offspring were subject to a complete macroscopic examination. Any abnormality in the appearance or size of any organ and tissue was recorded and the required tissue samples preserved in appropriate fixative. Decedents offspring ≤21 days of age, (found dead or welfare kill), where possible, were examined and carcass retained.

For F0 females the implantation site count was recorded.

For females of Cohort 1A, counts were performed for the number of ovarian follicles and corpora lutea.

The organs weighed, tissue samples fixed and sections examined microscopically (if applicable) are detailed as follows:

Table 1
Pathology procedures - F0 Animals

Tissue and regions examined	Necropsy		Histology	Pathology
	Weigh	Fix		Light microscopy
Abnormalities		*	*	*
Adrenals	*	*	*	*
Brain (cerebellum, cerebrum, midbrain)	*	*	*	*
Cecum		*	*	*
Colon		*	*	*
Duodenum		*	*	*
Epididymides	L+R	R	R	R
Esophagus		*	*	*
Eyes		*	*	*
Femurs - (longitudinal section through joint)		a)	*	*
Heart (including auricular and ventricular regions)	*	*	*	*
Ileum		*	*	*
Jejunum		*	*	*
Kidneys	*	*	*	*
Liver (section from two lobes)	*	*	*	*
Lungs (section from two major lobes including bronchi)		*	*	*
Optic nerves		*	*	*
Ovaries	*	*	*	*
Pancreas		*	*	*
Pituitary	*	*	*	*
Prostate - dorsolateral and ventral combined	*	*	*	*
Rectum		*	*	*
Sciatic nerves		*	†	†
Seminal vesicles (with coagulating gland)	*	*	*	*
Skeletal muscle		*	†	†
Skin with mammary glands (inguinal area)		*	*	*
Spinal cord (transverse and longitudinal sections at the cervical, thoracic and lumbar levels)		*	*	*
Spleen	*	*	*	*
Sternum - bone marrow		*	*	*
Stomach		*	*	*
Testes	L+R	R	R	R
Thymus	*	*	*	*
Thyroid with parathyroids	b)	*	*	*
Trachea		*	*	*
Urinary bladder		*	*	*
Uterus with cervix and oviducts	*	*	*	*
Vagina		*	*c)	*
Vas Deferens		†	†	†

a) Both hindlimbs retained, one sectioned where appropriate.
b) Weighed after partial fixation.
c) Section approximately 5mm from vulva
* Organs weighed, samples fixed or sections examined microscopically.
† Only one examined.
L Left
R Right.
Animal ID retained

Table 2
Pathology procedures - F1 Cohort 1A - Tissue retention, organ weights and tissue processing

Tissue and regions examined	Necropsy		Histology	Pathology
	Weigh	Fix		Light microscopy
Abnormalities		*	*	*
Adrenals	*	*	*	*
Brain (cerebellum, cerebrum, midbrain)	*	*	*	*
Cecum		*	*	*
Colon		*	*	*
Duodenum		*	*	*
Epididymides	L+R	R	R	R
Esophagus		*	*	*
Eyes		*	*	*
Femurs - (longitudinal section through joint)		a)	*	*
Heart (including auricular and ventricular regions)	*	*	*	*
Ileum		*	*	*
Jejunum		*	*	*
Kidneys	*	*	*	*
Liver (section from two lobes)	*	*	*	*
Lungs (section from two major lobes including bronchi)		*	*	*
Lymph nodes - mesenteric	*	*	*	*
- left axillary	*	*	*	*
Optic nerves		*	*	*
Ovaries	L+R	L+R	L+R b)	L+R
Pancreas		*	*	*
Pituitary	*	*	*	*
Prostate – dorsolateral and ventral combined	*	*	*	*
Rectum		*	*	*
Sciatic nerves		*	†	†
Seminal vesicles (with coagulating gland)	*	*	*	*
Skeletal muscle		*	†	†
Skin with mammary glands (inguinal area)		*	*	*
Spinal cord (transverse and longitudinal sections at the cervical, thoracic and lumbar levels)		*	*	*
Spleen	*	#	*	*
Sternum - bone marrow		*	*	*
Stomach		*	*	*
Testes	L+R	R	R	R
Thymus	*	*	*	*
Thyroid with parathyroids	c)	*	*	*
Trachea		*	*	*
Urinary bladder		*	*	*
Uterus with cervix and oviducts	*	*	*	*
Vagina		*	*d)	*
Vas Deferens		*	*	*

a) Both hindlimbs retained, one sectioned where appropriate.
b) Fixed identified as L+R. Five sections cut at approximately 100 micron intervals from the inner third of each ovary
c) Weighed after partial fixation.
d) Section approximately 5mm from vulva
* Organs weighed, samples fixed or sections examined microscopically.
† Only one examined.
# 3-5mm section of spleen preserved for histopathological examination; remaining used for splenic lymphocyte subpopulation analysis (CD4+ and CD8+ T lymphocytes and natural killer cells).
L Left
R Right
Animal ID retained

Table 3
Pathology procedures - F1 Cohort 1B - Tissue retention, organ weights and tissue processing

Tissue and regions examined	Necropsy		Histology
	Weigh	Fix	
Abnormalities		*	*
Adrenals		*	
Brain (cerebellum, cerebrum, midbrain)		*	
Cecum		*	
Colon		*	
Duodenum		*	
Epididymides	*	*	*
Esophagus		*	
Eyes		*	
Femurs - (longitudinal section through joint)		a)	
Heart (including auricular and ventricular regions)		*	
Ileum		*	
Jejunum		*	
Kidneys		*	
Liver (section from two lobes)		*	
Lungs (section from two major lobes including bronchi)		*	
Lymph nodes – mesenteric		*	
- left axillary		*	
Optic nerves		*	
Ovaries	L+R	L+R	L+R
Pancreas		*	
Pituitary	*	*	*
Prostate – dorsolateral and ventral combined	*	*	*
Rectum		*	
Sciatic nerves		*	
Seminal vesicles (with coagulation gland)	*	*	*
Skeletal muscle		*	
Skin with mammary glands (inguinal area)		*	
Spinal cord (transverse and longitudinal sections at the cervical, thoracic and lumbar levels)		*	
Spleen		*	
Sternum - bone marrow		*	
Stomach		*	
Testes	*	*	*
Thymus		*	
Thyroid with parathyroids		*	
Trachea		*	
Urinary bladder		*	
Uterus with cervix and oviducts	*	*	*
Vagina		*	*
Vas Deferens		*	

a) Both hindlimbs retained, one sectioned where appropriate.
* Organs weighed, samples fixed or sections examined microscopically.
L Left
R Right
Animal ID retained

Table 4
Pathology procedures - Unselected F1 offspring on Day 22 of age
Ten male and ten females per group; one male or one female from each litter to ensure that all litters are represented.

Tissue and regions examined	Necropsy	
	Weigh	Fix
Abnormalities		*
Brain (cerebellum, cerebrum, midbrain)	*	*
Epididymides		*
Ovaries		*
Pituitary		*
Prostate		*
Seminal vesicles		*
Skin with mammary glands (inguinal area)		*
Spleen	*	*
Testes		*
Thymus	*	*
Uterus with cervix and oviducts		*
Vagina		*

Animal ID retained

The retained tissues were checked before disposal of the carcass.

3.8.4 Sperm Analysis - F0 and F1 Cohort 1A Generation

Immediately after scheduled sacrifice of each F0 and F1 Cohort 1A male and collection of blood, the left vas deferens, epididymis and testis were removed and the epididymis and testis were weighed.

The following tests were performed:

Sperm motility: all groups	A sample of sperm was expressed from the left vas deferens (F1 Group 4 animal 462 right vas deferen used) into prewarmed (target 37°C) medium M199, which contained 0.5% w/v bovine serum albumin (BSA Fraction V). A sample for assessment was taken into a 100 µm depth cannula by capillary action and, at least 200 sperm per animal analyzed using the Hamilton Thorne IVOS II Computer Assisted Sperm Analyzer (CASA). There was insufficient sperm to assess 200 sperm for Group 1 male 7 and no viable sperm in sample for Group 3 male 54 for F0 generation.
Sperm morphology: F0 - Groups 1 and 4 F1 Cohort 1A – all groups	A 200 µL aliquot of the sperm/medium mixture (described above) was diluted with 800 µL of 10% neutral buffered formalin. After staining with nigrosine and eosin an air-dried smear was prepared. Slides were examined by light microscopy for the assessment of sperm morphology. At least 200 sperm were assessed for each male.
Sperm morphology: Groups 2 and 3	Fixed samples retained for possible future assessment.

Sperm count: Groups 1 and 4	The left cauda epididymis of each male (F1 Group 4 animal 462 right cauda epididymis used) was weighed and then the tunica was removed, then homogenized for at least 30 seconds in 10 mL of a mixture of 0.9% saline and 0.01% merthiolate (SM). An aliquot of this mixture was added to a pre-prepared IDENT stain tube before being assessed for sperm count using CASA.
Sperm count: Groups 2 and 3	Samples frozen for possible future assessment.
Homogenization-resistant spermatid counts: Groups 1 and 4	After removal of the tunica, the left testis of each male (F1 Group 4 animal 462 right cauda epididymis used) then homogenized for at least 30 seconds in 25 mL of SM. An aliquot of this mixture was added to a pre-prepared IDENT stain tube before being assessed for homogenization-resistant spermatid count using CASA.
Homogenization-resistant spermatid counts: Groups 2 and 3	Samples frozen for possible future assessment.

3.8.5 Organ Weights

For bilateral organs, left and right organs were weighed together, unless specified in the relevant pathology procedures table. Requisite organs were weighed for animals killed at scheduled intervals (See Section 4).

For unselected F1 offspring on Day 22 of age, organs were weighed from ten males and ten females per sex per group from as many litters as possible.

3.8.6 Fixation

F0 animals, unselected F1 animals, Cohorts 1A and 1B

Tissues were routinely preserved in 10% Neutral Buffered Formalin with the exception of those detailed below:

Testes - F0 and F1 adults only	Initially in modified Davidson's fluid.
Eyes	In Davidson's fluid.

3.8.7 Histology

F0 animals and Cohort 1A

Processing	Tissue samples were dehydrated, embedded in paraffin wax and sectioned at a nominal four to five micron thickness. For bilateral organs, sections of both organs were prepared. A single section was prepared from each of the remaining tissues required.
Full List	All terminal adult animals of Groups 1 and 4 killed at a scheduled interval.

Processing - abnormalities only	All terminal adult animals of Groups 2 and 3 killed at a scheduled interval.
Processing - reproductive organs only	The reproductive organs were examined from F0 animals in Groups 2 and 3 that showed reduced fertility. This included males that failed to sire a pregnancy and females that were not pregnant or failed to litter.
Processing - stomach	F0/F1 Cohort 1A: All terminal female animals of Groups 2 and 3.
Routine staining	Sections were stained with hematoxylin and eosin.
Cohort 1B	
Processing	Tissue samples were dehydrated and embedded in paraffin wax.
Reproductive organs (to slide)	All animals.
Abnormalities (to block)	All animals.

3.8.8 Immunophenotyping of Spleen Leucocytes - Cohort 1A

Ten males and ten females per group from F1Cohort 1A were selected for immunophenotyping. Where possible, one male or one female was assigned from each selected litter.

The whole spleen was weighed. After weighing, a 3-5 mm mid transverse section was removed and retained for histopathological evaluation. The remaining portions of the spleen was then weighed, placed into a vial of chilled Hank's Balanced Salt Solution (HBSS) and held in wet ice until processing for analysis.

Samples were sent via courier to the Department of Immunology and Immunotoxicology (I&I), [redacted] A copy of the whole spleen and partial spleen weights were provided to I&I.

The sample processing, method of analysis and results are presented in Attachment 14.5.

3.8.9 Light Microscopy - F0 Animals and Cohort 1A

Tissues preserved for examination were examined as follows:

Category	Generation/Cohort	Animals	Tissues
Terminal sacrifice	F0	All animals of Groups 1 and 4.	All specified in Table 1.
		All animals of Groups 2 and 3.	Abnormalities only.
		All females of Groups 2 and 3.	Stomach
		All animals of Groups 2 and 3 with suspect fertility	Reproductive organs only
	F1 Cohort 1A	All animals of Groups 1 and 4.	All specified in Table 3
		All animals of Groups 2 and 3.	Abnormalities only.
		All females of Groups 2 and 3.	Stomach
	F1 Cohort 1B	All animals.	Abnormalities only.

Right testis (except F1 Group 4 male no 462)	A detailed qualitative examination was made, taking into account the tubular stages of the spermatogenic cycle. The examination was conducted in order to identify treatment related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and sloughing of spermatogenic cells into the lumen. Any cell- or stage-specificity of testicular findings was noted.
Ovaries	F0 and F1 Cohort 1A – Qualitative evaluation of one section from each ovary Cohort 1A – Qualitative evaluation of five sections from each ovary with quantitative assessment of primordial follicle and small growing follicle populations as well as corpora lutea.
Vagina	The stage of vaginal estrus was evaluated based on vaginal epithelial morphology (and appearance of the uterus and endometrial glands).

All other findings were either reported as "present" or assigned a severity grade. In the latter case one of the following five grades was used – minimal, slight, moderate, marked or severe. A reviewing pathologist undertook a peer review of the microscopic findings.

3.9 Data Evaluation

This report contains serial observations pertaining to all days or weeks of treatment completed, together with signs data collected during the necropsy period. No serial observations relating to the acclimatization period are included in this report.

Summary statistics (e.g. means and standard deviations) presented in this report were calculated from computer-stored individual raw data. The summary statistics and the individual data were stored in the computer to a certain number of decimal places, different for each parameter. For presentation purposes, however, they were usually rounded to fewer places. It is, therefore, not generally possible to reproduce the presented means and standard deviations exactly using the presented individual data.

For the F1 generation the day numbers in the 'Treatment' phase refer to Day of age and the day numbers in the 'Treatment 2' phase refer to the Day of the formal F1 generation.

3.9.1 Serial Observations

Achieved Dose

Achieved dose is presented for the relevant phases before pairing, during gestation and lactation (F0) and treatment (selected F1).

The group mean achieved dose for each sex, expressed as mg/kg/day, was calculated for each phase from the nominal dietary test item concentration, food consumption and body weight data.

The following formula was used:

$$\text{Achieved dose (mg/kg/day)} = \frac{\text{Food consumed (g/rat) x dietary concentration (ppm)}}{\text{Mid-phase body weight (g) x number of days in phase}}$$

The 'food consumed' was calculated as indicated in the Food Consumption section. The mid-phase body weight was calculated for each individual animal and the mean used in the formula.

Overall group mean values were calculated from the weekly group mean values presented.

Clinical Observations
Clinical observations are presented for each animal that showed signs, providing detail of the type of sign, day of occurrence and information on the duration of the sign applicable.

Body Weight
Group mean values and SD were calculated from individual body weight data on each recorded occasion. For the offspring, litter mean body weight (+SD) was calculated separately for males and females and the group mean values derived from the individual litter values.

Group mean weight changes were calculated from the weight changes of individual animals. Offspring body weight change was calculated relative to Day 1 of age.

Body weights were plotted graphically with respect to the first day of the relevant period.

Food Consumption
Group mean food consumptions and standard deviations for each period were derived from unrounded cage values. Where animals were gang housed, values were presented for the average amount of food consumed per animal in each cage.

After Day 14 of lactation, food consumption is increasingly influenced by the offspring and is no longer an accurate reflection of maternal consumption.

The column header day numbers represent the days on which the full feeder and empty feeder were recorded.

Estrous Cycles – F0 and F1 Cohort 1A and 1B Generation
The incidence and percentage of F0 and F1 Cohort 1A showing the following classifications of estrous cycles during the 2-week smearing period were presented as:

Regular:	All observed cycles of 4 or 5 days (divided into cycles of 4, 4 and 5 and 5 days)
Irregular:	At least one cycle of 2, 3 or 6 to 10 days
Acyclic:	At least 10 days without estrus

Results of smears from vaginal opening until first estrus for F1 Cohort 1A females was presented in terms of the days elapsing between vaginal opening and the first estrus smear.

Results of pre-termination smears for F0 and F1 Cohort 1A and 1B females was presented in terms of numbers of animals that showed estrus during the period and the cycle stage at termination (See Section 4).

Pre-coital Interval – F0 Generation
Individual intervals were tabulated for the time elapsing between initial pairing and mating. Percentage of females with pre-coital intervals calculated for durations of 1-4, 5-8, 9-12 or 13-14 days of pairing.

Mating Performance and Fertility – F0 Generation
Individual data was tabulated. Group values were calculated for males and females separately for the following:

$$\text{Percentage mating (\%)} = \frac{\text{Number of animals mating}}{\text{Animals paired}} \times 100$$

$$\text{Conception rate (\%)} = \frac{\text{Number of animals achieving pregnancy}}{\text{Animals mated}} \times 100$$

$$\text{Fertility index (\%)} = \frac{\text{Number of animals achieving pregnancy}}{\text{Animals paired}} \times 100$$

Gestation Length and Gestation Index – F0 Generation
Gestation length was calculated as the number of gestation days up to and including the day on which offspring were first observed, with Day 1 = day of mating for calculation purposes. Where parturition had started overnight, this value was adjusted by subtracting half of one day.

Gestation index was calculated for each group as:

$$\text{Gestation index (\%)} = \frac{\text{Number of live litters born}}{\text{Animals paired}} \times 100$$

Sexual Maturation – F1 Generation (Cohorts 1A and 1B)
Individual values were tabulated for age and body weight at completion. Group mean values were calculated from individual values presented.

Blood Chemistry – F0 and F1 Cohort 1A Generation
Albumin to globulin ratio (A/G Ratio) was calculated as:

$$\text{A/G Ratio} = \frac{\text{Albumin concentration}}{\text{Total protein} - \text{albumin concentration}}$$

Urinalysis – F1 Cohort 1A Generation
Group means and standard deviations are presented for volume, Ph, specific gravity, protein and electrolytes only.

Litter Size – F0 Generation
Individual litter values were tabulated for the number of implantation sites, total at Day 1 and live at Days 1, 4 (before and after culling), 7, 14 and 21 of age. Group mean litter size and SD were calculated from the individual litter values.

Survival Indices – F0 Generation
The following were calculated for each litter:

$$\text{Post implantation survival index (\%)} = \frac{\text{Total number of offspring born}}{\text{Total number of uterine implantation sites}} \times 100$$

Post-implantation survival index was expressed as 100% where the number of offspring exceeded the number of implantation sites recorded.

$$\text{Live birth index (\%)} = \frac{\text{Number of offspring on Day 1 after littering}}{\text{Total number of offspring born}} \times 100$$

$$\text{Viability index (\%)} = \frac{\text{Number of live offspring on Day 4 before culling}}{\text{Number of live offspring on Day 1 after littering}} \times 100$$

$$\text{Lactation index (\%)} = \frac{\text{Number of live offspring on Day 21 after littering}}{\text{Number of live offspring on Day 4 (after culling)}} \times 100$$

Group mean values were calculated from individual litter values.

Sex Ratio – F0 Generation
The percentage of male offspring in each litter was calculated at Day 1, and for live offspring on Days 1, 4 (before and after culling) and 21 of age.

$$\text{Percentage males} = \frac{\text{Number of males in litter}}{\text{Total number of offspring in litter}} \times 100$$

Group mean values were calculated from individual litter values.

Offspring Examinations – F0 Generation
Ano-genital distance were presented both as absolute/unadjusted and adjusted for body weight, using the weight recorded on Day 1 of age.

A check was performed to assess for the presence or absence of nipple/areolae for the male offspring on Day 13 of age. As no nipples were present, no data are included.

3.9.2 Terminal Investigations

Sperm Analysis – F0 and F1 Cohort 1A Generation
Individual values were tabulated for the following:

Motility	The percentages of motile and progressively motile sperm and sperm motion parameters were reported.
Morphology	The number and percentages of normal and abnormal sperm were reported. A summary of the types of abnormalities seen was not made because there was no evidence of an effect on the percentage normal sperm.
Count (Testis and Cauda epididymis)	The sperm concentration (Million/g) and total number were reported.

The following definitions relate to the sperm motion data:

VAP	the average path velocity, this is the average velocity of the smoothed cell path.
VSL	the progressive or straight line velocity, this is the average velocity measured in a straight line from the beginning to the end of the track.
VCL	the curvilinear velocity or track speed, this is the average velocity measured over the actual point to point track followed by the cell.
ALH	amplitude of lateral head displacement, this is the mean over all cell tracks of twice the maximum displacement between each sperm track and its average path. This corresponds to the average of the sperm track width.
BCF	beat cross frequency, this is the frequency with which the sperm head crosses the sperm average path.
STR	straightness, the average value of the ratio VSL/VAP which measures the departure of the cell path from a straight line.
LIN	linearity, the average value of the ratio VSL/VCL which measures the departure of the cell track from a straight line.
Rapid	the fraction of cells moving with VAP > progressive minimum VAP.
Medium	the fraction of cells moving with slow VAP cut-off < VAP < progressive minimum VAP.
Slow	the fraction of cells moving with VAP< slow VAP cut-off or VSL < slow VSL cut-off.
Static	the fraction of all cells which are not moving at all.

Organ Weights
Where paired organ weights were weighed separately, these were summed for the presentation of group mean values. For adults and offspring organ weights, group mean values and SD were calculated for absolute weights and also for weights expressed relative to body weight (%) using the body weight recorded on the day of necropsy.

Macroscopic Pathology
Findings from examination of offspring were presented in the appendix on an individual basis for affected litters and offspring. There were no macroscopic findings at scheduled termination for F1 offspring and consequently no data were presented in this report.

3.10 Statistical Analysis
Statistical analyses were performed on the majority of data presented and results of these tests, whether significant or non-significant, are presented on the relevant tables. The similarity of the data was such that analyses were not considered to be necessary.

All statistical analyses were carried out separately for males and females. Data relating to food consumption were analyzed on a cage basis (except during gestation and lactation). For all other adult parameters, the analyses were carried out using the individual animal as the basic experimental unit. For litter/fetal findings the litter was taken as the treated unit and the basis for statistical analysis and biological significance was assessed with relevance to the severity of the anomaly and the incidence of the finding within the background control population.

