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# Final Report

Study Title	Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration
Study Director	[REDACTED]
Test Facility	[REDACTED]
[REDACTED] Study Number	8437242
Co - Sponsors	Bayer AG Crop Science Division Alfred-Nobel-Straße 50 40789 Monheim Germany  Rhodia Operations - Solvay 25, rue de Clichy Paris 75009 France
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Page Number	1 of 431

On 25 June 2021 the legal entity [REDACTED] was renamed as [REDACTED]  
[REDACTED] No other changes to the legal entity have occurred.

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Regulation (EC) No 1049/2001

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## 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 2004/10/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.

Study Director

27 October 2021  
Date

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001.

## QUALITY ASSURANCE STATEMENT

### Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage 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.

#### Study based inspections:

Type of Inspection	Date(s) of Inspection	Date Reporting to Study Director, Test Facility Management
Study Plan Verification	18 Jun 2020	18 Jun 2020
Study Plan/Amendment No.1	12 Aug 2020	12 Aug 2020
Study Plan/Amendment No.2	01 Oct 2020	01 Oct 2020
Study Plan Amendment No.3	23 Nov 2020	23 Nov 2020
Draft Report and data Review DEA	28 Aug 2020	28 Aug 2020
Draft Report and Data Review	29 Nov 2020 – 03 Dec 2020	03 Dec 2020
Revised Draft Report and Data Review	18 Jan 2021	18 Jan 2021
Study Plan Amendment No.4	19 May 2021	19 May 2021
Study Plan Amendment Nos. 5 and 6	23 Jun 2021	23 Jun 2021
Revised Draft Report and Data Review	05 Jul 2021	05 Jul 2021
Revised Draft Report and Data Review	23 Aug 2021	23 Aug 2021

#### Dose Formulations:

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Test Item Tracking and Traceability	23 Jul 2020	23 Jul 2020
Control / Vehicle Procedures	23 Jul 2020	23 Jul 2020

Dose Formulation	23 Jul 2020	23 Jul 2020
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**Dose Formulation Analysis:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Formulation preparation and preparation for analysis : Standards Preparation	04 Jun 2020	09 Jun 2020
Formulation Analysis - Data processing, batch approval, reporting results	30 Jun 2020	30 Jun 2020

**Toxicology:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Study Set-up	12 Jun 2020	12 Jun 2020
Study Direction	10 Jun 2020, 12 Jun 2020	12 Jun 2020
Archiving	05 Jun 2020	05 Jun 2020

**Animal Operations:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Dosing Procedures	09 Jun 2020	09 Jun 2020
Animal Data Collection	30 Jun 2020	30 Jun 2020
Terminal Procedures	09 Jul 2020	09 Jul 2020
Husbandry	09 Jul 2020	09 Jul 2020
Animal Receipt Procedures and Study Set Up	10 Feb 2020	10 Feb 2020

**Necropsy:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Necropsy - Reproduction	13 Jul 2020	24 Jul 2020

**Histology:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Histology Process	08 Jul 2020-10 Jul 2020 30 Apr 2021-07 May 2021	24 Jul 2020 07 May 2021

**Pathology:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Pathology Procedures	12 Nov 2020 11 Aug 2021	12 Nov 2020 11 Aug 2021

**Archives:**

Process Based Inspection	Date(s) of Inspection	Date Reporting to Test Facility Management
Archive procedures	15 Apr 2021	15 Apr 2021

Quality Assurance Unit

26 October 2021  
Date

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**STUDY CONTACTS****Co - Sponsors**

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**Study Monitors**

[REDACTED]  
Bayer AG

[REDACTED]  
Solvay Industrial Function - HSE

**Test Facilities  
Primary Location**

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**Formulation Analysis**

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]

**Study Director**

- up to 06 August 2020

[REDACTED]

- from 07 August 2020

[REDACTED]

**Contributing Scientists**

Toxicologist

[REDACTED]

Formulation Analysis

[REDACTED]

Pathology

[REDACTED]

Internal Pathology Peer Review

[REDACTED]  
[REDACTED]

## 1. SUMMARY

The purpose of this study was to assess the influence of Sodium Trifluoroacetate on embryo-fetal survival and development when administered during the organogenesis and fetal growth phases of pregnancy in the New Zealand White rabbit.

Three groups of 24 females received Sodium Trifluoroacetate at doses of 180, 375 or 750 mg/kg/day by oral gavage administration, from Day 6 to 28 after mating. A similarly constituted Control group received the vehicle, water at the same volume dose as treated groups. Animals were killed on Day 29 after mating for reproductive assessment and fetal examination.

Clinical observations, body weight and food consumption were recorded. Adult females were examined macroscopically at necropsy on Day 29 after mating, the gravid uterus weight and liver weight were recorded; the maternal liver from females at scheduled termination were subject to histopathological examination. All fetuses were examined macroscopically at necropsy and subsequently by detailed internal visceral examination of the head or skeletal examination. In addition selected Control and treated bouins fixed fetuses were subject to histopathological examination of the eyes.

### Results

#### F0 maternal responses

Signs observed in association with dose administration were limited to one female at 375 mg/kg/day that showed underactive behavior and a dilated pupil on GD27/28 and one female at 750 mg/kg/day that showed irregular breathing and an unsteady gait on GD7. Although these incidences were isolated and inconsistent, these observations were similar to those seen on the preliminary study and as such, a relationship to treatment cannot be discounted.

Group mean body weight gain during the treatment period (GD6-28) was unaffected by treatment at dose levels up to and including 750 mg/kg/day.

The gravid uterine weight for females that received 375 or 750 mg/kg/day was low when compared with Controls and the subsequent maternal weight loss, following adjustment for the gravid uterine weight, was less for females that received 375 and 750 mg/kg/day when compared with Controls.

On GD6 food consumption was low in all treated groups and remained low at 180 mg/kg/day until GD14, at 375 mg/kg/day until GD15 and at 750 mg/kg/day until GD16. At the end of the treatment period (GD26-28) females receiving Sodium Trifluoroacetate showed high food consumption when compared with Controls.

Body weight adjusted liver weights for females at scheduled termination on GD29 were high when compared with Controls; a dose response was apparent and the difference from control was statistically significant at all dose levels.