The following data types were analyzed at each timepoint separately:

Body weight, using absolute weights and gains over appropriate study periods
Food consumption, over appropriate study periods
Hematology
Blood chemistry
Urinalysis
Thyroid hormones
F0 Estrous cycles
F0 Gestation length
F1 Cohort 1A estrus before termination
Litter (implantations, litter size, sex ratio – percentage male, post implantation survival index, live birth index and viability index), for before cull study periods
Ano-genital distance, adjusted for Day 1 pup body weight
Sexual maturation, age and body weight at completion
Sperm analysis motility, morphology and counts
Organ weights, absolute and relative to body weight

The following comparisons were performed:

Group 1 vs 2, 3 and 4
Group 1 vs 4 (as applicable)

The following sequence of statistical tests was used for body weight, food consumption, implantations, litter size, sex ratio – percentage male, post implantation survival index, ano-genital distance, sexual maturation, sperm analysis, organ weight and clinical pathology data:

A parametric analysis was performed if Bartlett's test for variance homogeneity (Bartlett, 1937) was not significant at the 1% level. For pre-treatment data, analysis of variance was used to test for any group differences. Where this was significant ($p<0.05$) inter group comparisons using *t*-tests, with the error mean square from the one-way analysis of variance, were made. For all other analyses the F_1 approximate test was applied. This test is designed to detect significant departure from monotonicity of means when the main test for the comparison of the means is a parametric monotonic trend test, such as Williams' test (Williams, 1971; 1972). The test statistic compares the mean square, NMS, for the deviations of the observed means from the maximum likelihood means, calculated under a constraint of monotonicity with the usual error mean square, EMS. The null hypothesis is that the true means are monotonically ordered. The test statistic is F_1 = NMS/EMS which can be compared with standard tables of the *F* distribution with 1 and error degrees of freedom. If the F_1 approximate test for monotonicity of dose-response was not significant at the 1% level, Williams' test for a monotonic trend was applied. If the F_1 approximate test was significant, suggesting that the dose response was not monotone, Dunnett's test (Dunnett, 1955; 1964) was performed instead. Where there were only two groups, comparisons were made using *t*-tests.

A non-parametric analysis was performed if Bartlett's test was still significant at the 1% level following both logarithmic and square-root transformations. For pre-treatment data, Kruskal-Wallis' test (Kruskal and Wallis, 1952; 1953) was used to test for any group differences. Where this was significant ($p<0.05$) inter group comparisons using Wilcoxon rank sum tests (Wilcoxon, 1945) were made. For all other analyses the H_1 approximate test, the non-parametric equivalent of the F_1 test described above, was applied. This test is designed to be used when the main test for comparison of the means is a non-parametric monotonic trend test, such as Shirley's test (**Error! Reference source not found.**, 1977). The test statistic compares the non-monotonicity sums of squares, NRSS, for the deviations of the observed mean ranks from the maximum likelihood mean ranks with the non-parametric equivalent of the error sums of squares, ERSS = N(N+1)/12. The test statistic is H_1 = NRSS/ERSS which can be compared to standard tables of the χ^2-distribution with 1 degree of freedom. If the H_1 approximate test for monotonicity of dose-response was not significant at the 1% level, Shirley's test for a monotonic trend was applied. If the H_1 approximate test was significant, suggesting that the dose-response was not monotone, Steel's test (Steel, 1959) was performed instead. Where there were only two groups, comparisons were made using Wilcoxon rank sum tests (Wilcoxon, 1945).

For clinical pathology and sperm analysis data, if 75% of the data (across all groups) were the same value, for example c, Fisher's exact tests (Fisher, 1973) were performed. Treatment groups were compared using pairwise comparisons of each dose group against the control both for i) values <c versus values ≥c, and for ii) values ≤c versus values >c, as applicable.

For live birth and viability indices dichotomized to 1 when 100% and 0 otherwise, if the Cochran-Armitage test (Armitage, 1955) was significant at the 5% level, then the direction of the trend was established and one-tailed step-down testing in this direction was performed. If the Cochran-Armitage test was not significant at the 5% level, then a Chi-square test (Armitage et al., 2002) was applied. If the Chi-square test was significant at the 5% level, the treatment groups were compared using pairwise comparisons of each dose group against the Control using Fisher's exact tests (Fisher, 1973); otherwise, no further comparisons were made.

For F0 gestation length an exact two-tailed Linear-by-linear test (Cytel, 1995), with equally spaced scores, was applied to all groups. If the test was statistically significant ($p<0.05$), the highest dose group was excluded and the test re-applied. This 'step-down' process was repeated until the test was no longer statistically significant ($p\geq0.05$). If the exact version of the Linear-by-linear test could not be calculated (due to the size of the table containing the data), then the asymptotic version was used instead.

For F0 estrous cycles an exact one-tailed (upper-tail) Linear-by-linear test (Cytel, 1995) was applied to all groups, using scores appropriate to the severity of the observation assuming 4 day cycles to be normal. The categories were scored as follows: a 4 day cycle was scored as 4, a 4/5 day cycle was scored as 4.5, a 5 day cycle was scored as 5 and irregular and acyclic cycles were scored as 6. If the test was statistically significant ($p<0.05$), the highest dose group was excluded and the test re-applied. This 'step-down' process was repeated until the test was no longer statistically significant ($p\geq0.05$). If the exact version of the Linear-by-linear test could not be calculated (due to the size of the table containing the data), then the asymptotic version was used instead.

For F1 Cohort 1A estrus before termination,an exact one-tailed (lower-tail) Cochran-Armitage test (Cytel, 1995) was applied to all groups. If the test was statistically significant (p<0.05), the highest dose group was excluded and the test re-applied. This 'step down' process was repeated until the test was no longer statistically significant (p≥0.05).

For the litter average ano-genital distance, analysis of covariance was performed using the average pup bodyweight for each litter as the covariate (Angervall and Carlstrom, 1963), unless non-parametric methods were applied. The treatment comparisons were made on adjusted group means in order to allow for differences in body weight which might influence the organ weights.

Significant differences between the groups compared were expressed at the 5% (p<0.05) or 1% (p<0.01) level. The key to the annotation used on the tables that contain statistical results is given below:

l	Data were log transformed for the statistical analysis
Av	Pre-treatment comparison of all groups using Analysis of variance followed by pairwise *t*-tests.
CA	Trend test using Cochran-Armitage test
Ch	Comparison of all groups using Chi-square test
Du	Treated groups compared with Control using Dunnett's test
Fe	Treated groups compared with Control using Fisher's exact test
Lt	Comparison of all groups using Linear by Linear tests
Sh	Treated groups compared with Control using Shirley's test
Tt	Group 4 compared to Control using the *t*-test.
Wc	Treated groups compared with Control using Wilcoxon's test
Wi	Treated groups compared with Control using Williams' test
*	p<0.05
**	p<0.01

Codes placed above the adjusted means indicate that the comparisons were based on adjusted means.

4. DEVIATIONS FROM STUDY PLAN

Category	Deviations
Animal Data Collection	It was noted at data check on 26 Jan 2021 that no ano-genital distances were recorded for 4F (Dam 283) on female pups 9-12. This omission has no impact on study integrity because of the group size and sample size.
Environment	On the 10 Nov 2020 the maximum temperature in the study room was recorded as 48c and the minimum 46c. It appears the values were recorded incorrectly in error or there was a failure with the thermo-hygrometer due to the extreme values. There is a comment on the study log to confirm that the values were in range at the time of the data check. Temperature was out of range on the 12 and 13 November 2020. The expected range was 20 to 24°C and the minimum temperature was recorded as 18°C on both occasions On 3/4 December 2020 humidity recorded at 33% at initial check, humidity should be 40-70%. Animal room back in range at initial check on 05 December 2020. No adverse effect on the animals noted. As the deviations were slight and the clinical condition of the animals was not affected these had no impact on study integrity.
Missed/Extra Procedure	Noted nipple count not performed on Litter 225 at day 13 in error in 8439567. The isolated omission for a Group 1 litter has no impact on study integrity.
Early/Late Procedure	It has been noted that the incorrect Day 25 had been calculated for some of the group 3 female animals in Cohort 1B. This meant that animals have had vaginal opening checks starting one day late: 3F 723-729 were day 25 on 15 Feb 2021 however did not receive vaginal opening checks until the 16 Feb; 3F 731-733 were day 25 on 16 Feb but did not have vaginal openings performed until the 17 Feb; 3F 739 was Day 25 on 17 Feb but did not have vaginal opening performed until 18 Feb. All of the animals affected did not complete vaginal openings for several days after they were initially checked so the error did not affect any completion dates. As all animals were incomplete at the start of the assessment there was no impact on study integrity.
Missed/Extra Procedure	Contrary to protocol, the brain weight for animal 406 and the adrenal weight for 646 were not taken. No valid brain weight was taken for animal 622, as it was found to be erroneous at data check and has been excluded. In addition, a figure has been entered into the immuno-spleen weight for animal 456, which did not have this sample taken. These isolated data recording errors will not impact on study integrity

These study deviations neither affected the overall interpretation of study findings nor compromised the integrity of the study.

5. ARCHIVING

Records and documentation relating to this study (including electronic records) will be maintained in the archives of [redacted] for a period of five years from the issue of the final report. This will include raw data, specimens, and sample of test and reference items that support the reconstruction of the study. Test Facility-generated electronic raw data will be stored on the computer system on which the data application resides or archived off-line. Specimens that no longer afford evaluation will be discarded in accordance with Standard Operating Procedures and without further notice.

At termination of the aforementioned period, the Sponsor will be contacted in order to determine the final disposition of these records and materials. After the specified period, the Sponsor is responsible for all costs associated with the retention, retrieval, onward transfer or destruction/disposal of these materials. If the Sponsor is unresponsive the records will be destroyed in accordance with the [redacted] Standard Operating Procedure.

In case records are transferred, the Sponsor should ensure that the materials and records in support of regulatory studies are retained and maintained under conditions that guarantee their integrity and continued access according to archiving requirements of the principles of GLP. The Sponsor should also ensure that such materials and records are retained for as long as required by relevant authorities.

[redacted] will retain the study plan (electronically), final report and any amendments indefinitely.

6. RESULTS

6.1 Formulation Analysis

Attachment 14.2

The mean achieved concentrations for formulation samples taken during the course of this study were within – 15%/+10% of nominal concentrations confirming the accuracy of formulation. Mean recovery results obtained at each concentration on each analytical occasion were within ±10% of nominal (except for 300 ppm at lactation with a mean 88.9% of nominal), demonstrating the continued accuracy of the method.

6.2 Thyroid Hormone Analysis

6.2.1 Thyroxine (T4)

Attachment 14.3; Attachment 14.8

Mean serum T4 concentrations in F0 males at 3000 ppm and females at 3000/1500 ppm were low when compared with Controls ($p<0.01$).

At 1500 ppm mean serum T4 concentrations for F1 male and female offspring on Day 22 of age were low when compared with Controls ($p<0.01$), with most individual values below the lowest value in the concurrent Controls. The mean serum T4 concentration in male offspring only at 300 ppm was slightly low ($p<0.05$) and as the value was very close to the mean historical control data (HCD) value no effect of treatment was inferred.

Mean serum T4 concentrations in F1A males at 600 or 3000 ppm were low when compared with Controls ($p<0.01$), with most individual values below the lowest value in the concurrent Controls. At 120 ppm, the mean T4 level in F1A males was lower than the concurrent Controls ($p<0.05$) but the value was less than 1 SD away from the HCD mean and no effect of treatment was inferred.

6.2.1 Thyroid stimulating hormone (TSH)

Attachment 14.4

Assessment of TSH serum levels in F0 males, F0 females, F1 offspring on Day 22 of age and selected F1 Cohort 1A animals at scheduled termination did not reveal any differences that could be attributed to administration of Sodium Trifluoroacetate at dietary concentrations up to and including 3000 ppm.

6.3 Spleen Cell Immunophenotyping

Attachment 14.5

Overall, minor fluctuations were observed in the immunophenotyping parameters (percentages and cells/spleen) across the different treatment groups for males and females but there were no differences that could be related to dietary administration of Sodium Trifluoroacetate at dietary concentrations up to and including 3000 ppm.

6.4 F0 Generation

6.4.1 Achieved Dose

Table 12.1, Table 12.2

The mean achieved dose levels over the ten-week pre-pairing treatment period at 120, 600 and 3000 ppm were 9.71, 49.2 and 248 mg/kg/day for males and 10.26, 53.9 and 265 mg/kg/day for females, respectively.

During gestation mean achieved dose levels were 8.65, 44.3 and 223 mg/kg/day for females receiving 120, 600 and 3000 ppm and during lactation the mean achieved dose levels were 9.85, 47.5 and 233 mg/kg/day for females receiving 60, 300 and 1500 ppm, respectively.

6.4.2 Clinical Observations

Table 12.3, Table 12.4, Table 12.5, Appendix 13.1

There were no unscheduled deaths and there were no signs at routine physical examination that could be attributed to administration of Sodium Trifluoroacetate.

6.4.3 Body Weight

Figure 11.1, Figure 11.2, Figure 11.3, Figure 11.4, Table 12.6, Table 12.7, Table 12.8, Appendix 13.2, Appendix 13.3, Appendix 13.4

During Week one of treatment body weight gain for males and females receiving 3000 ppm and males receiving 600 ppm was low when compared with Controls ($p<0.01$).

Overall body weight gain for males at 3000 ppm was slightly low at approximately 92% of Controls ($p<0.01$); overall weight gain for males at 120 or 600 ppm or females at all dose levels were similar to Controls.

During gestation body weight gain at 3000 ppm was slightly but statistically significantly low from GD7 to GD14 ($p<0.01$) and the mean body weight on GD14 at this dietary concentration was slightly low when compared with Controls ($p<0.05$).

On Day 1 of lactation group mean body weight was slightly low at 3000/1500 ppm when compared with Controls ($p<0.05$).

Overall body weight gain during gestation and lactation was unaffected by administration of Sodium Trifluoroacetate at dietary concentrations up to and including 3000/1500 ppm .

6.4.4 Food Consumption

Table 12.9, Table 12.10, Table 12.11, Appendix 13.5, Appendix 13.6, Appendix 13.7

Overall food consumption during the ten-week pre-pairing treatment period showed no clear dose-related adverse effects of Sodium Trifluoroacetate administration.

There was no clear effect on food consumption during gestation; however, at 3000 ppm mean food consumption values from GD7-19 were slightly but statistically significantly low when compared with Controls ($p<0.01$) and during GD7-13 mean consumption was also slightly low at 120 and 600 ppm ($p<0.05$).

During lactation food consumption was low for females receiving 3000/1500 ppm, with statistical significance attained from LD4 to LD20 ($p<0.05/0.01$); consumption during lactation for females at 120/60 ppm or 600/300 ppm was similar to Controls.

6.4.5 Estrous Cycles
Table 12.12, Table 12.16, Appendix 13.8

Estrous cycles were unaffected by administration of Sodium Trifluoroacetate at dietary concentrations up to and including 3000 ppm.

The majority of females showed an estrus smear prior to termination.

6.4.6 Pre-Coital Interval
Table 12.13, Appendix 13.8

Pre-coital was unaffected by treatment with the vast majority of animals mating within the first four days of pairing.

6.4.7 Mating Performance and Fertility
Table 12.14, Appendix 13.8

Mating performance and fertility was unaffected by administration of Sodium Trifluoroacetate at dietary concentrations up to and including 3000 ppm.

6.4.8 Gestation Length and Gestation Index
Table 12.15, Appendix 13.8

There was no adverse effects on either gestation length or gestation index at all dose levels.

6.4.9 Hematology
Table 12.17, Appendix 13.9

Males at 3000 ppm and females at 3000/1500 ppm showed slightly but statistically significant low hemoglobin ($p<0.05/0.01$) and low mean cell hemoglobin ($p<0.05$). Females at 3000/1500 ppm also showed low hematocrit ($p<0.05$) and low mean cell hemoglobin concentration ($p<0.01$).

At 3000 ppm males showed low monocyte counts ($p<0.05$) and short activated partial thromboplastin time ($p<0.01$) and at 3000/1500 ppm females showed high platelet counts ($p<0.01$).

6.4.10 Blood Chemistry
Table 12.18, Appendix 13.10

Alkaline phosphatase activity for males at 600 or 3000 ppm was elevated when compared to Controls ($p<0.01$).

Males and females at all dose levels showed low plasma glucose levels ($p<0.05/0.01$) and low levels of non-esterified fatty acids ($p<0.01$); males at all dose levels also showed low triglyceride concentrations ($p<0.01$) when compared to Controls.

Other statistically significant differences were as follows:

- bilirubin concentrations at all dose levels were slightly low for females only ($p<0.05$ at 120/60 ppm; $p<0.01$ at 600/300 or 3000/1500 ppm)
- sodium concentrations at 3000 ppm were high for males ($p<0.05$)
- potassium concentrations were high at 3000/1500 ppm for females ($p<0.05$)
- calcium concentrations were low at 3000 ppm in males ($p<0.01$)
- A/G ratio was high in males at 600 or 3000 ppm and females at 3000/1500 ppm ($p<0.01$)

6.4.11 Sperm Assessment

Table 12.24, Table 12.25, Table 12.26, Appendix 13.17, Appendix 13.18, Appendix 13.19, Attachment 14.8

There were no statistical effects observed on sperm motility/motion or testis, the cauda epididymis however was considered to have been affected by administration of Sodium Trifluoroacetate at 3000 ppm.

At 3000 ppm there were slight non statistical significant decreases in progressive % sperm and the motion parameter Rapid, along with correlating increases in slow and static sperm compared with Control, but within historical control data (HCD) range (Rapid was above HCD but is not considered adverse). The motion parameter STR was highlighted as statistically significant but was similar to all other dose groups and within HCD.

At 3000 ppm there were also statistically significant decreases in cauda weights and total sperm along with a non-statistically significant decrease in cauda epididymal sperm number per gram when compared with Controls; however the mean values were within HCD, whilst the mean Control values exceeded the HCD range. (Mean epididymal weight at termination showed no significant difference to Controls at termination)

Morphologically there was a slight but statistically significant decrease in normal % and an increase in total abnormal % sperm with no particular abnormality, when compared with Controls but within HCD range. The abnormality head misshapen was highlighted as statistically significant but the incidence was lower than that in the control values.

6.4.12 Organ Weights

Attachment 14.6

Body weight relative kidney weights and liver weights were high for males at 3000 ppm and females at 3000/1500 ppm ($p<0.01$); males at 600 ppm also had high bodyweight relative kidney weight ($p<0.01$), when compared with Controls.

	Sodium Trifluoroacetate							
Sex	Males				Females			
Dietary concentration (ppm)								
Main Phase	0	120	600	3000	0	120	600	3000
Lactation Phase	N/A	N/A	N/A	N/A	0	60	300	1500
Kidney								
Absolute Weight (g)	2.607	2.696	2.676	2.713	1.699	1.681	1.756	1.767
Body Weight Ratio (%)	0.571	0.585	0.602**	0.632**	0.711	0.700	0.724	0.762**
Liver								
Absolute Weight (g)	13.709	14.118	14.042	14.990	9.298	9.365	9.938	10.264
Body Weight Ratio (%)	2.98	3.06	3.14	3.47**	3.87	3.88	4.08	4.41**

N/A = Not applicable.

The statistically significant high absolute and body weight relative thyroids and parathyroids weights in the females given 3000/1500 ppm were considered not test item-related. This was based on the lack of correlative microscopic findings, low numbers of individual animal weights outside the study control range and presence in only one sex and generation.

All other differences in organ weight parameters, statistically significant or not, were consistent with normal variation and considered incidental. These differences were characterized by one or more of the following: inconsistency between sexes; presence only in absolute weight or in relative (to body weight) ratios but not both; lack of a dose relationship or correlative findings; and/or the magnitude was considered small.

6.4.13 Macropathology

Attachment 14.6

All macroscopic findings were considered spontaneous and/or incidental because they occurred at a low incidence, were randomly distributed across groups (including concurrent Controls), and/or were as expected for animals of this age and strain. Therefore, they were considered not test item-related.

There was a low incidence of dark areas in the stomach at all dose levels. This finding was not present in control females. This finding often correlated microscopically with minimal to slight congestion of the glandular mucosa. The mucosal congestion is considered to be a post-mortem change and therefore not test item-related.

The depressions within the glandular stomach are considered to be a background finding based on the similar incidence between Controls and treated groups. This finding correlated microscopically to erosion of the glandular mucosa.

In the treated females there was a higher incidence of pale areas in the lungs at all dose levels without an apparent dose response when compared to Controls. This finding correlated microscopically with alveolar macrophage aggregates. The incidence and severity of this microscopic finding was similar in Controls and all treated groups and therefore this macroscopic finding is considered not test item-related.

6.4.14 Histopathology

Attachment 14.6

There was a test item-related increased incidence of minimal gland dilatation in the stomachs of the females given 600/300 ppm and 3000/1500 ppm. This finding was present in the fundic portion of the glandular stomach. This finding was considered non-adverse based on the minimal severity.

	Sodium Trifluoroacetate							
Sex	Males				Females			
Dietary concentration (ppm)								
Main Phase	0	120	600	3000	0	120	600	3000
Lactation Phase	N/A	N/A	N/A	N/A	0	60	300	1500
Stomach								
Number Examined	25	1	0	25	23	23	24	23
Dilatation, Glands								
Minimal	3	0	0	7	4	6	12	15
Total	3	0	0	7	4	6	12	15

Very low numbers of multinucleated cells with a moderate amount of eosinophilic to amphophilic cytoplasm were seen in the lamina propria of the fundic mucosa in the glandular stomach at minimal severity. This finding was considered not test item-related based on the low incidence in all treated groups (1/23 in female Controls, 2/23 in females at 120/60 ppm, 3/24 in females at 600/300 ppm, 5/23 in females at 3000/1500 ppm) and presence only in one generation and sex.

In the majority of the males the testes exhibited normal progression of the spermatogenic cycle, and the expected cell associations and proportions in the various stages of spermatogenesis were present. The tubular degeneration and atrophy, which occurred at a low incidence in treated and control males, was considered not test item-related based on the similar incidence between treated and control groups:

		Number of animals affected			
	Group/Sex	1M	2M	3M	4M
Tissue/Organ and Findings	No. of animals	25	25	25	25
Testis Rt	No. examined	25	2	1	25
Degeneration/Atrophy, Tubular	Minimal	0	0	0	1
	Slight	0	0	0	1
	Marked	1	0	0	0
	Severe	0	0	1	0
	Total	1	0	1	2

All other microscopic findings were considered spontaneous and/or incidental because they occurred at a low incidence, were randomly distributed across groups (including concurrent Controls), and/or their severity was as expected for this animal age and strain. Therefore, they were considered not test item-related.

6.5 F1 Litter Responses

6.5.1 General Condition of Offspring

Appendix 13.11

The general condition of F1 offspring was unaffected by parental treatment.

6.5.2 Litter Size, Survival Indices and Sex Ratio

Table 12.19, Table 12.20, Table 12.21, Appendix 13.12, Appendix 13.13, Appendix 13.14

Post-implantation loss was slightly high at 3000/1500 ppm ($p<0.05$), however the mean value was within the historical control range and the litter size was unaffected by treatment.