Macroscopic examination on Day 29 after mating revealed an irregular surface of the liver in one female (no. 63), that received 375 mg/kg/day.



Histopathological examination of the liver revealed minimal to moderate bile duct hyperplasia/fibrosis and minimal generalized hepatocellular hypertrophy in all treated group; a dose response was apparent.

### **F1 Litter Responses**

Litter data as assessed by the number of implantations, resorptions, live young and sex ratio, and the extent of pre-/post-implantation loss did not show any differences that could be attributed to maternal treatment

Mean placental weights were unaffected by maternal treatment.

Overall mean fetal weights and consequently mean total litter weights were low at 375 and 750 mg/kg/day; a dose response was apparent.

Treatment at 375 or 750 mg/kg/day was associated with clear increase in the numbers of fetuses/litters with major abnormalities compared with Controls and the 180 mg/kg/day group.

At 375/750 mg/kg/day, a high incidence of the major eye abnormalities, multiple folded retina and absent aqueous/vitreous humour was induced by treatment and the incidences were well above that in the concurrent controls and the historical control data (HCD) range. There were also single fetuses with retina ruptured into surrounding tissues and microphthalmia in each of these groups and the ruptured retina was not present in the HCD. There were also low incidences of the minor abnormalities small eye and haemorrhage aqueous/vitreous humour at both doses, and folded retinas at 750 mg/kg/day only, above the HCD range.

At 180 mg/kg/day, one fetus had microphthalmia, with multiple folded retina and absent aqueous/vitreous humour; these incidences were within the HCD range, since higher incidences of fetuses had these extremely rare eye abnormalities at higher doses a relationship to treatment could not be completely ruled out.

### **Conclusion**

Oral gavage administration of Sodium Trifluoroacetate at dose levels of 180, 375 and 750 mg/kg/day had no adverse effect on maternal body weight or food consumption and F1 embryo-fetal survival showed no adverse effect of maternal treatment.

Microscopic liver changes of minimal generalized hepatocellular hypertrophy and minimal to moderate bile duct hyperplasia/fibrosis were seen in the livers of maternal animals at dose levels up to and including 750 mg/kg/day and correlated with the high body weight adjusted liver weights for females.

Detailed fetal examination revealed an increased incidence of major fetal abnormalities at 375 or 750 mg/kg/day; these abnormalities mainly affected the eye and showed consistency and/or exceeded the historical control range. At 180 mg/kg/day, one fetus had microphthalmia, with multiple folded retina and absent aqueous/vitreous humour; although these incidences were within the HCD range, since higher incidences of fetuses had these same extremely rare eye abnormalities at 375/750 mg/kg/day a relationship to treatment could not be completely ruled out.

In view of the maternal liver pathology showing moderate bile duct hyperplasia/fibrosis at 375 and 750 mg/kg/day, 180 mg/kg/day was considered to be the maternal no observed adverse effect level (NOAEL), and as major fetal abnormalities were observed at all dose levels, the fetal NOAEL could not be established on this study.

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## 2. GENERAL STUDY INFORMATION

### 2.1 Purpose

The purpose of this study was to assess the influence of Sodium Trifluoroacetate on embryo-fetal survival and development when administered during the organogenesis and fetal growth phases of pregnancy in the New Zealand White rabbit.

#### 2.1.1 Animal Model

The rabbit was chosen as the test species because of the requirement for a non-rodent species by regulatory agencies. The New Zealand White strain was used because of the historical control data available in this laboratory.

### 2.2 Route of Administration

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

### 2.3 Rationale for Dose Level Selection

Dose levels for this study were chosen in conjunction with the Study Monitors based on the results of a preliminary embryo-fetal study in the New Zealand White rabbit with Sodium Trifluoroacetate in water at dose levels of 250, 500 or 750 (1000) mg/kg/day (Study Number YQ44HR).

In that study an initial dose at 1000 mg/kg/day resulted in four females found to be unsteady and/or underactive in their home cage. By Day 7 (following two doses at 1000 mg/kg/day) all females were unsteady and/or underactive with two females also observed to have impaired locomotion (limited use of limbs), and a further female shown to have rapid breathing, reduced body tone and flattened posture. Consequently, the decision was made to reduce this dose level to 750 mg/kg/day for the remainder of the treatment period; at 750 mg/kg/day these signs improved, until no longer present by Day 12. For females treated at 250 or 500 mg/kg/day, isolated incidences of unsteady gait and decreased activity were similarly observed however to a much lesser magnitude and as such were not considered to be adverse. Body weight and food consumption at doses up to and including 750 mg/kg/day were not adversely affected. Macroscopic examination revealed some abnormalities of the lungs and heart amongst fetuses from litters of females treated with Sodium Trifluoroacetate, however these were considered to be either non-adverse or, the incidence of the findings were within background Control data ranges. As such, a high dose level of 750 mg/kg/day was considered to be a suitable high dose for this main embryo-fetal development study. The low and intermediate dose levels of 180 and 375 mg/kg/day (respectively) were selected to allow evaluation of any dose related trends.

### 2.4 Study Schedule

#### 2.4.1 Duration of Treatment

Females Day 6 to 28 after mating

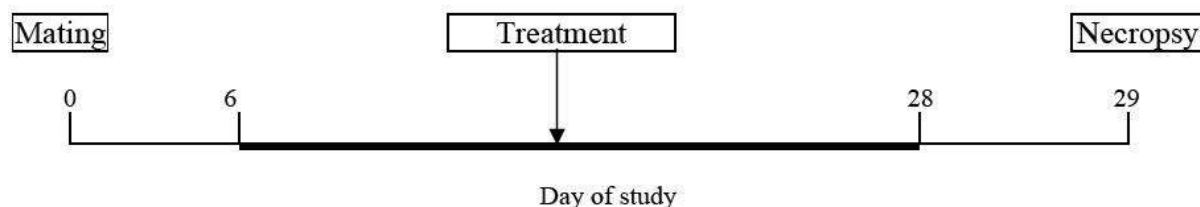
#### 2.4.2 Time Schedule

Study initiation (Study Plan signed by Study Director)	16 June 2020
Experimental start date (arrival of pre-mated animals)	23 June 2020
Arrival of pre-mated animals	23 to 26 June 2020
Treatment commenced	28 June 2020
Necropsy	21 to 24 July 2020

Experimental completion date (maternal and fetal histopathology)

19 August 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 guidelines:

- Current EU, OECD 414 and EPA (OPPTS 870.3700) Guidelines.
- Japanese Ministry of Agriculture, Forestry and Fisheries, Test Data for Registration of Agricultural Chemicals, 12 Nohsan No. 8147, Agricultural Production Bureau, November 24, 2000.