Live birth, viability and lactation indices were unaffected by administration of Sodium Trifluoroacetate.

Sex ratio was unaffected by treatment.

6.5.3 Ano-Genital Distance

Table 12.22, Appendix 13.15

Ano-genital distance for both male and female offspring were similar across the groups and showed no effects of parental treatment.

6.5.4 Nipple Counts

On Day 13 of age male offspring were assessed for the presence or absence of nipple/areolae and no nipples were observed.

6.5.5 Offspring Body Weight

Figure 11.5, Figure 11.6, Table 12.23, Appendix 13.16

Offspring body weight on Day 1 of age and subsequent weight gain up to Day 4 of age showed no effects of parental treatment.

From Day 4 to Day 14 of age male and female offspring at 3000/1500 ppm showed statistically significantly low body weight gain when compared with Controls ($p<0.05/0.01$) and overall body weight gain from Day 1 of age up to weaning on Day 21 of age at 3000/1500 ppm was low when compared with Controls ($p<0.05$); however as the weight gain was only 7% lower than Controls, this affect was considered minor and was considered non-adverse.

Body weight gain for offspring at 120/60 ppm or 600/300 ppm was unaffected by administration of Sodium Trifluoroacetate.

6.5.6 Offspring Organ Weights

Attachment 14.6

Brain, spleen and thymus weights were unaffected by parental treatment with Sodium Trifluoroacetate.

6.5.7 Offspring Macropathology

Attachment 14.6

Macroscopic examination of offspring that either died prematurely, were culled on Day 4 of age or terminated on Day 22 of age did not reveal any findings that could be related to administration of Sodium Trifluoroacetate.

6.6 F1 Generation

6.6.1 Achieved Dose

Table 12.27

The mean achieved dose levels were 9.37, 47.3 and 242 mg/kg/day for males, and were 9.83, 49.4 and 248 mg/kg/day for females, at 120/60, 600/300 and 3000/1500 ppm respectively.

6.6.2 Clinical Observations

Table 12.28, Appendix 13.20

There were no unscheduled deaths and there were no signs at routine physical examination that could be attributed to administration of Sodium Trifluoroacetate.

6.6.3 Body Weight

Figure 11.7, Figure 11.8, Table 12.29, Appendix 13.21

At weaning on Day 21 of age mean bodyweights for selected F1 animals receiving 3000/1500 ppm were low when compared with Controls ($p<0.01$) and for females at these dietary concentrations the gain up to Day 25 of age was also low ($p<0.01$); this was not apparent for selected males.

The mean absolute body weights for selected F1 animals at 3000/1500 ppm remained low from Day 1 to Day 64 of the F1 generation, with males at these dietary concentrations also showing low overall weight gain during this period ($p<0.01$); overall weight gain for high dose females was similar to Controls over the same period.

Body weight and body weight gain at 120/60 or 600/300 ppm were unaffected by treatment.

6.6.4 Food Consumption

Table 12.30, Appendix 13.22

Overall, there was no adverse effect on food consumption during treatment of the F1 generation.

Females at 3000/1500 ppm showed slightly low food consumption ($p<0.05$) during Week 1, 8 and 10 of the F1 generation and males at 3000/1500 ppm also showed slightly low food consumption ($p<0.05$) during Week 4. Females at 600/300 showed slightly but statistically significantly high food consumption ($p<0.01$) during Week 5 of the F1 generation when compared with Controls; this was not evident for males at this dietary concentration.

6.6.5 Sexual Maturation

Table 12.31, Appendix 13.23

The age and body weight at attainment of balano preputial separation or vaginal opening was considered to be unaffected by administration of Sodium Trifluoroacetate at dietary levels up to and including 3000/1500 ppm.

The mean age on completion of vaginal opening at 600/300 or 3000/1500 ppm was 34.0 or 33.7 days vs 32.6 days in the Control animals with the mean differences of 1.5 or 1.1 days attaining statistical significance ($p<0.05$). As the animals are only looked at once a day this difference is not considered of toxicological significance.

6.6.6 Vaginal Opening to first estrus – Cohort 1A

Table 12.32, Appendix 13.24

There was no adverse effect on the duration between vaginal opening and first estrus smear at dietary concentrations up to and including 3000/1500 ppm.

6.6.7 Estrous Cycles – Cohort 1A

Table 12.33, Appendix 13.24

Estrous cycles were unaffected by administration of Sodium Trifluoroacetate.

6.6.8 Stage of Estrous Cycle at Termination

Table 12.35, Table 12.34, Appendix 13.24, Appendix 13.25

The majority of females showed an estrus smear prior to termination and no treatment related effect was inferred.

6.6.9 Hematology - Cohort 1A

Table 12.36, Appendix 13.26

Males at 3000/1500 ppm and females at 600/300 or 3000/1500 ppm showed low hematocrit and hemoglobin count.

Lymphocyte and monocyte counts were slightly low in males at 3000/1500 ppm ($p<0.05$); this was not evident for females at this dose level.

Females at 600/300 or 3000/1500 ppm had slightly high platelet counts ($p<0.05$); there was no evidence of a dose response, and it was not evident in males.

6.6.10 Blood Chemistry - Cohort 1A

Table 12.37, Appendix 13.27

Males at 3000/1500 ppm had slightly high alkaline phosphatase ($p<0.05$), high aspartate amino-transferase activity ($p<0.05$) and high alanine amino-transferase activity ($p<0.01$); slightly high alanine amino-transferase activity was also apparent in females at this dose level ($p<0.05$).

Bilirubin plasma concentrations were statistically significantly low in males at 600/300 or 3000/1500 ppm and females at 3000/1500 ppm ($p<0.01$).

Glucose plasma concentrations were statistically significantly low ($p<0.01$) when compared to Controls for both males and females at all dose levels, although there was no dose response.

Cholesterol concentrations were slightly low in males at 600/300 or 3000/1500 ppm ($p<0.05$); this was not evident in females.

Non-esterified fatty acid concentrations for males at all dose levels were statistically significantly low when compared with Controls ($p<0.05$-0.01); females at 3000/1500 ppm also had significantly low non esterified fatty acid concentrations ($p<0.01$).

Triglyceride concentrations were slightly low in males at all dose levels ($p<0.05$); there was no apparent dose response, and this difference was not evident in females.

Sodium plasma concentrations were statistically significantly high for males at all dose levels and calcium plasma concentrations were slightly low for males at 3000/1500 ppm ($p<0.05$); there were no similar differences in females.

Potassium plasma concentrations were statistically significantly high in females at all dose levels ($p<0.01$); this was not evident in males.

Total protein concentrations in males and females at 3000/1500 ppm were slightly low, with females attaining statistical significance ($p<0.05$), but no apparent dose response in either sex.

Albumin concentrations in males at 600/300 ppm and 3000/1500 ppm were high when compared with Controls ($p<0.01$). Albumin to globulin ratio was high for males at 3000/1500 ppm ($p<0.01$) and females at 600/300 or 3000/1500 ppm ($p<0.05$ and $p<0.01$, respectively).

6.6.11 Urinalysis - Cohort 1A

Table 12.38, Appendix 13.28

Specific gravity for females at 3000/1500 ppm was slightly low ($p<0.05$) when compared with Controls, but this was consistent with the slightly higher urinary volume; there was no similar finding in males.

Total sodium and protein levels were slightly high in males at 600/300 or 3000/1500 ppm; but these differences did not attain statistical significance

Total potassium levels were low and total sodium concentrations slightly high for females at 3000/1500 ppm ($p<0.05$).

6.6.12 Ovarian Follicle Counts and Corpora Lutea - Cohort 1A

Table 12.39, Appendix 13.29

Ovarian follicle and corpora lutea counts in Control and high dose groups did not reveal any differences that could be attributed to treatment with Sodium Trifluoroacetate.

6.6.13 Sperm Assessment - Cohort 1A

Table 12.40, Table 12.41, Table 12.42, Appendix 13.30, Appendix 13.31, Appendix 13.32

There were no adverse effects on % motile sperm and % progressive sperm although there appeared to be a slight effect on testis weight. Morphologically at 3000 ppm there was a statistically significant increase in abnormal sperm heads specifically flat head when compared with Controls and the incidence was outside of HCD range, however the overall % of normal sperm in the Control group exceeded the HCD range.

At 3000/1500 ppm there were statistically significant decreases in testis weight, testis spermatid count and testis total million compared with Control; however only the testis weight was outside of HCD. The effect on testis weight is consistent with the mean combined weight testis recorded at necropsy of both the F1A and F1B cohorts.

At 3000 ppm there was a statistically significant decrease in motion values VAP, VCL and BCF compared to concurrent control. At 600 ppm there was a statistical decrease in motion values VAP and VCL compared to concurrent control. At 120 ppm there was a statistical decrease in motion value VAP compared to concurrent control. All values were inside HCD range. The statistical significance of these parameters is considered to be due to the Control motion values being high (above the HCD range).

6.6.14 Organ Weights

Attachment 14.6

Cohort 1A

Mean body weight relative liver weights were high in the males and females that received 1500/3000 ppm ($p<0.01$) when compared to Controls.

Mean absolute testes weight was low ($p<0.01$) in the Cohort 1A males at 1500/3000 ppm when compared with Controls.

	Sodium Trifluoroacetate							
Sex	Males				Females			
Dietary concentration (ppm)								
Main Phase	0	120	600	3000	0	120	600	3000
Lactation Phase	0	60	300	1500	0	60	300	1500
Liver								
Absolute Weight (g)	12.356	12.656	13.373	13.393	7.258	7.662	8.074	7.914
Body Weight Ratio (%)	3.27	3.40	3.54	3.92**	3.35	3.45	3.63	3.87**
Testes								
Absolute Weight (g)	3.635	3.572	3.732	3.352**	N/A	N/A	N/A	N/A
Body Weight Ratio (%)	0.967	0.968	1.000	0.986	N/A	N/A	N/A	N/A

N/A = Not applicable.

Mean absolute weight of the epididymides was low ($p<0.05$) in the Cohort 1A males at 1500/3000 ppm when compared with Controls. This change is considered to be incidental based on the lack of statistically significant low epididymides weights in Cohort 1B males, the lack of microscopic and sperm analysis correlation and the low magnitude of this change.

Mean absolute weight of the pituitary was low in the cohort 1A females that received 1500/3000 ppm ($p<0.05$) when compared with Controls. This change is considered incidental as all individual weights are within the range of the control animals and this this difference was not apparent in Cohort 1A males or Cohort 1B females.

Terminal body weights were low for males ($p<0.01$) and females ($p<0.05$) at 1500/3000 ppm when compared with Controls. This caused statistically significant differences in organ weights of various organs including the thyroids and parathyroids, adrenals, kidneys and heart; these differences were not considered a direct effect of the test item.

Cohort 1B
Mean absolute testes weight was low in the males treated with 1500/3000 ppm ($p<0.05$) when compared to Controls.

	Sodium Trifluoroacetate							
Sex	Males				Females			
Dietary concentration (ppm)								
Main Phase	0	120	600	3000	0	120	600	3000
Lactation Phase	0	60	300	1500	0	60	300	1500
Testes								
Absolute Weight (g)	3.724	3.740	3.828	3.473*	N/A	N/A	N/A	N/A
Body Weight Ratio (%)	0.956	0.963	0.979	0.934	N/A	N/A	N/A	N/A

N/A = Not applicable.

6.6.15 Macropathology
Attachment 14.6

In Cohorts 1A and 1B all macroscopic findings were considered spontaneous and/or incidental because they occurred at a low incidence, were randomly distributed across groups (including concurrent Controls), and/or were as expected for rats of this age and strain. Therefore, they were considered not test item-related.

6.6.16 Histopathology - Cohort 1A
Attachment 14.6

There was a test item-related increased incidence of minimal to slight glandular dilatation in the stomachs of females given 1500/3000 ppm. This finding was present in the fundic portion of the glandular stomachs. This finding was also present in the F0 females given 600/300 ppm and 3000/1500 ppm.

In the glandular stomachs of females given 1500/3000 ppm there was a high incidence of minimal to slight decreased secretion in the fundic mucous neck cells. In affected animals the mucous neck cells were attenuated and exhibited a small amount of pale eosinophilic cytoplasm with minimal or no mucus content. The gastric surface epithelium was intact. These finding were considered non-adverse based on their low severity grades.

	Sodium Trifluoroacetate							
Sex	Males				Females			
Dietary concentration (ppm)								
Main Phase	0	120	600	3000	0	120	600	3000
Lactation Phase	0	60	300	1500	0	60	300	1500
Stomach								
Number Examined	20	0	0	20	20	20	20	20
Dilatation, Glands								
Minimal	1	0	0	4	0	2	6	8
Slight	0	0	0	0	0	0	0	1
Total	1	0	0	4	0	2	6	9
Secretion, Decreased, Glandular Region								
Minimal	0	0	0	0	1	2	2	9
Slight	0	0	0	0	0	0	0	6
Total	0	0	0	0	1	2	2	15

In the majority of the males the testes exhibited normal progression of the spermatogenic cycle, and the expected cell associations and proportions in the various stages of spermatogenesis were present. The tubular degeneration and atrophy, which occurred at a low incidence in treated and control males, was considered not test item-related based on the similar incidence between treated and control groups.

All other microscopic findings were considered spontaneous and/or incidental because they occurred at a low incidence, were randomly distributed across groups (including concurrent Controls), and/or their severity was as expected for this animal age and strain. Therefore, they were considered not test item-related.

7. DISCUSSION

Dietary administration of Sodium Trifluoroacetate to Han Wistar rats at dietary concentrations of 120, 600 or 3000 ppm reduced to 60, 300 or 1500 pm for F0 females during lactation and F1 offspring up to nominal Day 28 of age was well tolerated with no adverse effects on general condition, body weight or food consumption, reproductive performance, fertility or offspring development/sexual maturation.

There were test item-related microscopic findings in the fundic portion of the glandular stomachs of the F0 females and F1 Cohort 1A females with an increased incidence of minimal to slight gland dilatation in the F0 females at 600/300 ppm and 3000/1500 ppm and the F1 cohort 1A females at 1500/3000 ppm. The F1 cohort 1A females at 1500/3000 ppm also exhibited a high incidence of minimal to slight decreased secretion in the mucous neck cells located in the fundic region of the glandular stomach. As the severity of these findings were minimal to slight, the general condition of the females was unaffected and both bodyweight performance and food consumption of the females showed no adverse effects of treatment, these findings were considered non-adverse in this study.

In the F0 and F1 generation body weight relative liver weight was high at 3000/1500ppm in both male and female animals. In the F0 and F1 generation males and females showed low plasma glucose levels and low levels of non-esterified fatty acids, males at all dose levels also showed low triglyceride concentrations. Bilirubin plasma concentrations were low for F0 females at all dose levels, for F1 males at 600/300 or 3000/1500 ppm and F1 females at 3000/1500 ppm. The increased liver weight and changes in the biochemistry of the plasma indicate some alteration in liver metabolism however in the absence of any macroscopic or microscopic liver pathology, these effects are considered to be non-adverse.

Kidney weights were high for F0 males and females at 3000/1500 ppm and for F0 males at 600 ppm. Plasma sodium levels in F0/F1 males and potassium levels in F0/F1 females were high, however in the absence of an effect on kidney weight in the F1 animals, with no adverse effects on the urinary composition in the F1 generation or any correlative microscopic changes in either the F0 or F1 generation these changes were considered non-adverse within the context of this study.

In F1 generation Cohort 1A and 1B males had slightly low testes weights, however sperm assessment showed that the spermatid count in the Cohort 1A animals although slightly low was with in the historical control range. Histopathological examination of the Cohort 1A testes showed that the majority exhibited normal progression of the spermatogenic cycle, and the expected cell associations and proportions in the various stages of spermatogenesis were present. Tubular degeneration and atrophy occurred at a low incidence in both treated and control males but was considered unrelated to treatment as the incidence was similar across the groups.

Mean serum T4 concentrations in F0 males at 3000 ppm and females at 3000/1500 ppm, in F1 PND22 offspring at 1500 ppm and in F1 males receiving 600 or 3000 ppm were low when compared with Controls ($p<0.01$). These low T4 levels occurred in the absence of any statistically significant increases in serum TSH and any consistent or conclusive effects on thyroid weights or micropathology in the F0 or F1 adults.

F0 males and females at 3000 or 3000/1500 ppm and F1A males and females at 1500/3000 ppm had high body weight relative liver weights when compared with Controls ($p<0.01$), with no correlative microscopic findings.

Processes highly dependent on normal thyroid function in rats include growth, brain development, sexual maturation, normal development of reproductive organs and reproductive performance (Christina and Trenton 2003), successful parturition (Poppe and Glinoer 2003) and mediating many changes in the fetuses to ensure successful birth and post-natal survival (Forehead and Fowden 2014). In the absence of any effects greater than a slight effect on the growth of the animals, with no effect on reproductive performance, parturition, offspring, survival, clinical condition or sexual maturation, and in the absence of any test item related changes in the reproductive organs, the low T4 levels seen in F0 males and females, male and female F1 offspring on Day 22 of age and F1A males are considered not to represent an adverse effect of treatment within the context of this study.

It is therefore concluded that 3000 (1500ppm) was the no observed adverse effect level for both reproductive performance/offspring development and for general systemic toxicity.

8. CONCLUSION

Dietary administration of Sodium Trifluoroacetate to Han Wistar rats at dietary concentrations of 120, 600 or 3000 ppm reduced to 60, 300 or 1500 pm for F0 females during lactation and F1 offspring up to nominal Day 28 of age was well tolerated.

There were test item-related microscopic findings in the fundic region of the glandular stomachs of the F0 females and F1 Cohort 1A females with an increased incidence of minimal to slight gland dilatation. The F1 cohort 1A females also exhibited a high incidence of minimal to slight decreased secretion in the mucous neck cells located in the fundic region of the glandular stomach. These finding were considered non-adverse at the severity seen in this study.

Reproductive performance (encompassing mating performance, fertility and offspring development) showed no adverse effects of treatment.

It is therefore concluded that 3000/1500ppm (approximating to 242-265 mg/kg/day) was the no observed adverse effect level for both reproductive performance/offspring development and for general systemic toxicity.

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10. ABBREVIATIONS

The following lists of abbreviations are used by [redacted] Some, but not necessarily all, of this information may be needed for this report.

General Abbreviations

b.i.d.	*Bis in die*. Two times per day
F	Female
HR	Heart rate
IM	Intramuscular
IS	Injection site
Lt	Left
M	Male
N [or n]	Number contributing to the mean or Number of animals examined
N/A	Not applicable
Obs	Observations
R	Recovery
Rt	Right
SD [or sd]	Standard deviation
TK	Toxicokinetic
ULOQ	Upper Limit of Quantification

Units of Measure

amol	Attomole
BPM	Beats per minute
°C	Degrees Celsius
CFU, cfu, Cfu	Colony forming unit
cm	Centimeter
DL, dl, dL	Deciliter
EU	Ehrlich unit
FL, fl	Femtoliter
fmol	Femtomole
G, g	Gram
H, h	Hours
IU	International unit
KG, kg	Kilogram
L	Liter
MCG, UG, µg, ug	Microgram
MEQ	Milliequivalent
MG, mg	Milligram
MI	Million
ML, mL, ml	Milliliter
mm	Millimeter
mmHG/mmHg	Millimeter of mercury
MMOL, mmol	Millimole

MN, min	Minute
MOS	Milliosmole
Msec, msec	Millisecond
mU	Milliunit
ng	Nanogram
PG, pg	Picogram
pmol	Picomole
PPM, ppm	Parts per million
S, s, sec	Seconds
TH	Thousand
U	Units
UL, µL, uL	Microliter
UMOL, µmol	Micromole
um, µm	Micrometer

Clinical Pathology - General Abbreviations

AE	Analytical error
CTD	Clotted sample
INS	Insufficient sample
NR	Not reported/not required
NSR	No sample received
NVR	No valid result
US	Unsuitable sample

Clinical Pathology - Hematology

A	Abnormalities of blood morphology
APTT	Activated partial thromboplastin time
B	Basophils
E	Eosinophils
Fib	Fibrinogen
H	Heterophils
Hb	Hemoglobin concentration
Hbod	Heinz body formation
Hct	Hematocrit
HDW	Hemoglobin distribution width
L	Lymphocytes
LUC	Large unstained cells
M	Monocytes
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MPV	Mean platelet volume
N	Neutrophils
PCT	Platelet crit
PDW	Platelet distribution width

Plt	Platelet count
PT	Prothrombin time
RBC	Erythrocyte count
Retic	Reticulocyte counts
RDW	Red distribution width
SST1	Thrombin time
VACL	Vacuolated lymphocytes
WBC	Total white cell count
-	no abnormalities detected
+	slight
++	moderate
+++	marked

Clinical Pathology - Blood Chemistry

3DHY	D'3 Hydroxybutyrate
a1	α1 globulin
a2	α2 globulin
A/G Ratio	Albumin/globulin ratio
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMYL	Amylase
AST	Aspartate aminotransferase
BE1C	β1 globulin, Beta1
BE2C	β2 globulin, Beta2
BiAc	Total bile acids
Bili	Total bilirubin
BILD	Bilirubin direct
BUN	Urea nitrogen
Ca	Calcium
Chol	Total cholesterol
CK	Creatinine kinase
Cl	Chloride
CRPC	Canine CRP
Creat	Creatinine
CU	Copper
DDIM	D-dimer
Fe	Iron
Fruc	Fructosamine
Gamma	γ globulin
gGT	Gamma-glutamyl transpeptidase/transferase
GLDH	Glutamate dehydrogenase
Glob	Globulin
Gluc	Glucose
HBDH	Hydroxybutyrate - dehydrogenase

HCO3	Bicarbonate
HDL	HDL cholesterol
HPT	Haptoglobin
INDC	Bilirubin - indirect
K	Potassium
LDH	Lactate dehydrogenase
LDL	LDL cholesterol
LIP	Lipase
Mg	Magnesium
Na	Sodium
Phos	Inorganic phosphorus
Plip	Phospholipid
Total Prot	Total protein
Trig	Triglycerides
TRPI	Cardiac troponin
URAC	Uric acid
VLDL	Calculated VLDL

Clinical Pathology - Urinalysis

A	Other abnormal components
App	Clarity and color/Appearance
Bili	Bile pigments
Bili	Bilrubin
CAS	Casts
CNSE	Absolute non-squamous epithelial cells
CLEU	Absolute leucocyte count
Cryst	Crystals
CURB	Absolute erythrocytes count
Epi	Epithelial cells
Keto	Ketones
Leuc	Leucocytes
MICA	Micro albumin
NEG	Negative
NSEP	Non-squamous epithelial cells
Prot	Protein concentration
RBC	Erythrocytes
SEP	Squamous epithelial cells
SG	Specific gravity
Sperm	Spermatozoa
T-Ca	Total urinary calcium
T-Cl	Total urinary chloride
T-Creat	Total creatinine
T-Gluc	Total glucose
T-K	Total urinary potassium
T-Na	Total urinary sodium

T-NAG	Total N-acetyl glucosaminidase
TNQ	Too numerous to quantify
T-Prot	Total protein
TRA	Trace levels
UBld	Blood pigments
U-Ca	Urinary calcium concentration
U-Cl	Urinary chloride concentration
U-Creat	Urinary creatinine concentration
UGGT	Gamma glutamyl transpeptidase
U-Gluc	Urinary glucose concentration
UIP	Phosphate
U-K	Urinary potassium concentration
UMG	Magnesium
U-Na	Urinary sodium concentration
UNAG	N-acetyl glucosaminidase
URBC	Erythrocytes
UROB	Urobilinogen
Vol	Volume
WBC	Leucocytes
1+	small amount of analyte detected
2+	moderate amount of analyte detected
3+	large amount of analyte detected
4+	very large amount of analyte detected

Clinical Pathology - Urinalysis Appearance

CDB	Cloudy dark brown appearance
CDO	Cloudy dark orange appearance
CDR	Cloudy medium red appearance
CDY	Cloudy dark yellow appearance
CMB	Cloudy medium brown appearance
CMO	Cloudy medium orange appearance
CMR	Cloudy medium red appearance
CMY	Cloudy medium yellow appearance
COL	Colorless appearance
CPB	Cloudy pale brown appearance
CPO	Cloudy pale orange appearance
CPR	Cloudy pale red appearance
CPY	Cloudy pale yellow appearance
DB	Clear dark brown appearance
DO	Clear dark orange appearance
DR	Clear dark red appearance
DY	Clear dark yellow appearance
NY	Clear normal yellow appearance
MY	Clear medium yellow appearance
MB	Clear medium brown appearance

MO	Clear medium orange appearance
MR	Clear medium red appearance
PB	Clear pale brown appearance
PO	Clear pale orange appearance
PP	Clear pale pink appearance
PR	Clear pale red appearance
PY	Clear pale yellow appearance

Sperm Analysis

ALH	Amplitude of lateral head displacement
BCF	Beat cross frequency
LIN	Linearity
STR	Straightness
VAP	The average path velocity
VCL	The curvilinear velocity or track speed
VSL	The progressive or straight line velocity

11. FIGURES

FIGURE 11.1 Body weight - group mean values (g) for males (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

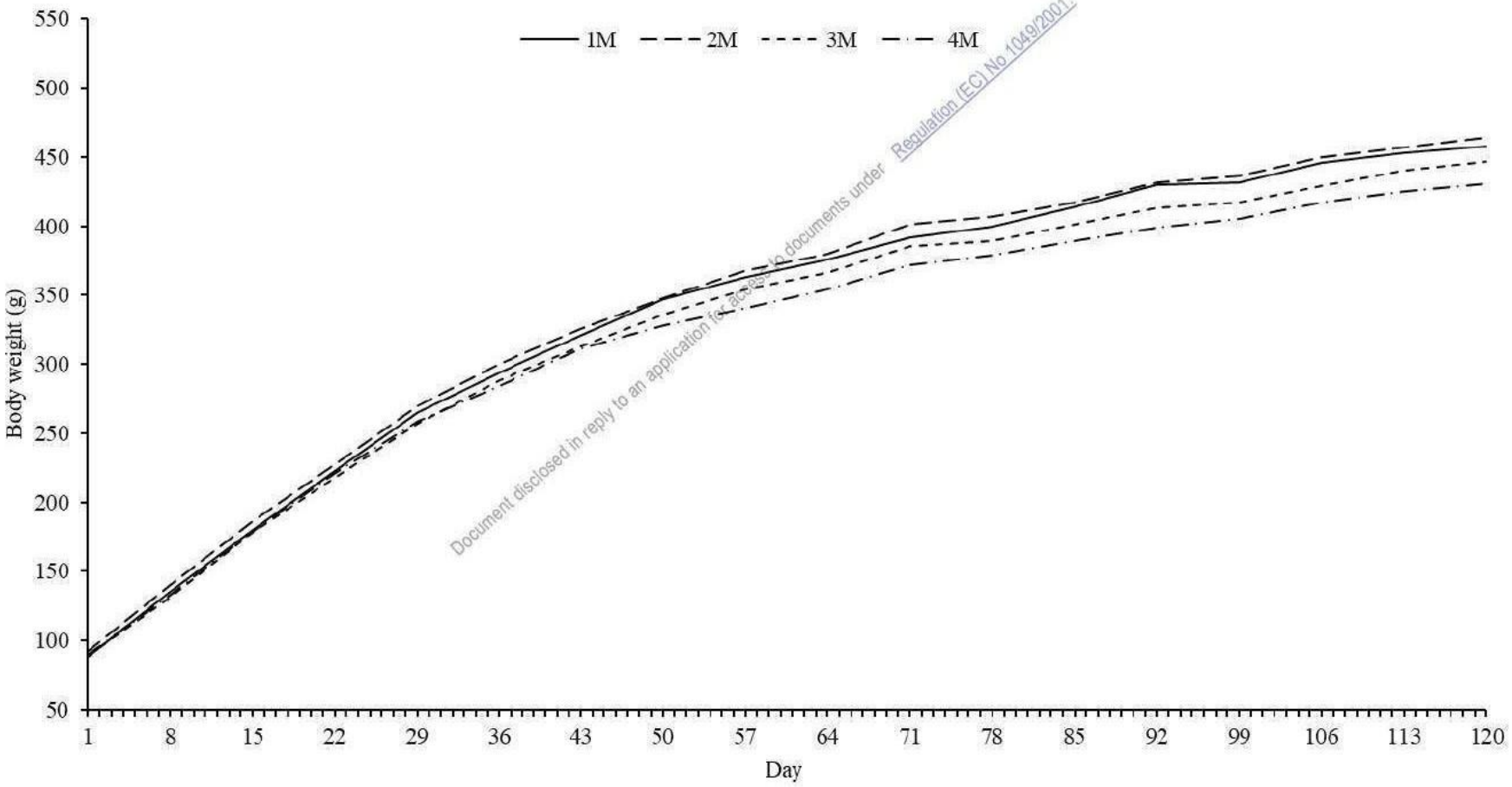


FIGURE 11.2 Body weight - group mean values (g) for females before pairing (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

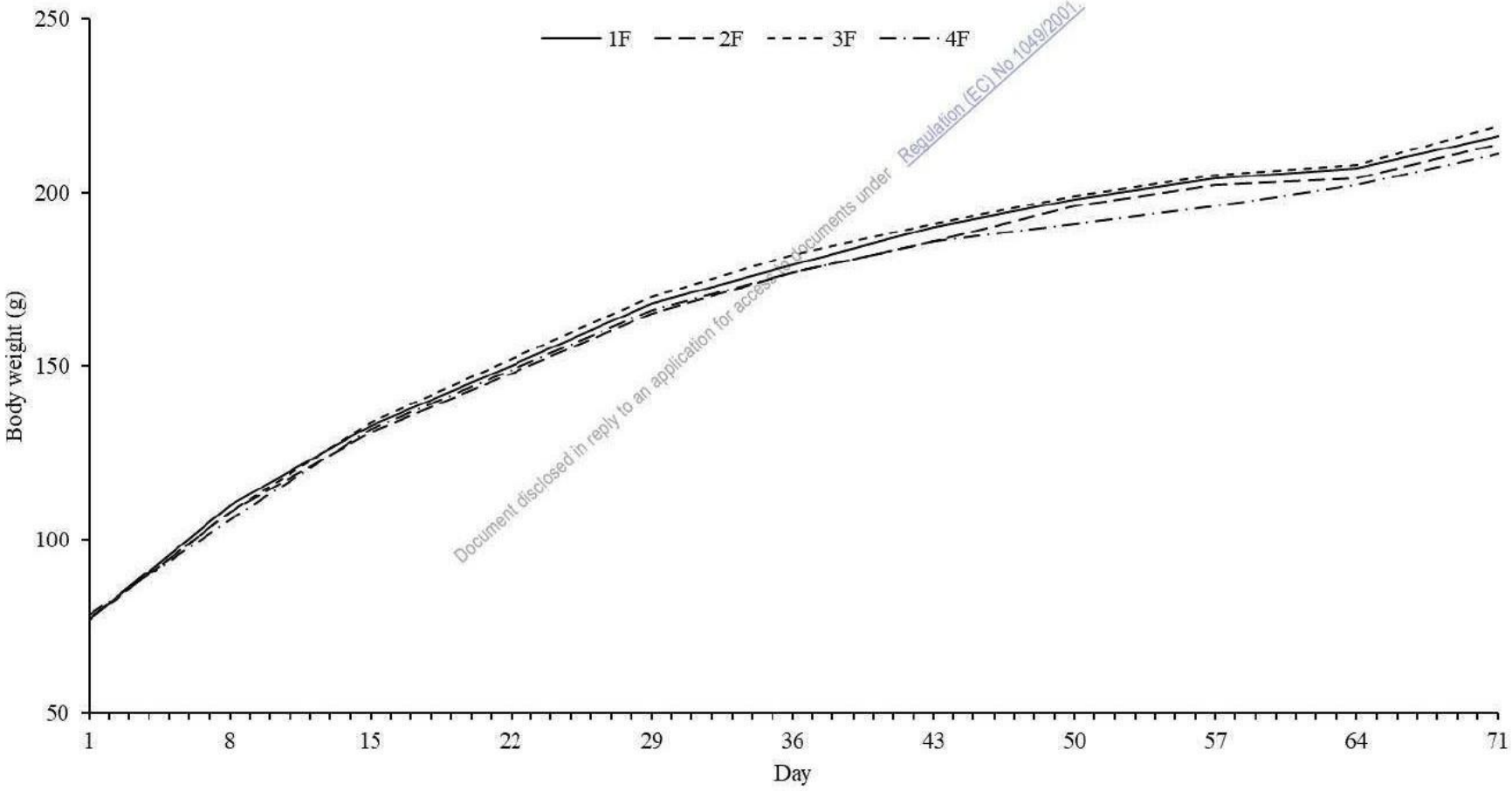


FIGURE 11.3 Body weight - group mean values (g) for females during gestation (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

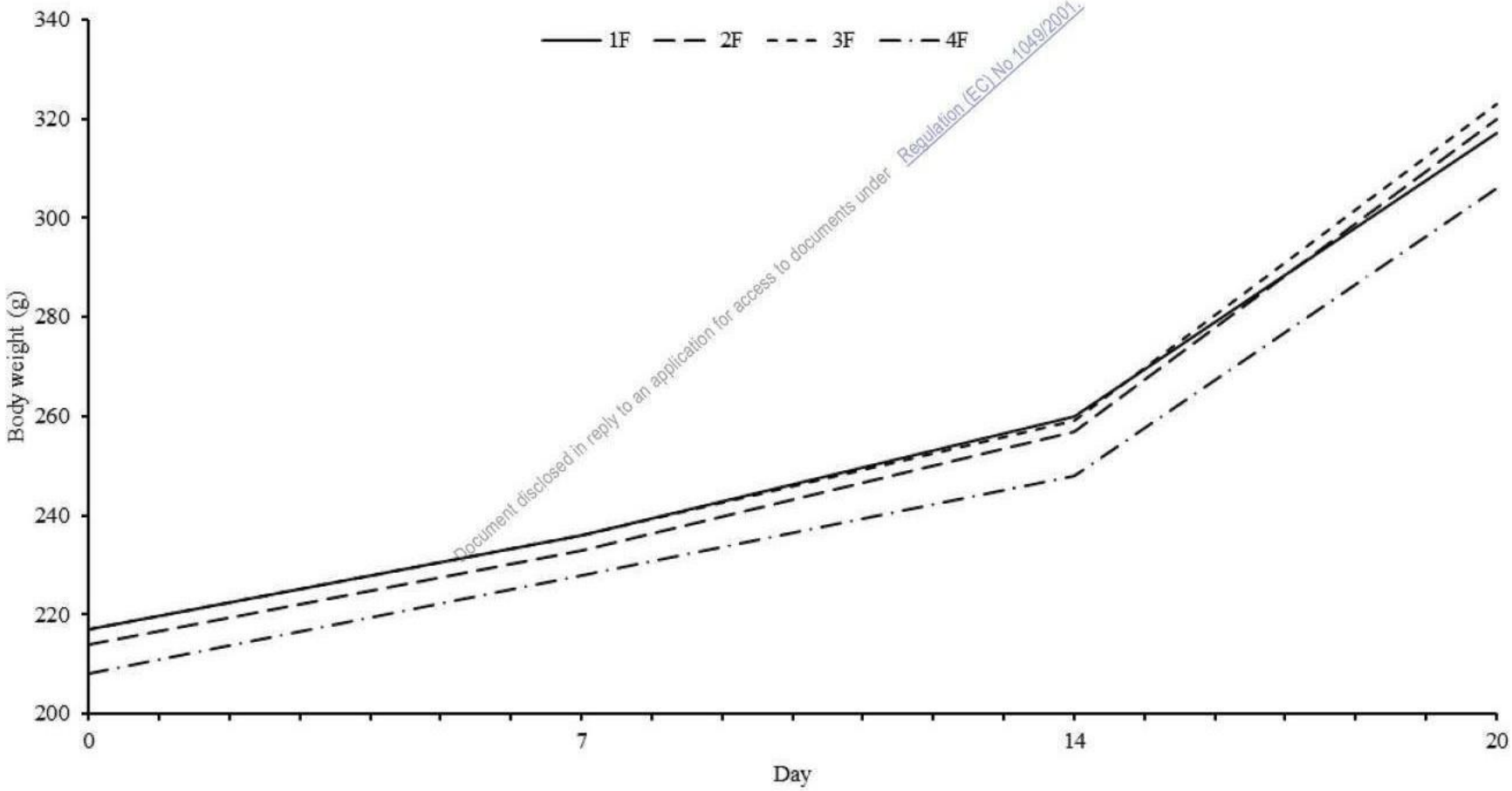


FIGURE 11.4 Body weight - group mean values (g) for females during lactation (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

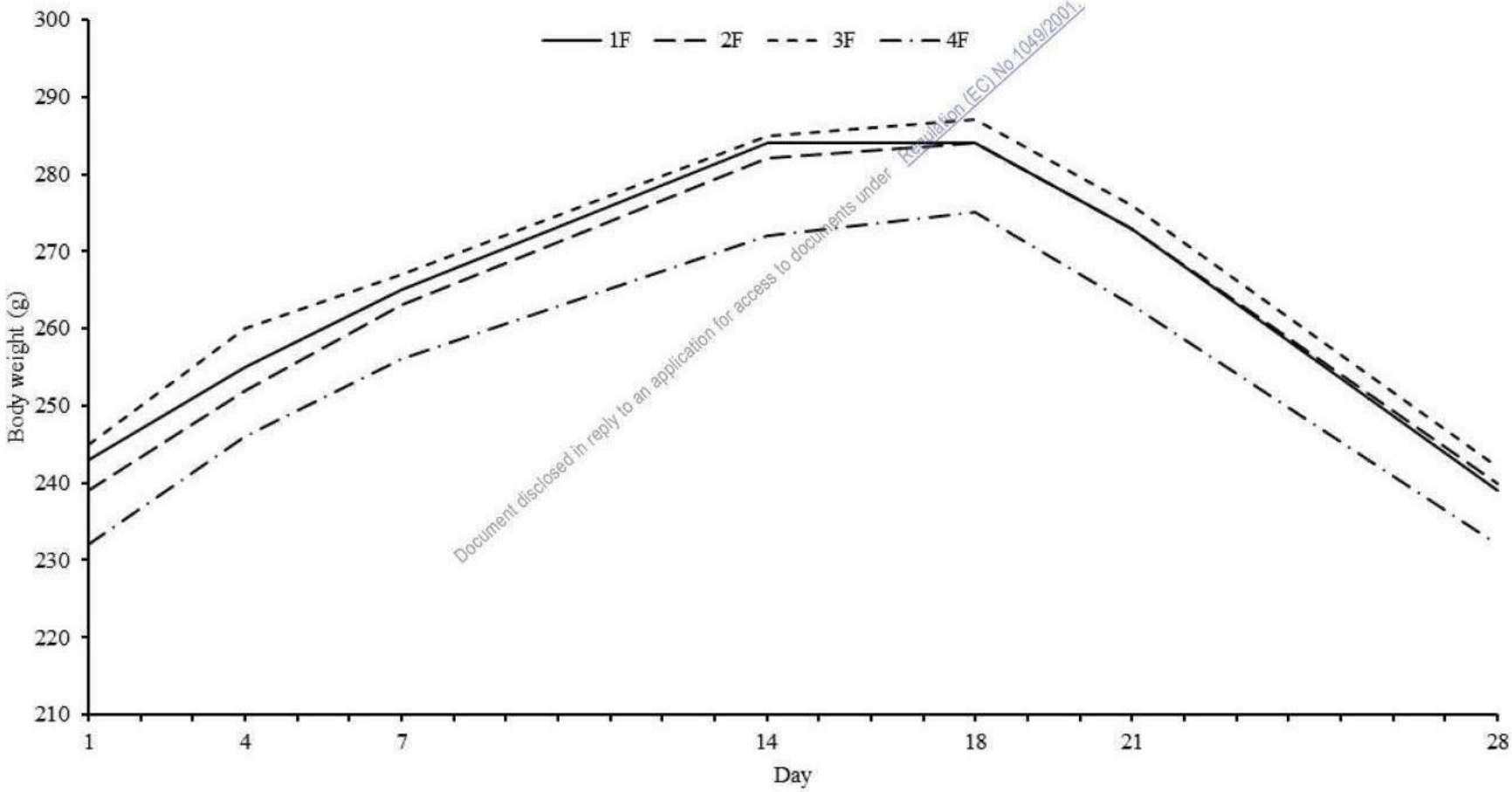


FIGURE 11.5 Body weight - group mean values (g) for male offspring (F1)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

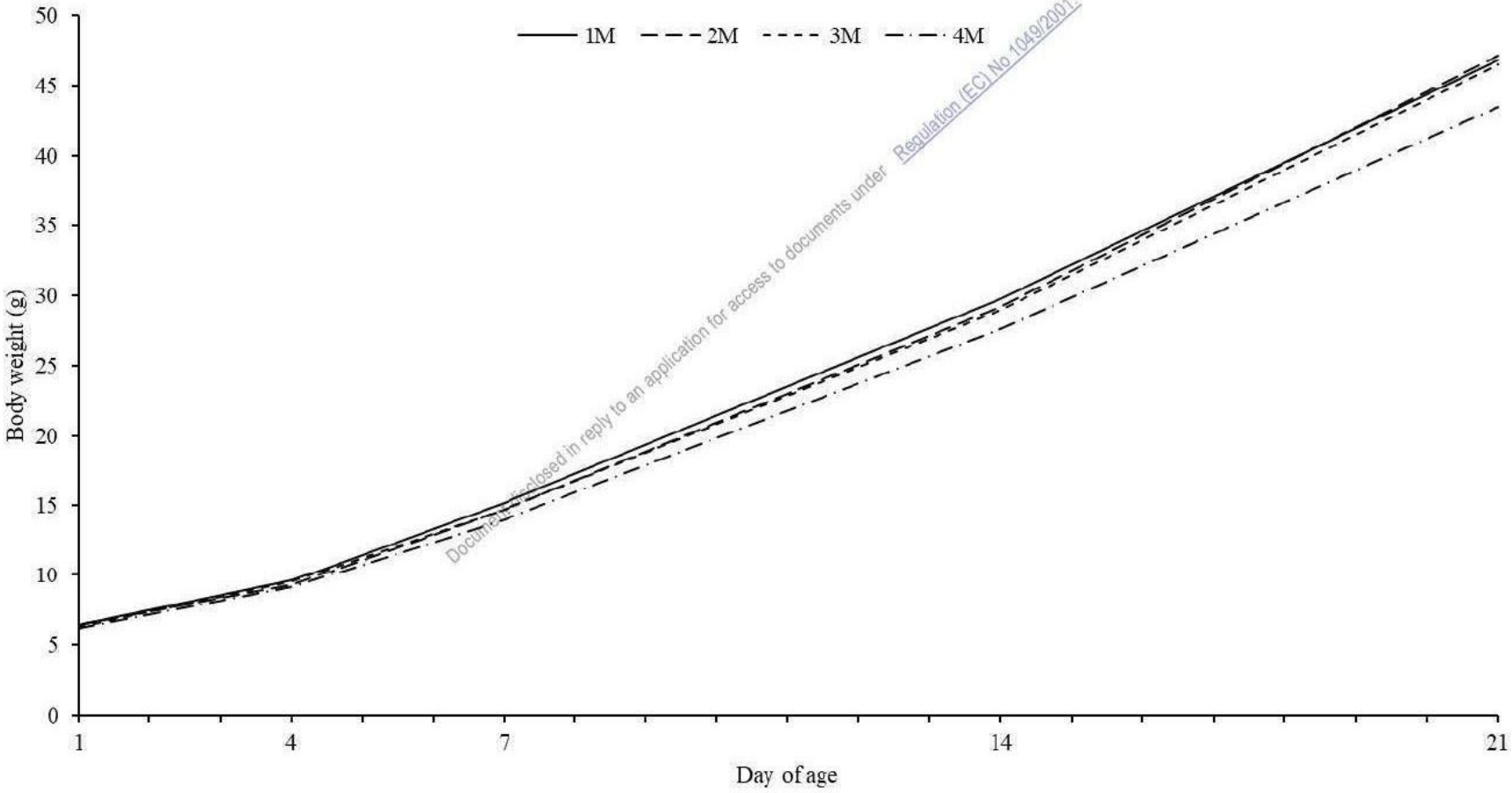


FIGURE 11.6 Body weight - group mean values (g) for female offspring (F1)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