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
Liberate Global	In-house system used for reporting in-life, necropsy, fetal pathology and statistics.
Xybion Pristima	Used for in-life, necropsy and fetal 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. MATERIALS AND TEST METHODS

#### 3.1 Test Item and Supporting Information

##### 3.1.1 Test Item

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 13.1](#)

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:	Industrial chemical Metabolite
Appearance:	White solid
Storage conditions:	At ambient temperature (15 to 25 °C)
Supplier:	Sponsor
Batch number:	2019052304
Stability/expiry	01 May 2021 (two years after analysis/issue date of Certificate of Analysis)
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, 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

Group	Treatment	Dose (mg/kg/day)	Volume dose (mL/kg)	Formulated concentration (mg/mL)
1	Vehicle	0	10	0
2	Sodium Trifluoroacetate	180	10	18
3	Sodium Trifluoroacetate	375	10	37.5
4	Sodium Trifluoroacetate	750	10	75

Correction factor	None.
Vehicle	Water.
Method of preparation	The required amount of test item was ground in a mortar using a pestle and mixed with some vehicle to form a paste. Further amounts of vehicle were gradually added and mixed to produce a smooth, pourable suspension. The suspension was quantitatively transferred and diluted to volume and finally mixed using a high-shear homogenizer.
Frequency of preparation	Weekly.
Storage of formulation	Refrigerated (2 to 8°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	<p>The suitability of the proposed mixing procedures was determined and specimen formulations at 2 and 200 mg/mL were analyzed to assess the stability and homogeneity of the test item in the liquid matrix in [REDACTED] Study Number LC59WX.</p> <ul style="list-style-type: none"> <li>• Ambient temperature (15 to 25°C): 24 hours</li> <li>• Refrigerated (2 to 8°C): 15 days</li> </ul>
Achieved concentration	Samples of each of the first and last formulation preparations were analyzed for achieved concentration of the test item.
Analysis	The method of analysis and results are presented in <a href="#">Attachment 13.2</a> .

### 3.3 Animal Information

#### 3.3.1 Animals

Strain/Species	New Zealand White rabbit.
Supplier	[REDACTED]
Number of animals ordered	96 time-mated females
Duration of acclimatization	Five days before commencement of treatment (Days 1 to 5 of gestation).
Day of delivery	Day 1 after mating.

Age of the animals at the start of the study (Day 1 of after mating) 18 to 22 weeks old.

Weight range of the animals at the start of the study (Day 1 of gestation) 2.47 to 4.52 kg

### 3.3.2 Mating

Method Natural mating with New Zealand White bucks of established fertility at the supplier's facility. Males and females were not closely related. After mating each female was injected intravenously with 25 i.u. luteinising hormone.

Day 0 of gestation On the day of mating.

Delivery to [REDACTED] Day 1 after mating.

### 3.3.3 Allocation and Identification

Allocation On arrival.

Method Randomly to group and cage position. Females mating on any one day were evenly distributed amongst the groups.

The identity of stock males mated with the females was provided by the supplier. Allocation was controlled to prevent any stock male from providing more than one mated female in each treated group and to prevent more than one sibling female in each group, where possible.

Identification of animals Each animal was assigned a number and identified uniquely within the study using a microchip.

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.

### 3.3.4 Animal Care and Husbandry

#### 3.3.5 Environmental Control

Multispecies 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 15-21°C and 45-70%.

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.

Lighting	Artificial lighting, 14 hours light: 10 hours dark.
Alarm systems	Activated on ventilation failure and when temperature/humidity limits exceeded.
Electricity supply	Public supply with automatic stand-by generators.

### 3.3.6 Animal Accommodation

Cages	Suspended cages fitted with perforated floor panels and mounted in batteries. Undertrays lined with absorbent paper were changed at least three times a week. Cages were also fitted with a plastic resting platform.
Cage distribution	The cages constituting each group were blocked by group and mounted in batteries.
Number of animals per cage	One

### 3.3.7 Environmental Enrichment

Aspen chew block	A soft white untreated wood block; provided to each cage throughout the study and replaced when necessary.
Stainless steel key ring	Attached to the cage.
Nesting paper	From Day 20 after mating, cage paper was placed into each cage to allow expression of nesting behavior; paper was replaced as necessary.

### 3.3.8 Diet Supply

Diet	Teklad 2930, pelleted diet.
	The diet contained no added antibiotic or other chemotherapeutic or prophylactic agent.
Availability	200 g/animal/day

In addition to this diet, a small supplement of autoclaved hay was given on a daily basis to promote gastric motility and a small amount of chopped fresh vegetables were given twice weekly. Consumption of hay and vegetables were monitored qualitatively but not quantitatively.



### 3.3.9 Water Supply

#### Supply

Potable water from the public supply via polycarbonate bottles with sipper tubes. Bottles were changed at appropriate intervals.

Water bowls were also used in addition to a bottle for some animals.

#### Availability

Non-restricted.

### 3.3.10 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 are provided by the water supplier.

Certificates of analysis were also received from the suppliers of the Aspen chew blocks.

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

## 3.4 Dose Administration

### 3.4.1 Identity of Treatment Groups

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

Group	Treatment	Dose mg/kg/day <sup>#</sup>	Number of animals	Animal numbers
1	Control	0	24	1-24
2	Sodium Trifluoroacetate	180	24	25-48
3	Sodium Trifluoroacetate	375	24	49-72
4	Sodium Trifluoroacetate	750	24	73-96

# Expressed in terms of material as supplied

### 3.4.2 Administration

#### Route

Oral gavage using a suitably graduated syringe and a rubber catheter inserted via the mouth.