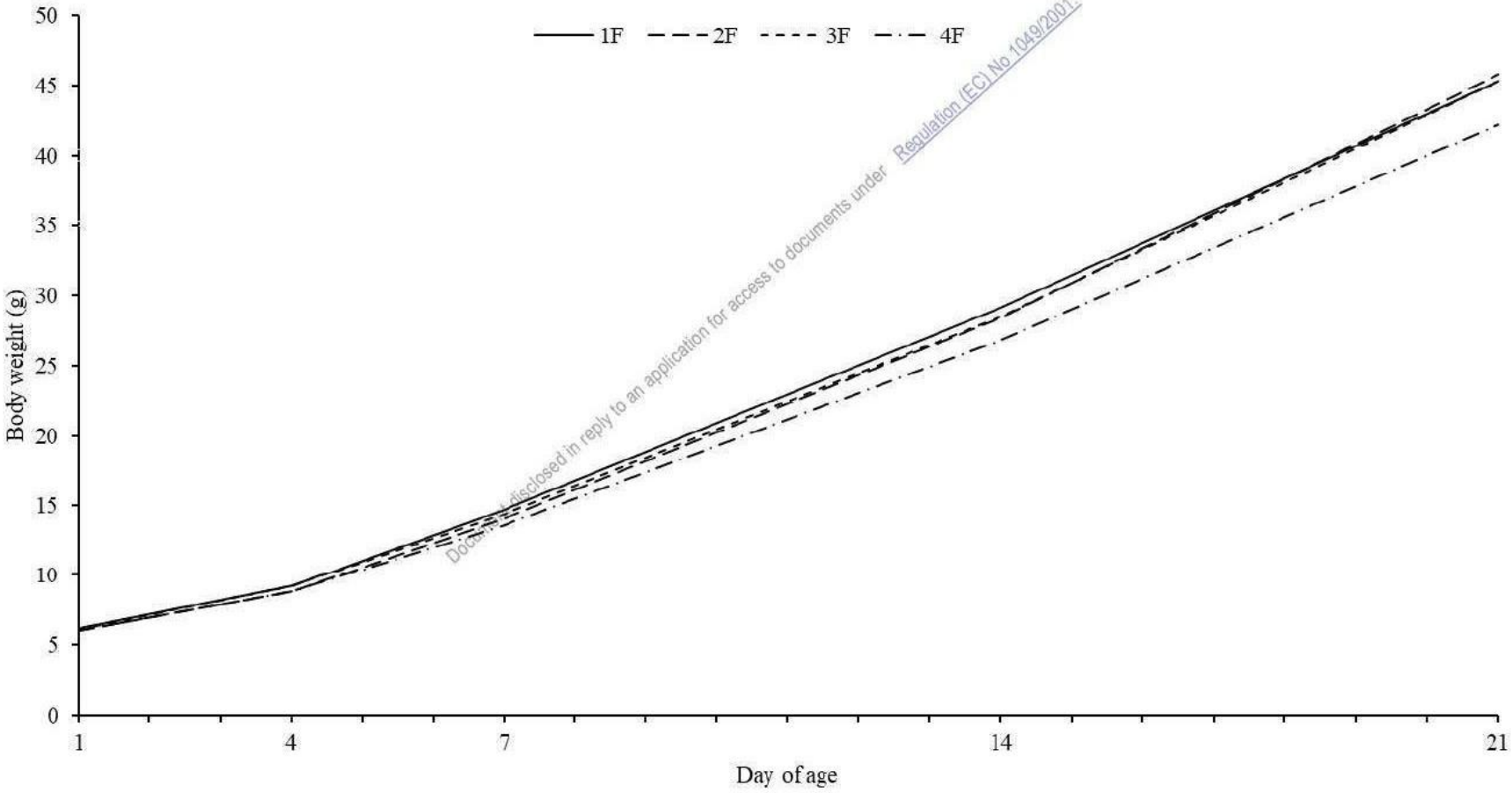


FIGURE 11.7 Body weight - group mean values (g) for males (F1)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

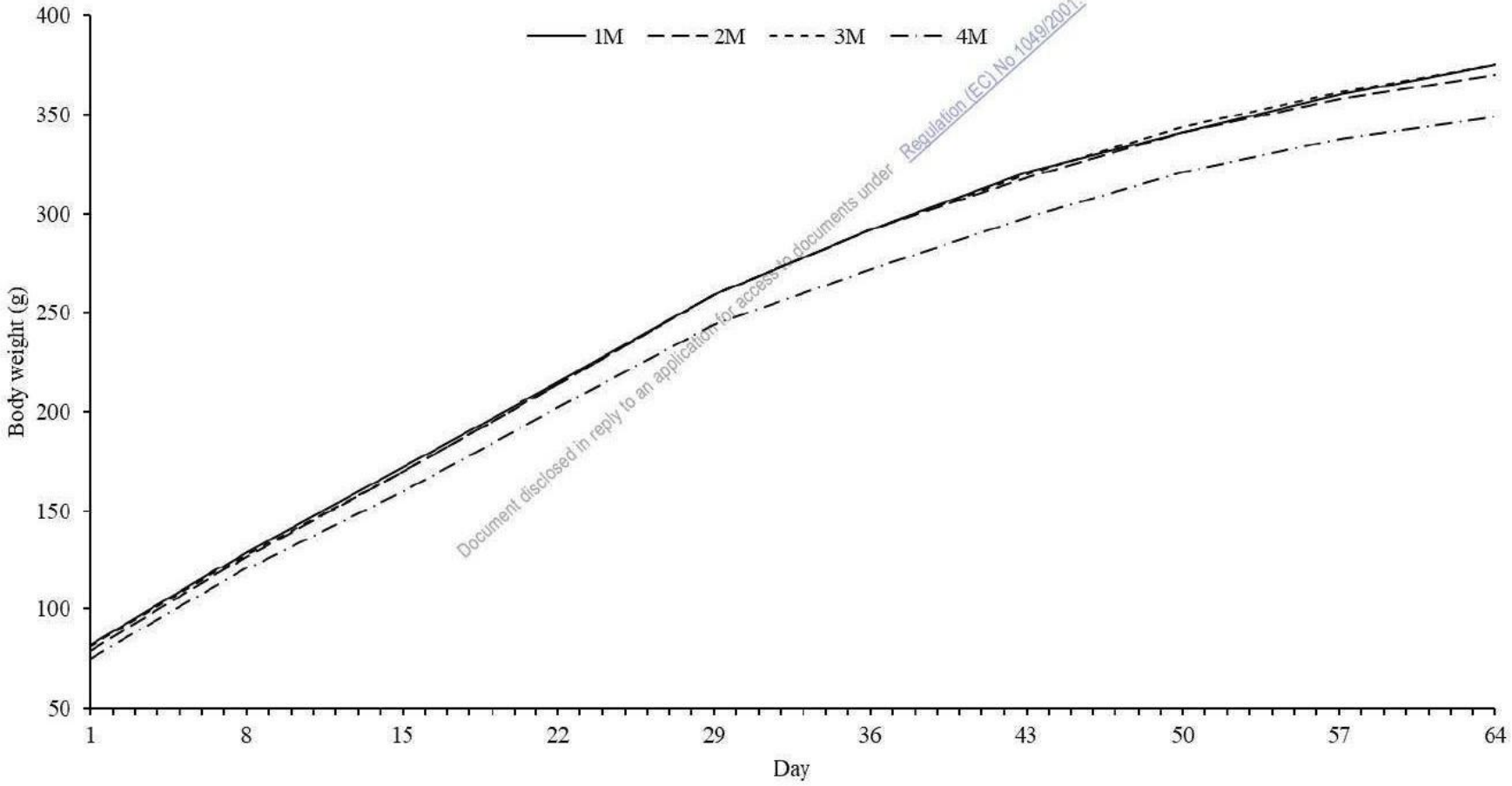
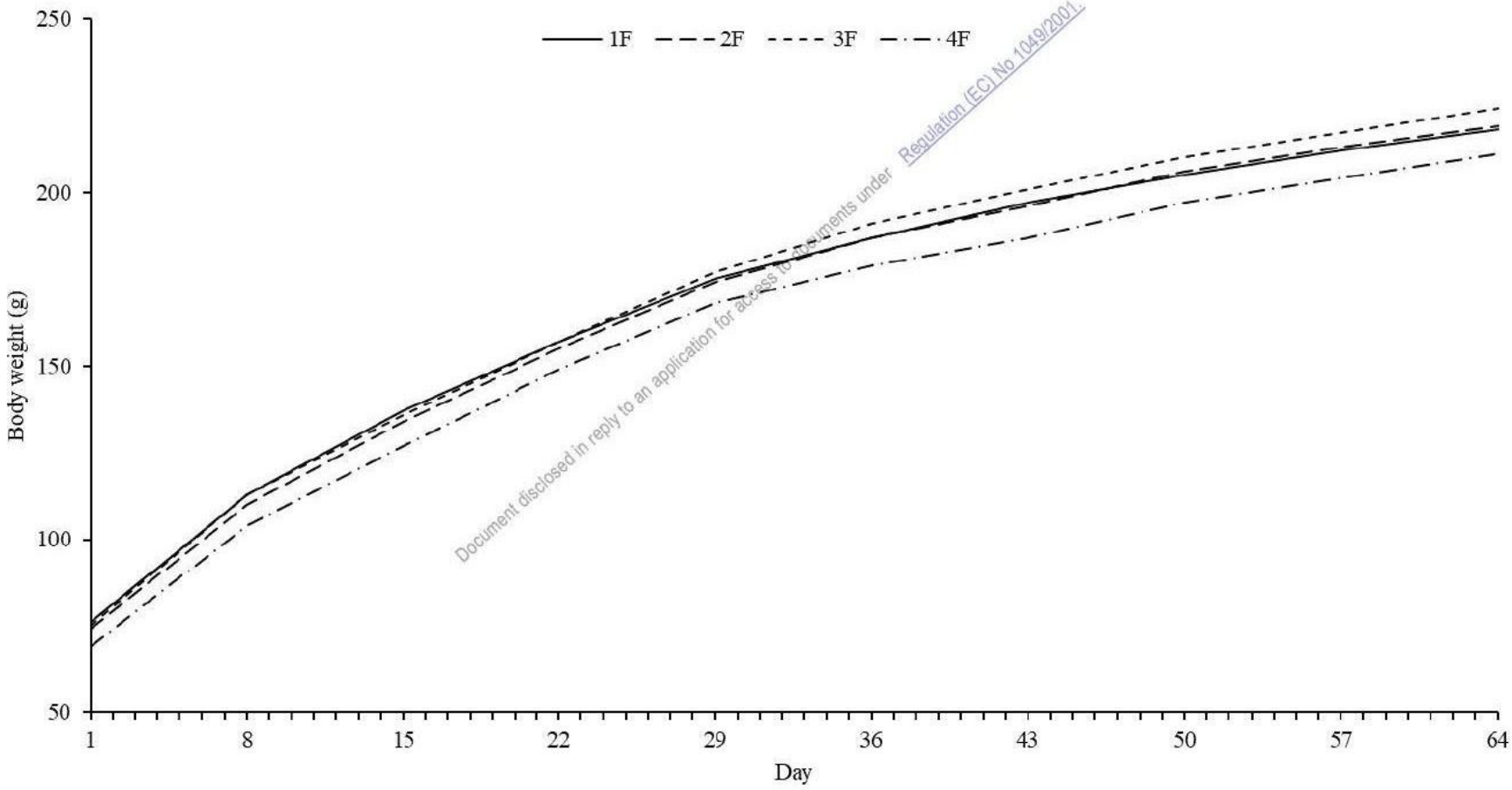


FIGURE 11.8 Body weight - group mean values (g) for females (F1)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500



12. TABLES

TABLE 12.1 Achieved dose - group mean values (mg/kg/day) before pairing (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

	Group/Sex					
Week	2M	3M	4M	2F	3F	4F
1	15.81	80.3	411	15.38	82.5	396
2	13.67	70.5	357	13.34	72.3	349
3	11.59	59.3	302	11.43	62.9	299
4	10.53	53.8	264	10.30	53.8	267
5	8.72	44.0	219	9.22	47.2	242
6	8.32	41.6	205	9.16	47.3	236
7	7.68	38.8	192	8.89	45.7	225
8	7.23	35.5	181	8.44	42.9	215
9	6.88	34.5	173	8.19	41.5	209
10	6.67	33.8	171	8.20	43.0	212
Mean 1-10	9.71	49.2	248	10.26	53.9	265

TABLE 12.2 Achieved dose - group mean values (mg/kg/day) for females during gestation and lactation (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Phase	Days	Group/Sex 2F	3F	4F
Gestation	0-6	9.13	45.0	234
	7-13	8.82	46.1	227
	14-19	7.90	41.2	206
	Mean	8.65	44.3	223
Lactation	1-3	6.35	34.5	169
	4-6	9.09	42.1	203
	7-13	11.67	55.4	273
	Mean	9.85	47.5	233

TABLE 12.3 Clinical signs - group distribution of observations for males and for females before pairing (F0) Request ID: 5433516

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Category	Observation	Group/Sex:	1M	2M	3M	4M	1F	2F	3F	4F
		Initial no:	25	25	25	25	25	25	25	25
			Number of animals affected							
Behavior	Irritable		0	0	0	1	0	0	0	1
	Vocalization		0	0	0	1	0	0	1	3
Coat	Hair loss, Forelimbs		0	1	0	0	0	0	0	0
	Hair loss, Ventral surface		0	1	0	0	0	0	0	0
Eyelids	Partially closed, Left		0	0	0	0	0	0	0	1
Staining	Chromodacryorrhea		0	1	0	0	0	0	0	0
Teeth	Abnormal color, Pale		0	0	0	0	0	0	0	1

TABLE 12.4 Clinical signs - group distribution of observations for females after mating (F0) Request ID: 5433529

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Category	Observation	Group/Sex:	Number of animals affected 1F	2F	3F	4F
		Initial no:	25	25	25	25
Behavior	Increased activity		0	0	0	1
	Irritable		1	0	0	0
Build (Deformity)	Kinked tail		0	0	0	1
Coat	Hair loss, Forelimbs		0	1	1	1
	Hair loss, Ventral surface		0	0	1	0
Discharge	Red, Vaginal area		0	1	0	1
Eyes	Pale, Bilateral		0	1	0	0
Skin	Encrustation, Forelimbs		0	0	0	1

TABLE 12.5 Clinical signs - group distribution of observations for females during lactation (F0) Request ID: 5433530

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Category	Observation	Group/Sex:	Number of animals affected 1F	2F	3F	4F
		Initial no:	23	23	24	23
Coat	Hair loss, Forelimbs		0	1	1	1
	Hair loss, Ventral surface		0	1	1	0
Discharge	Red, Vaginal area		1	2	2	0
Posture	Hunched		0	0	0	1

TABLE 12.6 Body weight and body weight change - group mean values (g) for males and for females before pairing (F0) Request ID: 5433519

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 1	8	15	22	29	36	43	50	57	64	71	78	85
Statistics test		Av	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	88	135	180	223	265	294	321	347	363	376	392	400	414
	SD	7.3	10.3	12.9	16.1	18.7	21.4	25.4	28.3	29.7	30.7	34.3	35.5	37.4
	N	25	25	25	25	25	25	25	25	25	25	25	25	25
2M	Mean	92	140	186	228	270	300	326	348	368	380	401	407	417
	SD	9.0	10.4	13.4	16.6	19.6	22.4	24.1	26.6	28.9	29.5	30.9	31.0	32.7
	N	25	25	25	25	25	25	25	25	25	25	25	25	25
3M	Mean	89	131	178	218	257	288	313	336	354	366	385	389	401
	SD	8.3	10.1	13.8	17.3	21.1	25.3	27.3	31.3	32.7	35.2	38.4	38.4	40.3
	N	25	25	25	25	25	25	25	25	25	25	25	25	25
4M	Mean	90	133	179	221	259	284	311	328*	341**	354*	372*	379*	389*
	SD	9.1	11.4	13.2	15.5	16.3	13.2	18.7	19.2	21.5	20.5	24.9	23.1	26.3
	N	25	25	25	25	25	25	25	25	25	25	25	25	25

TABLE 12.6 (cont) Body weight and body weight change - group mean values (g) for males and for females before pairing (F0) Request ID: 5433519

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 92	99	106	113	120	Change 1-8	Change 8-15	Change 15-22	Change 22-29	Change 29-36	Change 36-43
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Sh	Sh
1M	Mean	430	432	446	453	458	47	45	43	42	28	28
	SD	39.2	39.5	41.1	41.5	41.9	4.5	4.6	5.2	5.2	4.3	6.5
	N	25	25	25	25	25	25	25	25	25	25	25
2M	Mean	432	436	450	457	464	48	46	42	42	29	26
	SD	33.0	34.9	36.9	37.0	38.4	4.3	5.9	4.5	5.2	4.8	4.6
	N	25	25	25	25	25	25	25	25	25	25	25
3M	Mean	413	417	429	440	447	42**	46	41	39*	31	25
	SD	42.4	43.7	41.9	44.7	46.0	4.6	5.5	4.8	6.2	5.8	4.2
	N	25	25	25	25	25	25	25	25	25	25	25
4M	Mean	399**	405*	417*	425*	431*	43**	46	42	38**	26	26*
	SD	27.5	28.1	33.0	30.2	31.6	3.5	3.9	4.0	4.6	9.3	12.1
	N	25	25	25	25	25	25	25	25	25	25	25

TABLE 12.6 (cont) Body weight and body weight change - group mean values (g) for males and for females before pairing (F0) Request ID: 5433519

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Change 43-50	Change 50-57	Change 57-64	Change 64-71	Change 71-78	Change 78-85	Change 85-92	Change 92-99	Change 99-106	Change 106-113	Change 113-120	Change 1-120
Statistics test		lWi	Sh	Wi	Wi	Wi	Wi	Wi	Sh	Wi	Wi	Wi	Wi
1M	Mean	26	16	13	16	8	13	16	2	14	8	5	370
	SD	9.4	11.5	3.4	4.9	5.0	4.8	5.2	4.0	4.9	6.4	3.5	39.6
	N	25	25	25	25	25	25	25	25	25	25	25	25
2M	Mean	22	20	12	21	6	11	14	5	13	8	7	372
	SD	5.9	4.9	4.3	4.1	4.0	4.3	5.9	5.3	5.2	6.7	4.4	38.1
	N	25	25	25	25	25	25	25	25	25	25	25	25
3M	Mean	22	18	13	18	4	12	13*	4	12	12	7	358
	SD	5.2	4.1	5.3	5.2	4.1	3.4	6.6	8.0	7.4	6.8	3.8	43.1
	N	25	25	25	25	25	25	25	25	25	25	25	25
4M	Mean	18**	13**	13	17	7	10*	11**	5*	13	8	6	340**
	SD	4.9	5.4	4.7	7.1	6.9	4.5	3.8	5.3	6.7	5.6	4.0	30.9
	N	25	25	25	25	25	25	25	25	25	25	25	25

TABLE 12.6 (cont) Body weight and body weight change - group mean values (g) for males and for females before pairing (F0) Request ID: 5433519

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 1	8	15	22	29	36	43	50	57	64	71
Statistics test		Av	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	77	110	133	150	168	179	190	198	204	207	216
	SD	5.4	6.3	7.2	6.8	8.6	9.9	11.0	11.0	12.2	13.3	13.8
	N	25	25	25	25	25	25	25	25	25	25	25
2F	Mean	77	108	131	148	165	177	186	196	202	204	214
	SD	5.4	6.0	7.6	9.8	11.0	11.1	12.0	12.0	12.3	12.4	12.6
	N	25	25	25	25	25	25	25	25	25	25	25
3F	Mean	77	108	134	152	170	182	191	199	205	208	219
	SD	4.9	6.0	9.2	11.0	13.0	14.2	14.5	15.4	16.1	16.5	19.6
	N	25	25	25	25	25	25	25	25	25	25	25
4F	Mean	78	106*	132	149	166	177	186	191	196*	202	211
	SD	5.1	6.4	8.2	10.9	12.6	13.2	13.3	13.7	14.5	16.1	17.2
	N	25	25	25	25	25	25	25	25	25	25	25

TABLE 12.6 (cont) Body weight and body weight change - group mean values (g) for males and for females before pairing (F0) Request ID: 5433519

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Change 1-8	Change 8-15	Change 15-22	Change 22-29	Change 29-36	Change 36-43	Change 43-50	Change 50-57	Change 57-64	Change 64-71	Change 1-71
Statistics test		Wi	Wi	Wi	Sh	Sh	Wi	Wi	Wi	Wi	Sh	Wi
1F	Mean	33	22	17	18	11	11	8	7	3	9	139
	SD	4.1	5.0	2.5	3.4	4.2	2.8	4.7	4.1	3.6	4.0	13.7
	N	25	25	25	25	25	25	25	25	25	25	25
2F	Mean	31	23	17	18	11	9	10	5	3	10	137
	SD	3.9	4.0	4.3	3.9	2.4	3.6	3.6	5.5	3.8	3.1	12.6
	N	25	25	25	25	25	25	25	25	25	25	25
3F	Mean	32	26*	18	18	13	9**	8	6	3	11	143
	SD	3.0	5.3	3.9	4.7	3.3	3.1	3.8	4.8	4.0	8.8	18.1
	N	25	25	25	25	25	25	25	25	25	25	25
4F	Mean	29**	25*	17	16	12	9**	4**	5	6**	8	133
	SD	4.5	5.0	4.3	8.9	9.0	3.2	3.3	3.3	4.0	3.2	17.4
	N	25	25	25	25	25	25	25	25	25	25	25

TABLE 12.7 Body weight and body weight change - group mean values (g) for females during gestation (F0) Request ID: 5433520

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 0	7	14	20	Change 0-7	Change 7-14	Change 14-20	Change 0-20
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	217	236	260	317	19	24	57	100
	SD	12.5	12.4	13.3	16.6	4.3	4.3	11.3	11.5
	N	23	23	23	23	23	23	23	23
2F	Mean	214	233	257	320	19	23	63	106
	SD	13.6	15.6	16.6	24.7	6.3	3.1	10.6	14.3
	N	23	23	23	23	23	23	23	23
3F	Mean	217	236	259	323	19	23	64	106
	SD	17.1	18.4	20.2	28.2	5.1	3.8	11.8	17.3
	N	24	24	24	24	24	24	24	24
4F	Mean	208	228	248*	306	20	20**	58	98
	SD	18.4	18.8	21.0	33.0	4.6	4.4	13.9	17.7
	N	23	23	23	23	23	23	23	23

TABLE 12.8 Body weight and body weight change - group mean values (g) for females during lactation (F0) Request ID: 5433521