#### Treated at

Constant doses in mg/kg/day.

#### Volume dose

10 mL/kg/day.

#### Individual dose volume

Calculated from the most recently recorded scheduled body weight.

#### Control (Group 1)

Vehicle at the same volume dose as treated groups.

#### Frequency

Females were treated from Day 6 to Day 28 (inclusive) after mating, once daily at approximately the same time each day.

#### Formulation

A daily record of the usage of formulation was maintained based on weights. This balance was compared with the expected usage as a check of correct administration. No significant discrepancy was found.

Formulations were stirred using a magnetic stirrer before and throughout the dosing procedure.

### **3.5 Serial Observations**

#### **3.5.1 Mortality**

A viability check was performed near the start and end of each working day. Animals were killed if they exhibited evidence for pregnancy loss.

A complete necropsy was performed in all cases as described in Section 3.6.

#### **3.5.2 Clinical Observations**

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. 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.

#### **Signs Associated with Dosing**

Detailed observations were recorded daily during the treatment period at the following times in relation to dose administration:

- Pre-dose observation
- One to two hours after completion of dosing
- As late as possible in the working day.

#### **Clinical Signs**

A detailed physical examination was performed on each animal on Days 1, 6, 12, 18, 24 and 29 after mating to monitor general health.

#### **3.5.3 Body Weight**

The weight of each adult was recorded on Days 1, 3, and 6-29 after mating.

#### **3.5.4 Food Consumption**

The weight of food supplied to each animal, that remaining and an estimate of any spilled was recorded daily from Day 2 after mating.

### **3.6 Terminal Investigations**

#### **3.6.1 Method of Kill**

Method of kill for all adult animals                      Intravenous injection of sodium pentobarbitone.

Method of kill for fetuses                      Subcutaneous injection of sodium pentobarbitone.

#### **3.6.2 Necropsy**

All adult animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was performed. All external features and orifices were examined visually. Any abnormality in the appearance or size of any organ and tissue (external and cut surface) was recorded and the required tissue samples preserved in appropriate fixative.



Schedule	Animals surviving until the end of the scheduled study period were killed on Day 29 after mating.  Females that exhibited pregnancy loss were killed on the day of detection.
Sequence	To allow satisfactory inter-group comparison.

### Organ Weights

Requisite liver was weighed for animals killed at scheduled intervals.

### Fixation

Tissues were routinely preserved in 10% Neutral Buffered Formalin

### 3.6.3 Reproductive Assessment

For females surviving to term, the following was recorded:

Uterus	Gravid uterine weight (including cervix and ovaries).
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The following were recorded for all animals (including those prematurely sacrificed, where possible:

For each ovary/uterine horn	Number of:	Corpora lutea. Implantation sites. Resorption sites (classified as early or late). Fetuses (live and dead).
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Non-pregnant animals and for empty uterine horns	The absence or number of uterine implantation sites was confirmed.
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Females exhibiting pregnancy loss	Expelled uterine contents were identified and examined, as appropriate.
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### 3.6.4 Fetal Examination and Processing

Examination of all viable fetuses and placentae	Dissected from the uterus, individually weighed and identified within the litter using a coding system based on their position in the uterus. Examined externally with abnormalities recorded, sampled as appropriate and retained in appropriate fixative. All fetuses were subject to a gross internal examination of the viscera of the neck, thorax and abdominal cavities and the sex of each fetus was also recorded.
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Fixation	Approximately 50% of eviscerated fetuses were decapitated; heads were initially stored in Bouin's fluid.  Remaining eviscerated fetuses and torsos were fixed in Industrial Methylated Spirit.
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Processing Bouin's fixed fetal heads were subject to free-hand serial sectioning.

Industrial Methylated Spirit fixed fetuses and torsos were processed and stained with Alizarin Red.

### 3.6.5 Fetal Pathology Examination

Bouin's fixed heads Serial sections were examined for soft tissue abnormalities.

Alizarin Red stained fetuses and torsos Assessed for skeletal development and abnormalities.

## 3.7 Histology and Light Microscopy

### 3.7.1 Histology

#### Processing to slide

Liver All females (see Section 4)

Fetal eye section Initially four Control fetuses (four litters) were processed to assess suitability. One of the two main eye sections from the bouin's fixed fetal heads that were subject to free-hand serial sectioning were selected from the following fetuses/litters:

- Litter no. 3 – Fetus no. 7
- Litter no. 5 – Fetus no. 1
- Litter no. 9 – Fetus no. 3
- Litter no. 16 – Fetus no. 1

All bouins fixed fetuses with eye abnormalities identified either at necropsy or following examination of bouins fixed serial sections from groups that received Sodium Trifluoroacetate.

Group	Litter no	Fetus no
2	26	1
3	49	3
	57	5
	63	3
	64	1
		5
		11
	66	1
	70	3
4	73	1
		3
	76	2
	82	3
	87	1
	88	7
	91	1
		3
	92	7
	95	5
		7

## Staining

Routine staining 4-5 µm sections stained with haematoxylin and eosin.

### 3.7.2 Light Microscopy

Category	Animals	Tissues
Terminal sacrifice	All adult females (see Section 4)	Liver.
	Four Control fetuses	Fetal eye section
	All fetuses from treated groups with macroscopic eye abnormalities	Fetal eye section

Peer review Carried out by a reviewing pathologist to internationally accepted standards.

## 3.8 Data Evaluation

This report only contains serial observations pertaining to the gestation period (from Day 1 after mating).

Where appropriate, group mean values, each with standard deviation (SD), were calculated from individual data. Summary tabulated data was normally restricted to data derived from females/litters with live young at Day 29 after mating. Group mean values and standard deviations were frequently calculated using a greater number of decimal places than presented in the appendices. It is, therefore, not always possible to derive exact group values from the data presented in the appendices.

Throughout the report the following abbreviations are used:

F Female  
M Male  
N Number contributing to the mean (normally the number of animals/litters)  
SD Standard deviation

### 3.8.1 Serial Observations 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 weight changes were calculated from the weight changes of individual animals. Weight changes were calculated and plotted graphically with respect to Day 6 of gestation.

Adjusted body weights on Day 29 after mating were calculated from the body weight at termination minus the gravid uterine weight. Body weight change values for the period Day 6-29 were also presented, after being adjusted for the contribution of the gravid uterus.

#### Food Consumption

Group mean food consumptions and standard deviations for each period were derived from unrounded cage values.

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

Individual food consumption values are presented for all periods collected. Due to the tolerance limits of the balances used when measuring the diet fed and that remaining, the data capture system may present minor negative food consumption values for animals showing inappetance.

### 3.8.2 Terminal Investigations

#### Liver Weight

Liver weight was presented both as absolute/unadjusted and adjusted for terminal body weight, using the weight recorded on the day of necropsy.

#### Reproductive Assessment

Prenatal losses are separated into pre- and post-implantation phases. Pre-implantation loss was considered to reflect losses due to non-fertilization of ova and failure to implant. It was calculated from the formula:

$$\text{Pre-implantation loss (\%)} = \frac{(\text{Number of corpora lutea} - \text{Number of implantations})}{\text{Number of corpora lutea}} \times 100$$

Where the number of implantations exceeded the number of corpora lutea observed, pre-implantation loss was assumed to be zero (i.e. no pre-implantation loss was considered to have occurred).

Post-implantation loss was calculated from the formula:

$$\text{Post-implantation loss (\%)} = \frac{(\text{Number of implantations} - \text{Number of live fetuses})}{\text{Number of implantations}} \times 100$$

All group values and SD were calculated from the individual litter values.

#### Fetal, Litter and Placental Weights

Mean fetal weights were calculated for each litter. Values were presented for male, female and overall fetal weight. Litter weight was calculated as the sum of all fetal weights. Mean placental weight was also calculated for each litter.

Group mean values and SD were calculated using individual litter mean values.

#### Detailed Fetal Examination

Findings from external, visceral and skeletal examination of fetuses are tabulated on an individual basis for affected litters and fetuses, linking the results of initial external examinations with subsequent visceral and/or skeletal examinations to fetal weight.

Group incidences of observations on fetuses and litters are summarized in terms of major or minor abnormalities or as skeletal variants. The incidence of structural changes are presented as numeric fetal and litter incidences.

Findings observed were classified, according to severity and incidence, as:

**Major abnormalities:** normally rare, definitely detrimental to normal subsequent development, possibly lethal, e.g. partially open eyelids, absent kidney/ureter.

**Minor abnormalities:** minor differences from normal that are detected relatively frequently considered to have little detrimental effect and may be a transient stage in development e.g. bipartite centrum, dilated ureter.

**Variants:** alternative structures or stages of development occurring regularly in the control population, e.g. number of ribs and thoracolumbar vertebra, incomplete ossification of 5th and 6th sternbrae.

In the Fetal examinations appendix, observations on repeated structures like ribs, vertebrae and sternbrae are reported as the first and last affected element, in the form '5th 13th bilateral ribs', which should be interpreted as '5th to 13th bilateral ribs'.

### 3.9 Statistical Analysis

For all 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
- Gravid uterine weight and adjusted body weight
- Food consumption, over appropriate study periods
- C-section litter data (corpora lutea, implantations, pre/post implantation loss, live young and sex ratio - percentage male)
- Placental, litter and fetal weights
- Liver weight, absolute and adjusted for terminal body weight

The following comparisons were performed:

- Group 1 vs 2, 3 and 4

The following sequence of statistical tests was used for body weight, gravid uterus weight, food consumption, corpora lutea, implantations, pre/post implantation loss, live young, sex ratio - percentage male, placental, litter and fetal weights and liver weight 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  $F_1 = \text{NMS}/\text{EMS}$  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.

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 (Shirley, 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  $H_1 = \text{NRSS}/\text{ERSS}$  which can be compared to standard tables of the  $\chi^2$ -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.

For liver weight data, analysis of covariance was performed using terminal body weight as 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 liver weight.

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:

Av	Pre-treatment comparison of all groups using Analysis of variance followed by pairwise $t$ -tests.
KW	Pre-treatment comparison of all groups using Kruskal-Wallis test followed by pairwise Wilcoxon rank sum tests.
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

##### Histopathology of Maternal Livers

Histopathological examination of the liver was required from females at scheduled termination on GD29, however the liver from all animals including decedents and non-pregnant females were examined. Histopathological examination of more tissues than that required by the study plan had no impact on study integrity

Regulation (EC) No 1049/2001

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## 5. ARCHIVING

Records and documentation relating to this study (including electronic records) will be maintained in the archives of [REDACTED] for a period of one year from the issue of the final report. This will include raw data and specimens that support the reconstruction of the study. 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.

In the 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 a copy of the study plan, final report and any amendments indefinitely.

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001



## 6. RESULTS

### 6.1 Formulation Analysis

[Attachment 13.2](#)

The mean achieved concentrations of formulation samples taken from the first and last dose preparations were within 2% of the nominal concentration, confirming the accuracy of formulation. The difference from mean remained within 1%, confirming precise analysis.

### 6.2 Maternal Responses

#### 6.2.1 Mortality

[Appendix 12.1](#), [Appendix 12.2](#)

Two females died prior to scheduled termination:

On Day 27 of gestation (GD27), Control female no. 8 was observed to have a convulsion shortly after dosing and subsequently died. Macroscopic examination revealed a perforated trachea and consequently this death was attributed to dosing trauma.

On GD27 female no. 78 receiving 750 mg/kg/day was killed for reasons of animal welfare following evidence for pregnancy loss. Macroscopic examination of this female revealed an enlarged spleen and uterine examination revealed eight corpora lutea and two resorbing implantation sites. Enlarged spleen was not apparent for any other females on study and as this pregnancy loss was an isolated incidence it was not attributed to administration of Sodium Trifluoroacetate.