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 1	4	7	14	18	21	28	Change 1-4	Change 4-7	Change 7-14	Change 14-18	Change 18-21
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	243	255	265	284	284	273	239	12	11	19	0	-11
	SD	13.0	12.5	12.5	15.8	13.4	15.2	14.3	4.9	7.2	8.7	8.1	8.2
	N	23	23	23	23	23	23	23	23	23	23	23	23
2F	Mean	239	252	263	282	284	273	240	13	11	20	1	-10
	SD	15.4	16.8	20.5	22.2	21.4	23.0	17.0	5.9	6.2	9.2	10.0	13.7
	N	23	23	23	23	23	23	23	23	23	23	23	23
3F	Mean	245	260	267	285	287	276	242	15	7	18	2	-11
	SD	19.2	20.7	20.2	18.3	17.7	19.1	18.5	6.1	7.9	7.6	5.9	9.7
	N	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	232*	246	256	272*	275	263	232	14	10	16	3	-12
	SD	21.3	23.4	24.2	25.2	23.8	25.3	18.1	6.7	6.1	7.1	6.8	10.7
	N	23	23	23	23	23	23	23	23	23	23	23	23

TABLE 12.8 (cont) Body weight and body weight change - group mean values (g) for females during lactation (F0) Request ID: 5433521

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Change 21-28	Change 1-21	Change 1-28
Statistics test		Wi	Wi	Wi
1F	Mean	-34	31	-4
	SD	12.7	11.4	9.8
	N	23	23	23
2F	Mean	-33	35	2
	SD	18.5	13.2	10.8
	N	23	23	23
3F	Mean	-34	32	-2
	SD	13.7	12.1	11.7
	N	24	24	24
4F	Mean	-31	31	1
	SD	16.8	11.8	10.7
	N	23	23	23

TABLE 12.9 Food consumption - group mean values (g/animal/week) before pairing (F0) Request ID: 5433522

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Week 1	2	3	4	5	6	7	8	9	10
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	
1M	Mean	103	129	139	150	148	147	152	147	148	Δ
	SD	4.5	3.8	3.1	3.3	5.9	6.7	4.5	4.3	6.7	
	N	7	7	7	7	7	7	7	7	7	
2M	Mean	107	130	140	153	145	152	151	151	150	152
	SD	3.3	4.5	7.3	6.4	8.2	7.8	6.8	8.8	7.1	6.8
	N	7	7	7	7	7	7	7	7	7	7
3M	Mean	103	127	137	149	140*	146	147	143	145	148
	SD	4.1	5.0	4.8	4.4	5.7	8.0	5.4	4.5	6.5	6.6
	N	7	7	7	7	7	7	7	7	7	7
4M	Mean	107	130	141	148	139*	142	143**	141	140*	145
	SD	4.4	8.1	8.6	5.4	4.4	7.3	5.8	5.2	6.4	9.5
	N	7	7	7	7	7	7	7	7	7	7

Δ - Anomolous cage values, data excluded from group means

TABLE 12.9 (cont) Food consumption - group mean values (g/animal/week) before pairing (F0) Request ID: 5433522

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Week 1	2	3	4	5	6	7	8	9	10
Statistics test		Sh	Wi	Du	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	93	97	101	107	100	105	113	107	105	109
	SD	21.8	3.9	9.0	8.7	5.5	10.7	10.4	8.2	7.4	8.4
	N	7	7	7	7	7	7	7	7	7	7
2F	Mean	83	93	93	94*	92	97	99**	98	97	100
	SD	2.7	4.4	4.3	4.7	4.5	7.3	3.9	6.2	7.6	2.8
	N	7	7	7	7	7	7	7	7	7	7
3F	Mean	89	102	105	101*	97	103	104**	101	100	107
	SD	6.1	9.2	10.4	4.2	5.4	10.7	4.7	6.7	4.4	9.3
	N	7	7	7	7	7	7	7	7	7	7
4F	Mean	85	97	98	98*	97	100	99**	97*	97*	102
	SD	3.2	4.7	5.1	7.0	4.7	8.9	8.3	7.5	7.3	5.1
	N	7	7	7	7	7	7	7	7	7	7

TABLE 12.10 Food consumption - group mean values (g/animal/day) for females during gestation (F0) Request ID: 5433523

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 0-7	7-14	14-20
Statistics test		lWi	Wi	Wi
1F	Mean	18	20	20
	SD	3.3	1.9	1.4
	N	23	23	23
2F	Mean	17	18*	19
	SD	1.8	1.8	1.9
	N	23	23	23
3F	Mean	17	19*	20
	SD	1.8	2.0	1.8
	N	24	24	24
4F	Mean	17	18**	19**
	SD	2.1	1.6	2.1
	N	23	23	23

TABLE 12.11 Food consumption - group mean values (g/animal/day) for females during lactation (F0) Request ID: 5433524

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 1-4	4-7	7-14	14-18#	18-21#
Statistics test		Wi	Sh	Wi	Wi	Sh
1F	Mean	29	45	53	60	71
	SD	5.0	15.4	5.1	9.8	13.7
	N	23	23	23	23	23
2F	Mean	26	39	53	62	69
	SD	3.0	7.9	7.0	9.8	10.5
	N	23	23	23	23	23
3F	Mean	29	37	51	58	68
	SD	3.8	3.5	4.3	7.5	6.1
	N	24	24	24	24	24
4F	Mean	27	34**	48*	54*	63*
	SD	5.1	5.7	7.9	8.2	9.1
	N	23	23	23	23	23

- Includes diet consumed by offspring

TABLE 12.12 Estrous cycles - group values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number of animals		Regular cycles 4 day	4/5 day	5 day	Irregular cycle λ	Acyclic ψ
Statistics test Lt							
1	25	N	21	1	0	2	1
		(%)	(84)	(4)		(8)	(4)
2	25	N	22	1	1	1	0
		(%)	(88)	(4)	(4)	(4)	
3	25	N	23	1	0	0	1
		(%)	(92)	(4)			(4)
4	25	N	20	3	0	2	0
		(%)	(80)	(12)		(8)	

λ At least one cycle of two, three or six to ten days
ψ At least ten days without estrus

TABLE 12.13 Pre-coital interval - group values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number of animals		Pre-coital interval (days) 1-4	5-8	9-12	13-14
1	25	N	23	1	0	1
		(%)	(92)	(4)		(4)
2	25	N	25	0	0	0
		(%)	(100)			
3	25	N	24	1	0	0
		(%)	(96)	(4)		
4	25	N	24	0	1	0
		(%)	(96)		(4)	

TABLE 12.14 Mating performance and fertility - group values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group and sex	Number paired	Number mating	Number achieving pregnancy	Percentage mating	Conception rate (%)	Fertility index (%)
1MA	24	24	23	100	96	96
2M	25	25	24	100	96	96
3M	25	25	24	100	96	96
4M	25	25	23	100	92	92
1FA	24	24	23	100	96	96
2F	25	25	24	100	96	96
3F	25	25	24	100	96	96
4F	25	25	23	100	92	92

A Excludes one male and one female - pregnancy status not recorded in error

TABLE 12.15 Gestation length and gestation index - group values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number of pregnant animals		Gestation length (days) 22	22.5	23	23.5	Number of complete live litters born	Gestation index (%)
Statistics test					Lt			
1	23A	N	5	12	6	0	23	100
		(%)	(22)	(52)	(26)			
2	24B	N	3	13	6	1	23	96
		(%)	(13)	(57)	(26)	(4)		
3	24	N	6	8	10	0	24	100
		(%)	(25)	(33)	(42)			
4	23	N	6	10	5	2	23	100
		(%)	(26)	(43)	(22)	(9)		

A Excludes one female - pregnancy status not recorded in error
B Percentage distribution of gestation lengths calculated from 23 females - one pregnant female failed to litter

TABLE 12.16 Stage of estrous cycle at termination - group values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number smeared		Estrus before termination	Cycle stage at termination M	D	P	E
1	25	N	25	6	2	4	13
		(%)	(100)	(24)	(8)	(16)	(52)
2	25	N	24	8	5	7	5
		(%)	(96)	(32)	(20)	(28)	(20)
3	25	N	25	5	5	5	10
		(%)	(100)	(20)	(20)	(20)	(40)
4	25	N	25	8	4	1	12
		(%)	(100)	(32)	(16)	(4)	(48)

D Diestrus
E Estrus
M Metestrus
P Pro-estrus

TABLE 12.17 Hematology - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Hct L/L	Hb g/dL	RBC x10^{12}/L	MCH pg	MCHC g/dL	MCV fL
Statistics test		Sh	Wi	Wi	Wi	Wi	Wi
1M	Mean	0.456	15.9	8.60	18.6	35.0	53.0
	SD	0.0288	0.91	0.527	0.99	0.94	1.87
	N	10	10	10	10	10	10
2M	Mean	0.446	15.8	8.59	18.4	35.4	51.9
	SD	0.0117	0.47	0.323	0.86	0.89	1.28
	N	10	10	10	10	10	10
3M	Mean	0.454	15.9	8.62	18.4	34.9	52.8
	SD	0.0070	0.39	0.280	0.56	0.75	1.39
	N	10	10	10	10	10	10
4M	Mean	0.441	15.1*	8.49	17.8*	34.3	52.0
	SD	0.0193	0.71	0.391	0.38	0.75	1.01
	N	10	10	10	10	10	10

TABLE 12.17 (cont) Hematology - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		WBC x10⁹/L	N x10⁹/L	L x10⁹/L	E x10⁹/L	B x10⁹/L	M x10⁹/L	LUC x10⁹/L	Plt x10⁹/L	PT sec	APTT sec
Statistics test		Sh	lWi	Sh	lWi	Sh	lWi	Sh	Wi	Wi	Wi
1M	Mean	4.06	1.08	2.74	0.07	0.02	0.12	0.03	687	22.5	17.3
	SD	0.635	0.312	0.409	0.024	0.009	0.031	0.018	123.5	1.25	1.42
	N	10	10	10	10	10	10	10	10	10	10
2M	Mean	5.57	1.63	3.62	0.12	0.03	0.14	0.04	708	23.7	15.9
	SD	3.776	1.002	2.731	0.115	0.032	0.091	0.030	115.3	1.67	2.01
	N	10	10	10	10	10	10	10	10	10	10
3M	Mean	4.91	1.20	3.48	0.09	0.02	0.10	0.03	709	22.7	17.1
	SD	1.357	0.505	0.936	0.049	0.009	0.034	0.011	123.3	0.97	1.22
	N	10	10	10	10	10	10	10	10	10	10
4M	Mean	4.10	1.09	2.80	0.09	0.01	0.08*	0.02	744	22.9	15.4**
	SD	0.865	0.325	0.557	0.035	0.007	0.031	0.011	141.0	1.49	1.00
	N	10	10	10	10	10	10	10	10	10	10

TABLE 12.17 (cont) Hematology - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Hct L/L	Hb g/dL	RBC $x10^{12}/L$	MCH pg	MCHC g/dL	MCV fL
Statistics test		Wi	Wi	Wi	Wi	Sh	Wi
1F	Mean	0.473	16.7	8.33	20.0	35.2	56.9
	SD	0.0156	0.51	0.397	0.71	0.64	1.72
	N	10	10	10	10	10	10
2F	Mean	0.468	16.8	8.08	20.9	35.9	58.2
	SD	0.0236	0.79	0.640	1.14	0.90	2.45
	N	10	10	10	10	10	10
3F	Mean	0.471	16.4	8.35	19.6	34.8	56.4
	SD	0.0101	0.40	0.283	0.72	0.74	1.17
	N	10	10	10	10	10	10
4F	Mean	0.457*	15.7**	8.18	19.2*	34.3**	55.9
	SD	0.0153	0.51	0.265	0.51	0.24	1.46
	N	10	10	10	10	10	10

TABLE 12.17 (cont) Hematology - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		WBC x10⁹/L	N x10⁹/L	L x10⁹/L	E x10⁹/L	B x10⁹/L	M x10⁹/L	LUC x10⁹/L	Plt x10⁹/L	PT sec	APTT sec
Statistics test		Wi	Wi	Wi	lWi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	3.16	0.62	2.35	0.10	0.01	0.06	0.02	757	21.7	16.2
	SD	0.591	0.205	0.493	0.043	0.008	0.017	0.007	71.6	1.60	2.47
	N	10	10	10	10	10	10	10	10	10	10
2F	Mean	2.91	0.67	2.02	0.13	0.01	0.07	0.01	693	22.8	16.2
	SD	0.629	0.304	0.489	0.050	0.007	0.021	0.005	101.1	3.18	2.93
	N	10	10	10	10	10	10	10	10	10	10
3F	Mean	3.21	0.78	2.21	0.15	0.01	0.05	0.01	777	21.8	16.6
	SD	0.625	0.198	0.503	0.129	0.005	0.013	0.004	112.3	3.19	2.88
	N	10	10	10	10	10	10	10	10	10	10
4F	Mean	3.33	0.76	2.33	0.16	0.01	0.06	0.02	939**	21.2	15.9
	SD	0.792	0.242	0.624	0.060	0.009	0.019	0.008	143.6	1.87	2.87
	N	10	10	10	10	10	10	10	10	10	10

TABLE 12.18 Blood chemistry - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		ALP U/L	ALT U/L	AST U/L	gGT U/L	Bili µmol/L	Urea mmol/L	Creat µmol/L	Gluc mmol/L	Chol mmol/L	NEFA mmol/L	Trig mmol/L
Statistics test		Wi	Wi	lWi	~	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	65	52	87	0	1	7.27	38	8.21	2.12	1.52	1.41
	SD	7.7	13.8	34.1	0.0	0.3	0.974	3.7	1.053	0.526	0.156	0.357
	N	10	10	10	10	10	10	10	10	10	10	10
2M	Mean	71	47	84	0	1	6.56	37	7.21*	1.90	1.27**	0.91**
	SD	6.5	6.9	18.3	0.0	0.3	0.567	2.0	0.687	0.349	0.187	0.336
	N	10	10	10	10	10	10	10	10	10	10	10
3M	Mean	82**	48	81	0	0	6.91	36	6.72**	1.82	1.15**	0.95**
	SD	17.1	5.7	13.3	0.0	0.3	0.920	4.3	1.226	0.291	0.169	0.241
	N	10	10	10	10	10	10	10	10	10	10	10
4M	Mean	87**	49	78	0	0	6.69	38	7.12**	1.87	1.05**	0.87**
	SD	14.1	8.1	9.2	0.0	0.1	1.010	2.6	0.729	0.338	0.150	0.242
	N	10	10	10	10	10	10	10	10	10	10	10

~ - Statistical analysis not performed as all values were the same

TABLE 12.18 (cont) Blood chemistry - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Na mmol/L	K mmol/L	Cl mmol/L	Ca mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	142	3.75	99.5	2.62	1.53	66	37	1.25
	SD	1.3	0.190	1.12	0.046	0.210	2.5	1.5	0.082
	N	10	10	10	10	10	10	10	10
2M	Mean	143	3.69	100.1	2.63	1.66	66	38	1.31
	SD	1.6	0.159	1.26	0.029	0.209	2.2	1.2	0.072
	N	10	10	10	10	10	10	10	10
3M	Mean	143	3.92	100.0	2.59	1.70	65	38	1.41**
	SD	1.3	0.319	1.49	0.055	0.223	2.7	1.3	0.150
	N	10	10	10	10	10	10	10	10
4M	Mean	144*	3.90	100.8	2.53**	1.51	64	38	1.46**
	SD	1.4	0.247	1.57	0.069	0.163	3.6	1.9	0.117
	N	10	10	10	10	10	10	10	10

TABLE 12.18 (cont) Blood chemistry - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		ALP U/L	ALT U/L	AST U/L	gGT U/L	Bili µmol/L	Urea mmol/L	Creat µmol/L	Gluc mmol/L	Chol mmol/L	NEFA mmol/L	Trig mmol/L
Statistics test		lWi	Wi	Wi	~	Wi	Wi	lWi	Wi	Wi	Wi	Wi
1F	Mean	53	26	70	0	1	7.73	40	7.52	1.94	1.36	0.96
	SD	15.8	10.3	18.7	0.0	0.5	0.580	2.8	0.737	0.390	0.226	0.213
	N	10	10	10	10	10	10	10	10	10	10	10
2F	Mean	44	18	73	0	1*	7.63	40	6.47*	1.69	0.98**	0.92
	SD	6.1	9.4	22.6	0.0	0.3	0.674	3.1	1.170	0.408	0.247	0.343
	N	10	10	10	10	10	10	10	10	10	10	10
3F	Mean	66	32	86	0	1**	7.43	41	6.67*	1.72	1.07**	0.68
	SD	23.0	17.8	28.1	0.0	0.3	1.038	8.3	0.594	0.394	0.151	0.195
	N	10	10	10	10	10	10	10	10	10	10	10
4F	Mean	58	29	75	0	0**	7.37	38	6.46*	1.82	0.93**	0.90
	SD	17.7	11.2	12.3	0.0	0.2	0.615	4.4	0.862	0.285	0.210	0.350
	N	10	10	10	10	10	10	10	10	10	10	10

~ - Statistical analysis not performed as all values were the same

TABLE 12.18 (cont) Blood chemistry - group mean values at scheduled termination (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Na mmol/L	K mmol/L	Cl mmol/L	Ca mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
Statistics test		Sh	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	143	3.63	101.7	2.47	1.33	66	38	1.39
	SD	3.6	0.276	4.03	0.064	0.193	2.9	1.9	0.095
	N	10	10	10	10	10	10	10	10
2F	Mean	144	3.77	106.9	2.54	1.48	66	38	1.35
	SD	2.5	0.247	5.09	0.059	0.356	3.7	2.9	0.120
	N	10	10	10	10	10	10	10	10
3F	Mean	144	3.71	103.7	2.46	1.58	68	40	1.42
	SD	0.8	0.261	1.64	0.081	0.352	3.1	2.4	0.093
	N	10	10	10	10	10	10	10	10
4F	Mean	145	3.87*	104.3	2.44	1.31	65	39	1.51*
	SD	1.2	0.217	2.54	0.073	0.266	1.9	0.9	0.108
	N	10	10	10	10	10	10	10	10

TABLE 12.19 Litter size - group mean values (F1) Request ID: 5433525

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Implantations	Total @	Live on Day Before cull		After cull			
				1	4	4	7	14	21
Statistics test		Wi	Wi	Wi	Wi				
1F	Mean	12.0	11.6	11.6	11.6	9.6	9.6	9.6	9.6
	SD	2.45	2.33	2.33	2.37	1.20	1.20	1.20	1.20
	N	23	23	23	23	23	23	23	23
2F	Mean	12.8	12.2	12.0	12.0	9.8	9.8	9.8	9.8
	SD	1.81	1.86	1.87	1.88	0.83	0.83	0.83	0.83
	N	23	23	23	23	23	23	23	23
3F	Mean	12.4	11.7	11.6	11.6	9.6	9.6	9.6	9.6
	SD	2.18	2.49	2.52	2.52	1.13	1.13	1.13	1.13
	N	24	24	24	24	24	24	24	24
4F	Mean	12.0	11.0	10.9	10.8	9.3	9.3	9.3	9.3
	SD	2.96	2.98	2.99	2.92	1.79	1.79	1.79	1.79
	N	23	23	23	23	23	23	23	23

@ - Includes offspring that died prior to the designated Day 1 of age

TABLE 12.20 Offspring survival indices - group mean values (F1) Request ID: 5433526

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Post implantation survival index (%)	Live birth index (%)	Viability index (%) Day 4	Lactation index (%) Day 21
Statistics test		Wi	Ch	Ch	
1F	Mean	95.6	100.0	99.6	100.0
	SD	7.22	0.00	2.09	0.00
	N	23	23	23	23
	N<100%	9	0	1	0
2F	Mean	94.9	98.6	99.6	100.0
	SD	6.55	3.14	1.74	0.00
	N	23	23	23	23
	N<100%	11	4	1	0
3F	Mean	93.6	99.1	100.0	100.0
	SD	8.52	3.13	0.00	0.00
	N	24	24	24	24
	N<100%	12	2	0	0
4F	Mean	90.3*	98.5	99.3	100.0
	SD	11.72	5.24	2.18	0.00
	N	23	23	23	23
	N<100%	15	2	2	0
Historical Control data (5 studies 2018-2021)					
	Mean	93.24	99.16	99.16	99.58
	Min	89.4	98.0	98.0	99.4
	Max	95.5	99.7	100.0	100.0

The following data were used for the statistics tests, animal indices for post implantation survival index and animal indices dichotomized to 1 when 100% and 0 otherwise for live birth and viability indices.