#### 6.2.2 Clinical Observations

[Table 11.1](#), [Appendix 12.1](#), [Appendix 12.2](#)

Signs observed in association with dose administration were limited to one female (no. 56) at 375 mg/kg/day that showed underactive behavior and a dilated pupil on Days 27 and 28 and one female (no. 78) at 750 mg/kg/day that showed irregular breathing and an unsteady gait on Day 7 of gestation. Although these incidences were isolated and inconsistent, these observations are similar to those seen on the preliminary study and as such, a relationship to treatment cannot be discounted.

#### 6.2.3 Body Weight and Gravid Uterine Weight

[Figure 10.1](#), [Table 11.2](#), [Table 11.3](#), [Appendix 12.3](#), [Appendix 12.4](#)

Group mean body weight gain during the treatment period (GD6-28) was unaffected by treatment at dose levels up to and including 750 mg/kg/day.

On Day 29 of gestation, the gravid uterine weight for females that received 375 or 750 mg/kg/day was low when compared with Controls ( $p < 0.05$  and  $p < 0.01$ , respectively). The subsequent maternal weight loss, following adjustment with the gravid uterine weight, was less for females that received 375 and 750 mg/kg/day when compared with Controls ( $p < 0.05$  and  $p < 0.01$ , respectively).

#### 6.2.4 Food Consumption

Table 11.4, Appendix 12.5

From Day 6 of gestation (Day 1 of treatment) food consumption was low in all treated groups when compared with Controls. Food intake remained low at 180 mg/kg/day until GD14, at 375 mg/kg/day until GD15 and at 750 mg/kg/day until GD16.

At the end of the treatment period females receiving Sodium Trifluoroacetate showed high food consumption when compared with Controls (GD26-28).

#### 6.2.5 Liver Weight

Table 11.5, Appendix 12.6

Body weight adjusted liver weights for females at scheduled termination on GD29 were high when compared with Controls ( $p < 0.05$  at 180 mg/kg/day;  $p < 0.01$  at 375 and 750 mg/kg/day); a dose response was apparent.

#### 6.2.6 Macropathology

Appendix 12.7

Macroscopic examination on Day 29 after mating revealed an irregular surface of the liver in one female (no. 63), that received 375 mg/kg/day; there were no other findings that could be attributed to treatment with Sodium Trifluoroacetate.

#### 6.2.7 Maternal Histopathology

Table 11.6, Appendix 12.7, Attachment 13.3

In the liver, minimal to moderate bile duct hyperplasia/fibrosis and minimal generalized hepatocellular hypertrophy was seen in females of all treated groups and exhibited a dose relationship.

Group/Sex	Sodium Trifluoroacetate			
	1F	2F	3F	4F
Dose Level (mg/kg/day)	0	180	375	750
Liver				
Number Examined	24	24	24	24
Hyperplasia/Fibrosis, Bile Ducts				
Minimal	0	3	2	6
Slight	0	0	3	3
Moderate	0	0	1	2
Hypertrophy, Hepatocellular, Generalized				
Minimal	0	6	8	9

#### 6.3 Litter Responses

##### 6.3.1 Reproductive Assessment

Table 11.7, Appendix 12.8

Mean corpora lutea, the subsequent number of implantations and litter size were low for females that received 750 mg/kg/day; however, as treatment commenced at or around the time of implantation, this difference is considered unrelated to treatment.

Post-implantation loss (%) was slightly high at 750 mg/kg/day but this difference did not achieve statistical significance.

Mean number of resorptions (early or late) and sex ratio (%M) showed no clear effect of treatment.

### **6.3.2 Placental, Litter and Fetal Weights**

[Table 11.8](#), [Appendix 12.9](#)

Mean placental weights were unaffected by maternal treatment.

Overall mean fetal weights and consequently mean total litter weights were low at 375 and 750 mg/kg/day; a dose response was apparent.

### **6.3.3 Fetal Pathology**

[Table 11.9](#), [Table 11.10](#), [Table 11.11](#), [Appendix 12.10](#), [Attachment 13.3](#), [Attachment 13.4](#)

#### **6.3.3.1 Detailed Fetal Examinations**

Treatment at 375 or 750 mg/kg/day was associated with clear increase in the numbers of fetuses/litters with major abnormalities compared with Controls.

A high incidence of the major eye abnormalities, multiple folded retina and absent aqueous/vitreous humour was associated with treatment at 375/750 mg/kg/day and the incidences were well above that in the concurrent controls and the historical control data (HCD) range. There were also single instances of retina ruptured into surrounding tissues, small/misshapen lens and microphthalmia in each of these groups with the ruptured retina not present in the HCD. There were also low incidences of the minor abnormalities small eye and haemorrhage aqueous/vitreous humour at both doses, and folded retinas at 750 mg/kg/day only, above the HCD range.

In addition at 375/750 mg/kg/day, there were low incidences of major/minor abnormalities affecting heart and major blood vessels: transposition of ascending aorta/pulmonary trunk; narrow/dilated ascending aorta and pulmonary trunk; double outlet ventricle(s) and ventricular septal defects; multiple cervical/thoracic/lumbar/caudal vertebral and rib abnormalities; with associated minor abnormalities affecting the vertebrae, ribs, sternum and costal cartilages); kidneys: absent/displaced/fused. Only one fetus at both 375 or 750 mg/kg/day had a major abnormality multiple folded retina and absent aqueous/vitreous humour plus major abnormalities in other parts of the body so a relationship between treatment and the low incidences of major heart/major vessel, vertebral/rib and kidney abnormalities seems unlikely, and in any case the incidences of the vast majority of these abnormalities were within the HCD range.

There was also an increased incidence of the minor findings 20 thoracolumbar vertebrae, unossified 5th sternebra and epiphyses, incompletely ossified cervical/thoracic vertebrae and metacarpals and forepaw flexure compared to concurrent control. As most of these abnormalities are variants within the population and were mostly within or just outside of the historical control range they are not considered adverse but may still be related to treatment.

At 180 mg/kg/day, one fetus had microphthalmia, with multiple folded retina and absent aqueous/vitreous humour; although these incidences were within the HCD range, since higher incidences of fetuses had these extremely rare eye abnormalities at higher doses a relationship to treatment could not be ruled out. There was also a similar increase in

incidence of the minor non adverse variants 20 thoracolumbar vertebrae, unossified 5th sternebra and epiphyses.

### 6.3.3.2 Fetal Eye Histopathology

Fetal eyes from the Bouin's fixed tissue for fetuses that showed abnormality were subject to histopathological examination. Examination revealed slight to marked retinal folds in the majority (5 of 8) of fetuses whose dams were administered 375 mg/kg/day and in all fetuses (11 of 11) whose dams were administered 750 mg/kg/day and demonstrated a relationship to dose in terms of relative group incidences. Marked retinal folds were seen in the one fetus whose dam was administered 180 mg/kg/day. Lens degeneration was seen in several fetuses (6 of 20), and hemorrhage in the vitreous chamber was seen in a few fetuses (2 of 20), that had retinal folds. The majority of the fetuses that had retinal folds also had absence of aqueous and/or vitreous humor (13 of 20, generally bilateral) reported at macroscopic examination.

At microscopy, structural (anatomical) disorganisation of the eyes was seen in one male fetus and female fetus of each treated group whose dams were administered 375 or 750 mg/kg/day. The retinal rupture through the vitreous chamber reported at macroscopic examination could not always be reliably identified and/or confirmed at microscopy.

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## 7. DISCUSSION

Oral gavage administration of Sodium Trifluoroacetate at dose levels of 180, 375 and 750 mg/kg/day had no adverse effect on maternal clinical condition, body weight or food consumption and F1 embryo-fetal survival showed no adverse effect of maternal treatment.

However the body weight adjusted liver weight for F0 animals at dose levels up to and including 750 mg/kg/day were high and correlated with the histopathological liver findings:

- Minimal generalized hepatocellular hypertrophy was seen in females of all treated groups and exhibited a dose relationship. The hypertrophic changes noted in the liver were suggestive of an adaptive response to mixed function oxidase induction in the liver (Cattley et al., 2002; Maronpot et al., 2010; Thoolan et al., 2010) but the precise mechanism of hypertrophy cannot be determined by histopathological examination alone (Sahota et al., 2019). The change identified in this study was of minimal severity and not accompanied by other changes in the liver (degeneration or necrosis for example).
- Minimal to moderate bile duct hyperplasia/fibrosis was seen in females of all treated groups; a dose response was apparent. Bile duct hyperplasia can be a response to insult to the bile duct epithelium (Sahota et al., 2019), and is indicative of test article excretion in the bile. The bile duct finding appeared to have no adverse effect on maternal clinical condition, but in the absence of blood chemistry it is unknown whether there were any liver changes possibly attributable to the bile duct change. Therefore, in the context of this study the hyperplasia/fibrosis, at the moderate severity which was observed at the mid and high dose may possibly be considered as adverse.

Although embryo-fetal survival showed no adverse effect of maternal treatment, the mean fetal weights at 375 and 750 mg/kg/day were low when compared with Controls.

Treatment at 375 or 750 mg/kg/day was associated with clear increase in the numbers of fetuses/litters with major abnormalities compared with the Control group.

At 375/750 mg/kg/day a high incidence of the major eye abnormalities, multiple folded retina and absent aqueous/vitreous humour was induced by treatment and the incidences were well above that in the concurrent controls and the historical control data (HCD) range. There were also single fetuses with retina ruptured into surrounding tissues and microphthalmia in each of these groups and the ruptured retina was not present in the HCD. There was also low incidences of the minor abnormalities small eye and haemorrhage aqueous/vitreous humour at both doses, and folded retinas at 750 mg/kg/day only, above the HCD range.

In addition at 375/750 mg/kg/day, there were low incidences of major/minor abnormalities affecting heart and major blood vessels: transposition of ascending aorta/pulmonary trunk; narrow/dilated ascending aorta and pulmonary trunk; double outlet ventricle(s) and ventricular septal defects ; multiple cervical/thoracic/lumbar/caudal vertebral and rib abnormalities; with associated minor abnormalities affecting the vertebrae, ribs, sternum and costal cartilages); kidneys: absent/displaced/fused. Only one fetus at both 375 or 750 mg/kg/day had a major abnormality multiple folded retina and absent aqueous/vitreous

humour plus major abnormalities in other parts of the body so a relationship between treatment and the low incidences of major heart/major vessel, vertebral/rib and kidney abnormalities seems unlikely, and in any case the incidences of the vast majority were within the HCD range.

There was also an increased incidence of the minor findings 20 thoracolumbar vertebrae, unossified 5th sternebra and epiphyses, incompletely ossified cervical/thoracic vertebrae and metacarpals and forepaw flexure compared to concurrent control. As most of these abnormalities are variants within the population and were mostly within or just outside of the historical control range, they are not considered adverse but may still be related to treatment.

At 180 mg/kg/day, one fetus had microphthalmia, with multiple folded retina and absent aqueous/vitreous humour; the findings were inside the HCD range (1 in 5687 fetuses). Since higher incidences of fetuses had these extremely rare eye abnormalities at higher doses a relationship to treatment could not be completely ruled out. There was also a similar increase in incidence of the minor non adverse variants 20 thoracolumbar vertebrae, unossified 5th sternebra and epiphyses.

Review of the parentage for the F0 females and the bucks that were mated with the F0 females did not show any causal relationships.

In view of the maternal liver pathology showing moderate bile duct hyperplasia/fibrosis at 375 and 750 mg/kg/day, 180 mg/kg/day was considered to be the maternal no observed adverse effect level (NOAEL), and as major fetal abnormalities were observed at all dose levels, the fetal NOAEL could not be established on this study.

## 8. CONCLUSION

Oral gavage administration of Sodium Trifluoroacetate at dose levels of 180, 375 and 750 mg/kg/day had no adverse effect on maternal clinical condition, body weight or food consumption and F1 embryo-fetal survival showed no adverse effect of maternal treatment.

Microscopic liver changes of minimal generalized hepatocellular hypertrophy and minimal to moderate bile duct hyperplasia/fibrosis were seen in the livers of maternal animals at dose levels up to and including 750 mg/kg/day and correlated with the high body weight adjusted liver weights for females.