TABLE 12.21 Offspring sex ratio - group mean values (F1) Request ID: 5433587

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Total @			Live (before cull) on Day 1			Live (before cull) on Day 4			Live (after cull) on Day 4			Live (after cull) on Day 21		
		M	F	%M	M	F	%M	M	F	%M	M	F	%M	M	F	%M
Statistics test				Wi			Wi			Wi						
1F	Mean	5.7	5.9	51.0	5.7	5.9	51.0	5.7	5.9	50.8	4.9	4.7	51.9	4.9	4.7	51.9
	SD	1.98	2.55	18.15	1.98	2.55	18.15	1.99	2.55	18.07	1.22	1.66	14.89	1.22	1.66	14.89
	N	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23
2F	Mean	6.1	6.0	49.8	6.1	6.0	49.9	6.0	6.0	49.7	4.9	5.0	49.0	4.9	5.0	49.0
	SD	2.20	2.06	16.72	2.21	2.01	16.77	2.20	2.01	16.70	1.42	1.15	13.46	1.42	1.15	13.46
	N	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23
3F	Mean	6.0	5.8	50.6	5.9	5.7	50.6	5.9	5.7	50.6	4.9	4.7	50.7	4.9	4.7	50.7
	SD	2.20	2.15	16.12	2.22	2.16	16.04	2.22	2.16	16.04	1.35	1.16	12.86	1.35	1.16	12.86
	N	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	5.1	5.9	46.2	5.1	5.8	47.1	5.0	5.7	47.0	4.3	4.9	47.1	4.3	4.9	47.1
	SD	2.56	2.59	18.10	2.56	2.76	19.75	2.57	2.72	19.81	1.90	1.95	17.51	1.90	1.95	17.51
	N	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23

@ - Includes offspring that died prior to the designated Day 1 of age and excludes unsexed offspring

TABLE 12.22 Ano-genital distance - group mean absolute and adjusted values for offspring (F1)

		Control	Sodium Trifluoroa etate		
Dose Group		1	2	3	4
Dietary concentration (ppm)	- Main phase	0	120	600	3000
	- Lactation phase	0	60	300	1500

Group /Sex		Body weight (g) Day 1	Ano-genital distance (mm)
Statistics test		Wi	
1M	Mean	6.4	4.4
	SD	0.64	0.23
	N	23	23
2M	Mean	6.4	4.4
	SD	0.62	0.18
	N	23	23
3M	Mean	6.3	4.4
	SD	0.44	0.19
	N	24	24
4M	Mean	6.1	4.4
	SD	0.57	0.22
	N	21	21
Statistics test			Wi
1M	Adjusted Mean		4.3
2M	Adjusted Mean		4.4
3M	Adjusted Mean		4.4
4M	Adjusted Mean		4.4

TABLE 12.22 (cont) Ano-genital distance - group mean absolute and adjusted values for offspring (F1)

		Control	Sodium Trifluoroa etate		
Dose Group		1	2	3	4
Dietary concentration (ppm)	- Main phase	0	120	600	3000
	- Lactation phase	0	60	300	1500

Group /Sex		Body weight (g) Day 1	Ano-genital distance (mm)
Statistics test		Wi	
1F	Mean	6.2	2.4
	SD	0.63	0.20
	N	23	23
2F	Mean	5.9	2.2
	SD	0.52	0.15
	N	23	23
3F	Mean	6.1	2.3
	SD	0.51	0.15
	N	24	24
4F	Mean	6.0	2.4
	SD	0.54	0.20
	N	21	21
Statistics test			Wi
1F	Adjusted Mean		2.4
2F	Adjusted Mean		2.2
3F	Adjusted Mean		2.3
4F	Adjusted Mean		2.4

TABLE 12.23 Body weight and body weight change - group mean values (g) for offspring (F1) Request ID: 5433588

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day of age (before cull) 1	1 @	Day of age (after cull) 4	4	7	14	21	Change 1-4	Change 4-7	Change 7-14	Change 14-21	Change 1-21
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	6.4	6.4	9.6	9.6	15.2	29.8	46.8	3.2	5.6	14.6	17.1	40.4
	SD	0.64	0.64	1.21	1.19	1.57	2.83	5.01	0.61	0.58	1.69	2.39	4.60
	N	23	23	23	23	23	23	23	23	23	23	23	23
2M	Mean	6.4	6.4	9.2	9.3	14.7	29.2	47.1	2.9	5.5	14.4	17.9	40.7
	SD	0.62	0.60	1.04	1.01	1.28	2.47	4.20	0.48	0.63	1.59	2.22	3.77
	N	23	23	23	23	23	23	23	23	23	23	23	23
3M	Mean	6.3	6.3	9.4	9.5	14.7	29.0	46.5	3.1	5.3	14.2	17.5	40.1
	SD	0.44	0.40	1.04	1.01	1.52	2.94	4.35	0.74	0.77	1.67	1.97	4.13
	N	24	24	24	24	24	24	24	24	24	24	24	24
4M	Mean	6.2	6.2	9.1	9.1	14.0**	27.6**	43.5*	2.9	4.9**	13.6*	15.9	37.4*
	SD	0.57	0.53	0.97	0.96	1.18	1.98	3.83	0.57	0.52	1.12	2.25	3.62
	N	23	23	23	23	23	23	23	23	23	23	23	23

@ - Includes only those pups surviving after the cull

TABLE 12.23 (cont) Body weight and body weight change - group mean values (g) for offspring (F1) Request ID: 5433588

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day of age (before cull) 1	1 @	Day of age (after cull) 4	4	7	14	21	Change 1-4	Change 4-7	Change 7-14	Change 14-21	Change 1-21
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	6.2	6.2	9.2	9.2	14.7	29.1	45.3	3.0	5.5	14.4	16.1	39.1
	SD	0.63	0.61	1.06	1.07	1.54	2.91	4.59	0.56	0.65	1.79	2.30	4.22
	N	23	23	23	23	23	23	23	23	23	23	23	23
2F	Mean	5.9	6.0	8.8	8.8	14.1	28.4	45.8	2.9	5.3	14.3	17.4	39.8
	SD	0.52	0.52	0.99	0.97	1.32	2.49	4.21	0.53	0.62	1.64	2.13	3.85
	N	23	23	23	23	23	23	23	23	23	23	23	23
3F	Mean	6.1	6.1	9.2	9.2	14.4	28.5	45.3	3.1	5.2	14.1	16.8	39.2
	SD	0.51	0.51	1.04	1.03	1.55	3.19	4.71	0.65	0.81	1.82	2.07	4.42
	N	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	5.9	6.0	8.8	8.8	13.6*	26.8**	42.2*	2.9	4.8**	13.1*	15.5	36.3*
	SD	0.54	0.54	0.96	0.99	1.18	2.05	3.53	0.59	0.52	1.25	2.05	3.32
	N	23	23	23	23	23	23	23	23	23	23	23	23

@ - Includes only those pups surviving after the cull

TABLE 12.24 Sperm analysis - group mean values (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group		Motile sperm (%)	Progressively motile sperm (%)	---- Cauda epididymis ---- Weight (g)	Sperm count (millions/g)	Total (million)	----Testis ---- Weight (g)	Spermatid count (millions/g)	Total (million)
Statistical Test		Wi	Wi	Tt	Tt	Tt	Tt	Tt	Tt
1	Mean	94	42	0.253	484	123	1.98	91	180
	SD	4	9	0.035	138	41	0.15	19	36
	N	24	24	24	24	24	24	24	24
2	Mean	93	40						
	SD	5	10						
	N	25	25						
3	Mean	91	38						
	SD	5	6						
	N	24	24						
4	Mean	92	37	0.231*	437	101*	1.95	90	175
	SD	6	10	0.027	116	29	0.18	15	33
	N	25	25	25	25	25	25	25	25

TABLE 12.25 Sperm motion data - group mean values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group		VAP (µm/s)	VSL (µm/s)	VCL (µm/s)	ALH (µm)	BCF (Hz)	STR (%)	LIN (%)	Rapid (%)	Medium (%)	Slow (%)	Static (%)
Statistical Test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1	Mean	139	83	336	23	36	62	27	60	3	30	6
	SD	8	6	21	2	2	2	1	11	2	9	4
	N	24	24	24	24	24	24	24	24	24	24	24
2	Mean	137	80	336	23	36	62	27	59	4	30	7
	SD	11	8	29	1	2	3	2	13	3	9	5
	N	25	25	25	25	25	25	25	25	25	25	25
3	Mean	136	82	325	23	36	62	28	55	4	32	9
	SD	9	6	25	1	1	2	2	8	2	7	5
	N	24	24	24	24	24	24	24	24	24	24	24
4	Mean	140	81	330	23	36	61*	27	55	3	34	8
	SD	10	7	28	1	2	2	2	14	2	12	6
	N	25	25	25	25	25	25	25	25	25	25	25

TABLE 12.26 Sperm morphology data - group mean values (F0)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number of animals	Total Number examined		Normal Number	Normal %	Total Abnormal Number	Total Abnormal %	Decapitate Number	Decapitate %	Head abnormal Number	Head abnormal %	Neck abnormal Number	Neck abnormal %	Midpiece abnormal Number	Midpiece abnormal %
Statistical Test					Tt		Tt		Tt		Tt		Tt		Tt
1	24	4853	Mean	196	97.1	6	2.9	3	1.4	2	0.8	1	0.3	0.3	0.1
			SD	4	1.5	3	1.5	2	0.9	2	0.8	1	0.4	1	0.3
4	25	4910	Mean	188	95.8*	8	4.2*	4	2.0	2	1	1	0.3	1	0.3
			SD	27	2.3	4	2.3	3	1.5	2	0.8	1	0.6	1	0.3

Group		Tail abnormal Number	Tail abnormal %	Head flat Number	Head flat %	Pronounced hook Number	Pronounced hook %	Head short Number	Head short %	Head misshapen Number	Head misshapen %	Head S-shaped Number	Head S-shaped %	Neck bent/kink Number	Neck bent/kink %
Statistical Test					Tt		Fe		Fe		Fe		Fe		Fe
1	Mean	1	0.5	1	0.7	0.04	0.02	0.04	0.02	0.2	0.1	0	0	0.1	0.04
	SD	1	0.5	1	0.7	0.2	0.1	0.2	0.1	0.4	0.2	0	0	0.3	0.1
4	Mean	2	0.9	2	1	0	0	0	0	0	0*	0.04	0.02	0	0
	SD	2	0.8	2	0.8	0	0	0	0	0	0	0.2	0.1	0	0

TABLE 12.26 (cont) Sperm morphology data - group mean values (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group		Neck broken		Neck coiled		Neck folded		Midpiece bent/kink		Midpiece frayed		Midpiece folded	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Statistical Test			Tt		Fe		Fe		Fe		Fe		Fe
1	Mean	0.5	0.2	0	0	0.04	0.02	0.1	0.1	0.1	0.04	0.04	0.02
	SD	0.8	0.4	0	0	0.20	0.1	0.3	0.2	0.3	0.1	0.2	0.1
4	Mean	0.5	0.3	0.04	0.02	0.08	0.04	0.2	0.1	0.1	0.04	0.04	0.02
	SD	0.9	0.6	0.2	0.1	0.3	0.1	0.5	0.2	0.3	0.1	0.2	0.1

Group		Midpiece broken		Midpiece thin (part)		Midpiece irregular thin		MCD		Tail bent/kink		Tail broken	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Statistical Test			Fe		Fe		Fe		Fe		Fe		Fe
1	Mean	0	0	0.04	0.02	0	0	0.04	0.02	0.1	0.04	0.04	0.02
	SD	0	0	0.2	0.1	0	0	0.2	0.1	0.3	0.1	0.2	0.1
4	Mean	0.04	0.02	0.1	0.1	0.04	0.02	0.04	0.02	0.3	0.2	0	0
	SD	0.2	0.1	0.3	0.2	0.2	0.1	0.2	0.1	0.9	0.4	0	0

TABLE 12.26(cont) Sperm morphology data - group mean values (F0)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group		Tail coiled		Tail folded		Tail frayed		Tail detached		Tail looped	
		Number	%	Number	%	Number	%	Number	%	Number	%
Statistical Test			Fe		Tt		Fe		Wc		Fe
1	Mean	0.1	0.04	0.2	0.1	0	0	0.5	0.3	0	0
	SD	0.3	0.1	0.4	0.2	0	0	0.7	0.4	0	0
4	Mean	0.1	0.04	0.3	0.2	0.04	0.02	0.9	0.5	0.1	0.07
	SD	0.3	0.1	0.5	0.2	0.2	0.1	1	0.7	0.3	0.2

TABLE 12.27 Achieved dose - group mean values (mg/kg/day) for males and females (F1)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

	Group/Sex					
Day	2M	3M	4M	2F	3F	4F
1-7	8.16	40.2	199	7.83	38.3	208
8-14	13.74	72.5	363	12.79	67.5	338
15-21	11.88	59.4	298	11.63	57.3	304
22-28	10.66	53.3	269	10.94	53.9	265
29-35	9.15	47.9	244	9.97	52.2	242
36-42	8.66	43.1	221	9.40	45.9	230
43-49	8.01	39.8	213	8.96	46.7	234
50-56	7.21	35.7	191	8.59	42.2	209
57-63	6.92	34.2	183	8.33	40.8	202
Mean	9.37	47.3	242	9.83	49.4	248

TABLE 12.28 Clinical signs - group distribution of observations (F1) Request ID: 5433701

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Category	Observation	Group/Sex:	1M	2M	3M	4M	1F	2F	3F	4F
		Initial no:	40	40	40	40	40	40	40	40
			Number of animals affected							
Behavior	Irritable		0	0	0	0	2	2	6	0
	Vocalization		0	0	0	0	4	2	4	4
Build (Deformity)	Kinked tail		1	1	0	0	1	0	1	0
Coat	Hair loss, Dorsal surface		1	0	0	0	0	0	0	0
	Hair loss, Forelimbs		0	0	0	0	1	0	0	0
	Hair loss, Hindlimbs		0	0	0	0	1	0	0	0
	Hair loss, Ventral surface		0	0	1	0	1	0	0	0

TABLE 12.29 Body weight and body weight change - group mean values (g) for males and females (F1) Request ID: 5433702

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day of age 21	25	Day 1	8	15	22	29	36	43	50	57	64	71
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	46	64	82	129	172	215	259	292	321	341	360	375	385
	SD	3.5	4.8	8.9	10.6	12.6	15.0	16.0	18.7	21.1	22.7	23.8	24.9	30.5
	N	40	40	40	40	40	40	40	40	40	40	40	40	20
2M	Mean	46	65	79	127	170	214	259	292	318	341	358	370	385
	SD	3.9	5.3	9.9	13.2	14.9	18.0	20.8	22.7	24.8	26.2	27.5	27.8	32.1
	N	40	40	40	40	40	40	40	40	40	40	40	40	20
3M	Mean	45	63	81	128	170	214	259	292	320	344	361	375	386
	SD	3.5	4.6	8.7	11.4	12.8	16.4	19.7	23.3	26.6	28.8	31.4	33.8	30.5
	N	40	40	40	40	40	40	40	40	40	40	40	40	20
4M	Mean	42**	59**	75**	121**	160**	202**	244**	272**	298**	321**	338**	349**	365*
	SD	3.0	3.9	6.9	9.6	11.1	13.5	16.0	16.5	19.4	21.2	22.4	23.6	18.7
	N	40	40	40	40	40	40	40	40	40	40	40	40	20

TABLE 12.29 (cont) Body weight and body weight change - group mean values (g) for males and females (F1) Request ID: 5433702

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Change 21-25	Change 1-8	Change 8-15	Change 15-22	Change 22-29	Change 29-36	Change 36-43	Change 43-50	Change 50-57	Change 57-64	Change 64-71	Change 1-64	Change 1-71
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	18	47	43	44	44	33	29	21	19	14	15	293	304
	SD	2.9	3.2	4.4	3.7	4.3	5.6	5.3	4.8	4.0	3.5	4.8	23.5	30.2
	N	40	40	40	40	40	40	40	40	40	40	20	40	20
2M	Mean	19	47	43	44	45	33	27	23	17	12	16	291	305
	SD	2.3	4.4	4.1	4.1	5.1	4.9	5.5	4.3	3.6	3.9	4.1	23.3	25.1
	N	40	40	40	40	40	40	40	40	40	40	20	40	20
3M	Mean	18	47	42	44	45	33	28	24*	17*	14	13	294	306
	SD	2.1	4.0	4.8	4.8	5.2	6.3	5.7	4.7	5.1	5.5	3.9	32.0	28.1
	N	40	40	40	40	40	40	40	40	40	40	20	40	20
4M	Mean	17	45	40**	42	42	28**	27	22*	17*	12**	12	274**	289
	SD	2.1	4.1	4.6	3.8	4.9	5.0	5.6	4.8	3.5	4.7	3.7	23.5	20.2
	N	40	40	40	40	40	40	40	40	40	40	20	40	20

TABLE 12.29 (cont) Body weight and body weight change - group mean values (g) for males and females (F1) Request ID: 5433702

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day of age 21	25	Day 1	8	15	22	29	36	43	50	57	64	71
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	44	60	76	113	137	157	175	187	197	205	212	218	221
	SD	3.8	4.7	8.0	9.5	10.0	12.0	12.9	12.3	14.0	14.8	14.5	13.9	20.1
	N	40	40	40	40	40	40	40	40	40	40	40	40	20
2F	Mean	45	61	74	110	134	155	174	187	196	206	213	219	223
	SD	4.7	5.7	8.8	10.5	10.0	12.3	14.2	14.1	14.5	15.0	15.7	16.0	16.0
	N	40	40	40	40	40	40	40	40	40	40	40	40	20
3F	Mean	44	60	75	113	136	157	177	191	201	210	217	224	221
	SD	3.2	3.7	7.0	7.9	8.4	9.4	10.3	12.8	12.5	13.2	13.9	16.8	11.7
	N	40	40	40	40	40	40	40	40	40	40	40	40	20
4F	Mean	41**	55**	69**	104**	127**	149**	168**	179*	187**	197*	204*	211*	211
	SD	3.2	4.3	7.0	7.4	9.2	10.3	11.7	11.6	13.2	12.9	13.6	14.4	11.8
	N	40	40	40	40	40	40	40	40	40	40	40	40	20

TABLE 12.29 (cont) Body weight and body weight change - group mean values (g) for males and females (F1) Request ID: 5433702

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Change 21-25	Change 1-8	Change 8-15	Change 15-22	Change 22-29	Change 29-36	Change 36-43	Change 43-50	Change 50-57	Change 57-64	Change 64-71	Change 1-64	Change 1-71
Statistics test		Wi	Wi	Wi	Wi	Sh	Wi	Wi	Wi	Sh	Sh	Wi	Wi	Wi
1F	Mean	16	37	24	20	18	11	10	8	8	5	4	141	144
	SD	2.0	3.3	3.8	4.2	3.8	4.9	4.8	4.1	5.4	5.4	5.3	12.5	18.5
	N	40	40	40	40	40	40	40	40	40	40	20	40	20
2F	Mean	16	36	24	21	20	13	9	10*	7	6	6	146	149
	SD	2.0	3.2	4.1	4.3	4.1	4.5	4.4	5.2	4.7	6.4	5.6	12.8	12.8
	N	40	40	40	40	40	40	40	40	40	40	20	40	20
3F	Mean	16	37	23	21	21	14	10	10*	6	7	2	148	146
	SD	1.7	2.5	4.2	4.3	4.3	5.0	4.5	4.3	4.6	8.2	4.4	17.6	12.7
	N	40	40	40	40	40	40	40	40	40	40	20	40	20
4F	Mean	15**	35**	24	22	19	12	8*	10*	7	7	0*	142	141
	SD	2.0	3.3	4.7	5.4	6.1	4.1	4.3	4.4	2.9	4.4	4.4	13.8	11.6
	N	40	40	40	40	40	40	40	40	40	40	20	40	20

TABLE 12.30 Food consumption - group mean values (g/animal/day) for males and females (F1) Request ID: 5433837

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 1-8	8-15	15-22	22-29	29-36	36-43	43-50	50-57	57-64	64-71
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	14	18	19	21	21	22	22	21	21	21
	SD	1.0	0.9	0.8	0.7	0.5	0.7	0.7	0.6	0.5	0.5
	N	10	10	10	10	10	10	10	10	10	5
2M	Mean	14	17	19	21	21	22	22	21	21	21
	SD	1.2	1.0	0.8	0.9	1.0	1.1	0.8	0.8	0.8	0.9
	N	10	10	10	10	10	10	10	10	10	5
3M	Mean	14	18	19	21	22	22	22	21	21	21
	SD	0.8	0.7	0.9	0.9	1.1	1.2	1.3	1.3	1.1	0.6
	N	10	10	10	10	10	10	10	10	10	5
4M	Mean	13	17	18	20*	21	21	22	21	21	21
	SD	0.7	0.6	0.4	0.6	0.6	0.6	0.6	0.6	0.8	1.1
	N	10	10	10	10	10	10	10	10	10	5

TABLE 12.30 (cont) Food consumption - group mean values (g/animal/day) for males and females (F1)

Request ID: 5433837

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Day 1-8	8-15	15-22	22-29	29-36	36-43	43-50	50-57	57-64	64-71
Statistics test		Wi	Wi	Wi	Wi	Du	Wi	Wi	Wi	Wi	Wi
1F	Mean	12	14	14	15	15	15	15	15	15	15
	SD	0.8	0.6	0.7	0.7	0.7	0.6	0.5	0.4	0.4	0.8
	N	10	10	10	10	10	10	10	10	10	5
2F	Mean	12	13	14	15	15	15	15	15	15	15
	SD	0.9	0.6	0.7	0.7	0.7	0.8	0.8	0.7	0.7	0.3
	N	10	10	10	10	10	10	10	10	10	5
3F	Mean	12	14	14	15	16**	15	16	15	15	15
	SD	0.7	0.7	0.8	0.5	1.2	0.8	0.8	0.6	0.9	0.6
	N	10	10	10	10	10	10	10	10	10	5
4F	Mean	12*	13	14	14	14	14	15	14*	14	14*
	SD	0.7	0.8	0.8	0.9	0.8	0.9	0.9	0.9	1.0	0.9
	N	10	10	10	10	10	10	10	10	10	5

TABLE 12.31 Sexual maturation - group mean age and body weight at completion (F1)

		Control	Sodium Trifluoroa etate		
Dose Group		1	2	3	4
Dietary concentration (ppm)	- Main phase	0	120	600	3000
	- Lactation phase	0	60	300	1500

		Balano preputial separation		Vaginal opening	
Group		Age at completion	Body weight (g) at completion	Age at completion	Body weight (g) at completion
Statistics test		Wi	Wi	Wi	Wi
1	Mean	46.2	193.9	32.6	99.2
	SD	3.89	24.59	2.13	14.38
	N	40	40	40	40
2	Mean	46.9	202.4	32.9	99.7
	SD	4.17	28.76	2.28	12.80
	N	40	40	40	40
3	Mean	45.9	191.6	34.0*	103.6
	SD	4.09	28.53	3.40	17.88
	N	40	40	40	40
4	Mean	47.0	186.5	33.7*	94.9
	SD	3.29	20.88	2.47	11.01
	N	40	40	40	40

TABLE 12.32 Vaginal opening to first estrus - group values (F1 Cohort 1A)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number of animals		Interval between vaginal opening and first estrus (days) 0-1	2-3	4-5	6-7	8-9	10-11	12-13
1	20	N	7	7	3	2	1	0	0
		(%)	(35)	(35)	(15)	(10)	(5)		
2	20	N	10	4	5	1	0	0	0
		(%)	(50)	(20)	(25)	(5)			
3	20	N	11	5	2	1	1	0	0
		(%)	(55)	(25)	(10)	(5)	(5)		
4	20	N	12	4	3	0	0	0	1
		(%)	(60)	(20)	(15)				(5)

TABLE 12.33 Estrous cycles from approximately Day 75 of age - group values (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number of animals		Regular cycles 4 day	4/5 day	5 day	Irregular cycle λ	Acyclic ψ
1	20	N	20	0	0	0	0
		(%)	(100)				
2	20	N	18	1	0	1	0
		(%)	(90)	(5)		(5)	
3	20	N	18	1	0	1	0
		(%)	(90)	(5)		(5)	
4	20	N	18	0	2	0	0
		(%)	(90)		(10)		

λ At least one cycle of two, three or six to ten days
ψ At least ten days without estrus

TABLE 12.34 Stage of estrous cycle at termination - group values (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number smeared		Estrus before termination	Cycle stage at termination M	D	P	E
1	20	N	19	5	9	2	4
		(%)	(95)	(25)	(45)	(10)	(20)
2	20	N	17	4	6	3	7
		(%)	(85)	(20)	(30)	(15)	(35)
3	20	N	17	6	4	7	3
		(%)	(85)	(30)	(20)	(35)	(15)
4	20	N	20	7	9	1	3
		(%)	(100)	(35)	(45)	(5)	(15)

D Diestrus
E Estrus
M Metestrus
P Pro-estrus

TABLE 12.35 Stage of estrous cycle at termination - group values (F1 Cohort 1B)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group	Number smeared		Estrus before termination	Cycle stage at termination M	D	P	E
Statistics test			CA				
1	20	N	20	4	5	4	7
		(%)	(100)	(20)	(25)	(20)	(35)
2	20	N	19	4	10	0	6
		(%)	(95)	(20)	(50)		(30)
3	20	N	20	4	6	6	4
		(%)	(100)	(20)	(30)	(30)	(20)
4	20	N	18	6	6	3	5
		(%)	(90)	(30)	(30)	(15)	(25)

D Diestrus
E Estrus
M Metestrus
P Pro-estrus

TABLE 12.36 Hematology - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Hct L/L	Hb g/dL	RBC $x10^{12}$/L	MCH pg	MCHC g/dL	MCV fL
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	0.453	15.4	8.46	18.3	34.1	53.6
	SD	0.0178	0.43	0.538	0.87	0.56	1.99
	N	10	10	10	10	10	10
2M	Mean	0.455	15.7	8.58	18.2	34.4	53.0
	SD	0.0158	0.47	0.274	0.47	0.72	1.13
	N	10	10	10	10	10	10
3M	Mean	0.442	15.2	8.30	18.3	34.3	53.3
	SD	0.0081	0.37	0.242	0.65	0.58	1.19
	N	10	10	10	10	10	10
4M	Mean	0.436*	14.7**	8.23	17.9	33.8	53.0
	SD	0.0148	0.47	0.310	0.47	0.54	1.04
	N	10	10	10	10	10	10

TABLE 12.36 (cont) Hematology - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		WBC $x10^9$/L	N $x10^9$/L	L $x10^9$/L	E $x10^9$/L	B $x10^9$/L	M $x10^9$/L	LUC $x10^9$/L	Plt $x10^9$/L	PT sec	APTT sec
Statistics test		Sh	lWi	Sh	lWi	Sh	lWi	lWi	lWi	lWi	Wi
1M	Mean	5.48	1.14	4.08	0.09	0.02	0.12	0.03	744	21.2	16.1
	SD	4.397	1.110	3.116	0.068	0.041	0.094	0.038	268.2	2.55	2.71
	N	10	10	10	10	10	10	10	10	10	10
2M	Mean	4.73	1.22	3.27	0.07	0.02	0.12	0.02	677	19.3	17.4
	SD	1.166	0.507	0.860	0.020	0.012	0.033	0.011	83.3	0.72	2.41
	N	10	10	10	10	10	10	10	10	10	10
3M	Mean	4.46	1.28	2.97	0.07	0.02	0.11	0.02	720	19.3	16.3
	SD	1.303	0.880	0.553	0.024	0.014	0.057	0.009	100.8	1.28	3.23
	N	10	10	10	10	10	10	10	10	10	10
4M	Mean	3.71	0.96	2.59*	0.07	0.01	0.07*	0.02	743	20.2	16.4
	SD	0.729	0.331	0.558	0.023	0.007	0.026	0.008	115.8	1.93	2.89
	N	10	10	10	10	10	10	10	10	10	10

TABLE 12.36 (cont) Hematology - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Hct L/L	Hb g/dL	RBC $x10^{12}/L$	MCH pg	MCHC g/dL	MCV fL
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	0.440	15.0	8.04	18.7	34.1	54.7
	SD	0.0154	0.45	0.329	0.50	0.88	0.94
	N	10	10	10	10	10	10
2F	Mean	0.436	15.0	7.92	19.0	34.5	55.2
	SD	0.0116	0.39	0.315	0.70	0.53	1.91
	N	10	10	10	10	10	10
3F	Mean	0.423*	14.6*	7.75	18.9	34.5	54.6
	SD	0.0168	0.34	0.321	0.44	0.89	1.30
	N	10	10	10	10	10	10
4F	Mean	0.421**	14.4**	7.81	18.5	34.2	54.0
	SD	0.0142	0.45	0.206	0.54	0.49	1.35
	N	10	10	10	10	10	10

TABLE 12.36 (cont) Hematology - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		WBC x10⁹/L	N x10⁹/L	L x10⁹/L	E x10⁹/L	B x10⁹/L	M x10⁹/L	LUC x10⁹/L	Plt x10⁹/L	PT sec	APTT sec
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	3.20	0.56	2.52	0.05	0.01	0.05	0.02	683	19.5	14.6
	SD	0.767	0.137	0.756	0.021	0.006	0.017	0.009	82.6	1.64	3.35
	N	10	10	10	10	10	10	10	10	10	10
2F	Mean	3.62	0.83	2.62	0.05	0.01	0.08	0.02	713	19.0	14.2
	SD	0.941	0.369	0.597	0.033	0.007	0.027	0.009	56.5	1.04	3.08
	N	10	10	10	10	10	10	10	9	9	9
3F	Mean	3.30	0.74	2.42	0.05	0.01	0.06	0.02	811*	20.1	15.5
	SD	0.764	0.278	0.541	0.018	0.003	0.018	0.007	117.4	2.02	3.57
	N	10	10	10	10	10	10	10	10	10	10
4F	Mean	3.33	0.62	2.57	0.05	0.01	0.06	0.02	791*	19.2	15.7
	SD	0.597	0.212	0.612	0.014	0.004	0.022	0.011	124.3	2.34	2.55
	N	10	10	10	10	10	10	10	10	10	10

TABLE 12.37 Blood chemistry - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		ALP U/L	ALT U/L	AST U/L	gGT U/L	Bili µmol/L	Urea mmol/L	Creat µmol/L	Gluc mmol/L	Chol mmol/L	NEFA mmol/L	Trig mmol/L
Statistics test		Wi	Wi	lWi	Fe	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	95	30	75	0	1	6.69	26	7.97	1.82	1.50	0.62
	SD	13.9	4.8	7.5	0.0	0.4	0.964	3.0	0.562	0.257	0.123	0.138
	N	10	10	10	10	10	10	10	10	10	10	10
2M	Mean	91	34	88	0	1	6.65	25	6.45**	1.71	1.34*	0.46*
	SD	26.8	7.4	19.0	0.5	0.3	1.024	2.8	0.906	0.249	0.248	0.112
	N	10	10	10	10	10	10	10	10	10	10	10
3M	Mean	109	36	81	0	0**	6.78	26	6.04**	1.56*	1.19**	0.48*
	SD	26.0	4.8	7.6	0.0	0.2	1.138	3.6	0.856	0.347	0.146	0.157
	N	10	10	10	10	10	10	10	10	10	10	10
4M	Mean	127*	42**	85*	0	0**	6.77	27	6.14**	1.57*	1.10**	0.51*
	SD	36.2	8.1	7.4	0.3	0.3	0.893	3.4	0.750	0.225	0.150	0.107
	N	10	10	10	10	10	10	10	10	10	10	10

TABLE 12.37 (cont) Blood chemistry - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Na mmol/L	K mmol/L	Cl mmol/L	Ca mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	143	3.64	98.1	2.64	2.50	63	38	1.52
	SD	0.8	0.296	1.06	0.142	0.272	2.9	0.8	0.157
	N	10	10	10	10	10	10	10	10
2M	Mean	144*	3.68	98.0	2.65	2.44	63	39	1.58
	SD	1.6	0.125	1.40	0.110	0.328	1.6	0.7	0.055
	N	10	10	10	10	10	10	10	10
3M	Mean	144*	3.71	97.7	2.63	2.69	64	39**	1.61
	SD	1.6	0.402	1.47	0.129	0.330	2.9	1.0	0.117
	N	10	10	10	10	10	10	10	10
4M	Mean	145**	3.56	99.2	2.53*	2.24	61	39**	1.78**
	SD	1.1	0.230	1.21	0.064	0.287	2.0	1.3	0.076
	N	10	10	10	10	10	10	10	10

TABLE 12.37 (cont) Blood chemistry - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		ALP U/L	ALT U/L	AST U/L	gGT U/L	Bili µmol/L	Urea mmol/L	Creat µmol/L	Gluc mmol/L	Chol mmol/L	NEFA mmol/L	Trig mmol/L
Statistics test		Wi	Sh	Wi	Fe	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	46	28	79	0	1	8.38	32	7.74	1.73	1.35	0.45
	SD	8.7	9.3	14.1	0.3	0.4	1.245	3.2	0.852	0.382	0.281	0.072
	N	10	10	10	10	10	10	10	10	10	10	10
2F	Mean	48	26	79	0	1	7.80	33	6.38**	1.65	1.17	0.42
	SD	13.8	2.7	15.0	0.0	0.3	0.696	4.0	0.578	0.487	0.198	0.110
	N	10	10	10	10	10	10	10	10	10	10	10
3F	Mean	47	24	73	0	1	7.95	31	6.32**	1.78	1.25	0.48
	SD	12.2	2.8	8.1	0.0	0.3	0.625	3.5	0.806	0.444	0.216	0.124
	N	10	10	10	10	10	10	10	10	10	10	10
4F	Mean	50	32*	81	0	0**	8.60	34	6.60**	1.83	1.01**	0.48
	SD	8.4	4.7	13.3	0.0	0.2	0.874	2.1	0.654	0.377	0.147	0.099
	N	10	10	10	10	10	10	10	10	10	10	10

TABLE 12.37 (cont) Blood chemistry - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Na mmol/L	K mmol/L	Cl mmol/L	Ca mmol/L	Phos mmol/L	Total Prot g/L	Alb g/L	A/G Ratio
Statistics test		Wi	Wi	Wi	Sh	Wi	Wi	Wi	Wi
1F	Mean	142	3.21	98.9	2.60	2.18	66	40	1.58
	SD	1.4	0.303	1.21	0.058	0.366	3.3	2.0	0.056
	N	10	10	10	10	10	10	10	10
2F	Mean	143	3.70**	99.6	2.77	2.37	65	40	1.62
	SD	0.8	0.277	1.25	0.260	0.526	2.3	1.5	0.053
	N	10	10	10	10	10	10	10	10
3F	Mean	143	3.42**	99.4	2.60	1.98	66	41	1.68*
	SD	1.3	0.249	1.74	0.069	0.212	2.1	1.5	0.127
	N	10	10	10	10	10	10	10	10
4F	Mean	143	3.78**	99.7	2.72*	2.25	63*	40	1.76**
	SD	1.1	0.220	0.91	0.173	0.572	3.3	1.8	0.121
	N	10	10	10	10	10	10	10	10

TABLE 12.38 Urinalysis - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Vol mL	pH	SG g/L	T-Prot mg	T-Na mmol	T-K mmol	T-Cl mmol	Prot g/L	U-Na mmol/L	U-K mmol/L	U-Cl mmol/L
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1M	Mean	5.4	7.6	1036	4.977	0.374	0.949	0.459	0.94	72.3	187.0	89.4
	SD	1.49	0.59	9.3	1.4073	0.0854	0.1542	0.1078	0.225	19.37	59.41	26.71
	N	10	10	10	10	10	10	10	10	10	10	10
2M	Mean	5.5	7.4	1034	4.960	0.406	0.866	0.523	0.93	72.3	163.3	96.7
	SD	1.45	0.49	6.8	1.4383	0.1959	0.2063	0.2310	0.246	22.39	45.18	34.01
	N	10	10	10	10	10	10	10	10	10	10	10
3M	Mean	5.6	7.7	1037	6.048	0.471	0.976	0.555	1.13	88.2	186.2	103.8
	SD	1.94	0.58	8.3	2.6174	0.1806	0.1918	0.1754	0.430	28.02	42.95	28.14
	N	10	10	10	10	10	10	10	10	10	10	10
4M	Mean	6.0	7.5	1033	6.224	0.522	0.883	0.578	0.99	88.5	153.8	99.8
	SD	2.29	0.64	4.5	3.2240	0.1848	0.2114	0.1686	0.198	15.05	29.17	22.59
	N	10	10	10	10	10	10	10	10	10	10	10

TABLE 12.38 (cont) Urinalysis - group mean values at scheduled termination (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Vol mL	pH	SG g/L	T-Prot mg	T-Na mmol	T-K mmol	T-Cl mmol	Prot g/L	U-Na mmol/L	U-K mmol/L	U-Cl mmol/L
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	lWi	Wi	Wi	Wi
1F	Mean	3.6	6.2	1040	0.561	0.321	0.535	0.410	0.17	94.5	166.5	124.8
	SD	1.75	0.63	11.1	0.1491	0.1397	0.1490	0.1306	0.045	35.92	54.15	36.80
	N	10	10	10	10	10	10	10	10	10	10	10
2F	Mean	2.7	6.4	1040	0.536	0.229	0.368	0.329	0.25	90.9	154.1	132.5
	SD	1.36	0.65	11.1	0.1898	0.1046	0.1362	0.1474	0.148	19.72	47.81	33.06
	N	10	10	10	10	10	10	10	10	10	10	10
3F	Mean	3.9	6.3	1034	0.624	0.303	0.459	0.338	0.18	86.9	122.8*	93.2
	SD	1.63	0.72	13.0	0.2541	0.1180	0.1994	0.1569	0.062	30.95	27.78	32.45
	N	10	9	10	10	10	10	10	10	10	10	10
4F	Mean	4.4	6.5	1029*	0.602	0.443*	0.389*	0.487	0.14	102.8	89.4**	114.4
	SD	0.78	0.81	4.4	0.1021	0.0920	0.1123	0.0869	0.043	21.29	21.86	28.86
	N	10	10	10	10	10	10	10	10	10	10	10

TABLE 12.39 Ovarian follicle counts and corpora lutea - group mean values (F1 Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) - Main phase	0	120	600	3000
- Lactation phase	0	60	300	1500

Group /Sex		Follicle count	Corpora lutea
Statistics test		Tt	Tt
1F	Mean	17.8	20.5
	SD	4.02	4.70
	N	20	20
4F	Mean	16.3	21.2
	SD	4.36	4.53
	N	20	20

TABLE 12.40 Sperm analysis - group mean values (F1 Cohort 1A)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group		Motile sperm (%)	Progressively motile sperm (%)	---- Cauda epididymis ---- Weight (g)	Sperm count (millions/g)	Total (million)	----Testis ---- Weight (g)	Spermatid count (millions/g)	Total (million)
Statistics test		Wi	Wi	Tt	Tt	Tt	Tt	Tt	Tt
1	Mean	93	44	0.204	453	92	1.83	97	178
	SD	5	9	0.019	93	18	0.14	19	39
	N	20	20	20	20	20	20	20	20
2	Mean	92	41						
	SD	5	10						
	N	20	20						
3	Mean	94	43						
	SD	3	12						
	N	20	20						
4	Mean	94	43	0.191	478	92	1.70**	81**	136**
	SD	4	12	0.025	71	21	0.16	18	30
	N	20	20	20	20	20	20	20	20

TABLE 12.41 Sperm motion data - group mean values (F1 Cohort 1A)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group		VAP (µm/s)	VSL (µm/s)	VCL (µm/s)	ALH (µm)	BCF (Hz)	STR (%)	LIN (%)	Rapid (%)	Medium (%)	Slow (%)	Static (%)
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1	Mean	146	89	357	25	36	63	27	62	3	28	7
	SD	12	9	28	1	2	3	1	10	2	7	5
	N	20	20	20	20	20	20	20	20	20	20	20
2	Mean	137*	84	337	24	35	64	27	57	4	31	8
	SD	12	9	37	2	2	3	2	11	2	8	5
	N	20	20	20	20	20	20	20	20	20	20	20
3	Mean	138*	83	328*	24	35	63	27	60	3	30	6
	SD	14	11	37	2	3	5	2	14	2	11	3
	N	20	20	20	20	20	20	20	20	20	20	20
4	Mean	140*	84	331*	24	35*	62	27	61	3	30	6
	SD	12	10	36	2	3	4	2	14	2	12	4
	N	20	20	20	20	20	20	20	20	20	20	20

TABLE 12.42 Sperm morphology data - group mean values (F1Cohort 1A)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group	Number of animals	Total Number examined		Normal Number	Normal %	Total Abnormal Number	Total Abnormal %	Decapitate Number	Decapitate %	Head abnormal Number	Head abnormal %	Neck abnormal Number	Neck abnormal %	Midpiece abnormal Number	Midpiece abnormal %	Tail abnormal Number	Tail abnormal %
Statistics test					Sh		LWi		Wi		Sh		Wi		Wi		Sh
1	20	3833	Mean	185	96.4	7	3.6	3	1.7	2	1.1	0.4	0.2	0.4	0.2	3	1.3
			SD	34	2.2	5	2.2	3	1.6	2	1.0	1	0.3	1	0.4	4	2.1
2	20	4085	Mean	197	96.6	7	3.4	3	1.2	2	1.0	0.5	0.2	1	0.2	2	0.9
			SD	4	2.4	5	2.4	4	1.8	2	0.7	1	0.3	1	0.4	2	1.0
3	20	4046	Mean	195	96.3	7	3.7	4	1.8	2	1.0	0.3	0.1	1	0.3	2	1.2
			SD	7	2.6	5	2.6	4	2.0	2	1.0	1	0.3	1	0.4	3	1.5
4	20	4053	Mean	191	94.3	12	5.7	5	2.2	5	2.3*	1	0.4	1	0.3	4	1.8
			SD	12	5.4	11	5.4	7	3.1	4	2.1	1	0.5	1	0.7	8	4.1

TABLE 12.42 (cont) Sperm morphology data - group mean values (F1Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group		Head flat		Pinhead		Pronounced hook		Head misshapen		Head S-shaped		Neck bent/kink	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Statistics test			Sh		Fe		Fe		Fe		Fe		Fe
1	Mean	2	1.0	0	0	0	0	0.2	0.1	0	0	0	0
	SD	2	0.9	0	0	0	0	0.4	0.2	0	0	0	0
2	Mean	1	0.7	0.4	0.2*	0	0	0.3	0.1	0.1	0.02	0	0
	SD	1	0.6	1	0.3	0	0	0.6	0.3	0.2	0.1	0	0
3	Mean	2	0.9	0	0	0.1	0.03	0.3	0	0	0	0	0
	SD	2	1.0	0	0	0.2	0.1	1	0	0	0	0	0
4	Mean	4	2.1*	0	0	0	0	0.3	0.1	0	0	0.1	0.05
	SD	4	1.9	0	0	0	0	1	0.3	0	0	0.3	0.2

TABLE 12.42 (cont) Sperm morphology data - group mean values (F1Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group		Eccentric insertion		Neck broken		Neck coiled		Neck folded		Neck frayed		Midpiece bent/kink	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Statistics test			Fe		Fe		Fe		Fe		Fe		Fe
1	Mean	0.1	0.05	0.2	0.1	0	0	0.2	0.1	0	0	0.1	0.05
	SD	0.3	0.2	0.4	0.2	0	0	0.4	0.2	0	0	0.3	0.2
2	Mean	0.2	0.1	0.2	0.1	0	0	0.1	0.02	0	0	0.1	0.02
	SD	0.4	0.2	0.5	0.3	0	0	0.2	0.1	0	0	0.2	0.1
3	Mean	0	0	0.2	0.1	0	0	0.1	0.03	0	0	0.2	0.1
	SD	0	0	0.5	0.3	0	0	0.2	0.1	0	0	1	0.3
4	Mean	0.1	0.05	0.3	0.1	0.1	0.02	0.4	0.2	0.1	0.05	0.3	0.1
	SD	0.3	0.2	0.6	0.3	0.2	0.1	1	0.3	0.3	0.1	1	0.4

TABLE 12.42 (cont) Sperm morphology data - group mean values (F1Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group		Midpiece frayed		Midpiece folded		Midpiece broken		Midpiece detached		Midpiece coiled		Midpiece thin (part)	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Statistics test			Fe		Fe		Fe		Fe		Fe		Fe
1	Mean	0	0	0.1	0.03	0.2	0.1	0.1	0.04	0	0	0.1	0.03
	SD	0	0	0.2	0.1	0.4	0.2	0.4	0.2	0	0	0.2	0.1
2	Mean	0	0	0	0	0	0	0	0	0.1	0.05	0.2	0.1
	SD	0	0	0	0	0	0	0	0	0.3	0.2	0.5	0.2
3	Mean	0.1	0.02	0	0	0	0	0.05	0.03	0.2	0.1	0.1	0.05
	SD	0.2	0.1	0	0	0	0	0.2	0.1	0.4	0.2	0.4	0.2
4	Mean	0	0	0.1	0.02	0.1	0.05	0	0	0	0	0.2	0.1
	SD	0	0	0.2	0.1	0.3	0.2	0	0	0	0	1	0.3

TABLE 12.42 (cont) Sperm morphology data - group mean values (F1Cohort 1A)

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group		Midpiece irregular thin		MCD		Tail bent/kink		Tail broken		Tail coiled		Tail folded	
		Number	%	Number	%	Number	%	Number	%	Number	%	Number	%
Statistics test			Fe		Fe		Fe		Fe		Fe		Fe
1	Mean	0	0	0	0	0.1	0.03	0.1	0.05	0.3	0.2	0.1	0.05
	SD	0	0	0	0	0.2	0.1	0.3	0.1	0.4	0.3	0.3	0.2
2	Mean	0	0	0.2	0.1	1	0.3*	0.2	0.1	0	0*	0.3	0.1
	SD	0	0	0.4	0.2	1	0.6	0.4	0.2	0	0	1	0.3
3	Mean	0	0	0.1	0.05	1	0.4*	0.1	0.02	0.3	0.2	0.4	0.2
	SD	0	0	0.3	0.2	2	0.8	0.2	0.1	0.5	0.2	1	0.3
4	Mean	0.1	0.02	0	0	0.2	0.1	0.1	0.02	0.3	0.1	0.4	0.2
	SD	0.2	0.1	0	0	0.4	0.2	0.2	0.1	1	0.3	0.5	0.2

TABLE 12.42 (cont) Sperm morphology data - group mean values (F1Cohort 1A)

	Control	Sodium Trifluoroa etate		
Dose Group	1	2	3	4
Dietary concentration (ppm) Day 21 to day 35	0	60	300	1500
Dietary concentration (ppm) After day 35	0	120	600	3000

Group			Tail detached		Tail thin		Tail thin (part)	
			Number	%	Number	%	Number	%
Statistics test				Sh		Fe		Fe
1	Mean	2	1.1	0.1	0.02	0	0	
	SD	4	1.9	0.2	0.1	0	0	
2	Mean	1	0.3	0	0	0.2	0.1	
	SD	1	0.5	0	0	0.4	0.3	
3	Mean	1	0.3	0.1	0.03	0.2	0.1	
	SD	2	0.9	0.2	0.1	0.5	0.2	
4	Mean	3	1.5	0.1	0.02	0	0	
	SD	8	4.0	0.2	0.1	0	0	