Detailed fetal examination revealed an increased incidence of major fetal abnormalities at 375 or 750 mg/kg/day; these abnormalities mainly affected the eye and showed consistency and/or exceeded the historical control range. At 180 mg/kg/day, one fetus had microphthalmia, with multiple folded retina and absent aqueous/vitreous humour. These incidences were within the HCD range. Since higher incidences of fetuses had these same extremely rare eye abnormalities at 375/750 mg/kg/day a relationship to treatment could not be completely ruled out.

In view of the maternal liver pathology showing moderate bile duct hyperplasia/fibrosis at 375 and 750 mg/kg/day, 180 mg/kg/day was considered to be the maternal no observed adverse effect level (NOAEL), and the fetal NOAEL could not be established with certainty on this study.

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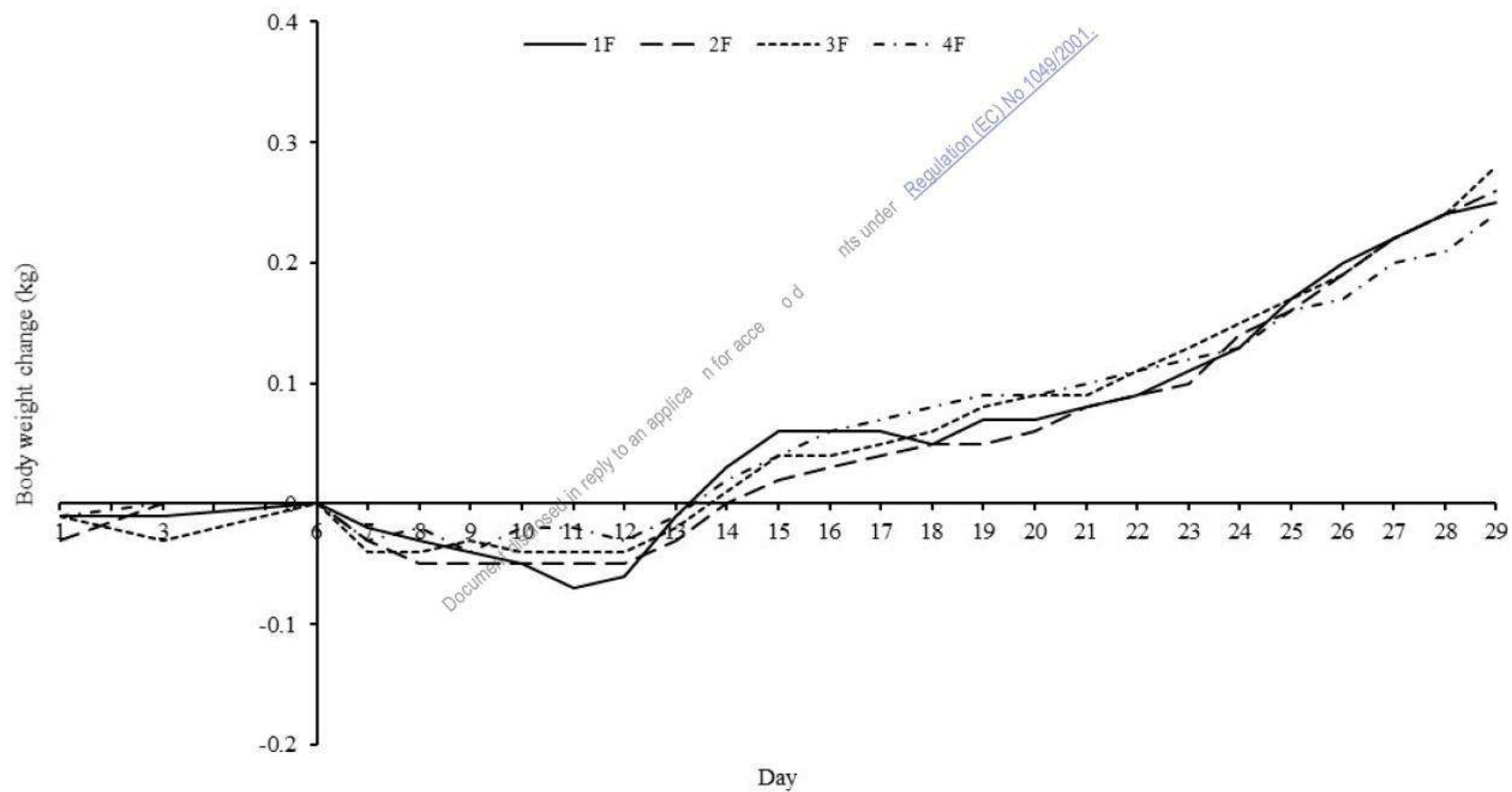
## 10. FIGURES

[Regulation \(EC\) No 1049/2001.](#)

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FIGURE 10.1 Body weight change - group mean values (kg) during gestation

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750



## 11. TABLES

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TABLE 11.1 Clinical signs - group distribution of observations

Request ID: 5376705

Dose Group	Control	Sodium Trifluoroacetate			Group/Sex: Initial no:	Number of animals affected			
	1	2	3	4		1F	2F	3F	4F
Dose (mg/kg/day)	0	180	375	750		24	24	24	24
Category	Observation								
Behavior	Decreased activity					0	0	1	0
Build (Deformity)	Swollen area, Perigenital					1	0	0	0
Build Conformation	Thin					1	1	0	0
Coat	Hair loss, Dorsal surface					0	0	1	0
	Hair loss, Hindlimbs					0	1	1	0
	Hair loss, Ventral surface					0	0	1	0
	Hair loss, Whole body					1	0	0	0
Excreta	Decreased fecal pellets					2	0	0	0
	Fecal pellets reduced in size					2	0	0	0
	Feces loose					0	0	2	1
	Feces mucoid					0	0	0	1

TABLE 11.1 (cont) Clinical signs - group distribution of observations

Request ID: 5376705

Dose Group	Control	Sodium Trifluoroacetate			Group/Sex: Initial no:	Number of animals affected			
	1	2	3	4		1F	2F	3F	4F
Dose (mg/kg/day)	0	180	375	750		24	24	24	24
Excreta	Reduced urine output					2	0	0	0
Muscle reaction	Convulsion, 1 - 2 minutes					1	0	0	0
Reason for dispatch	General poor clinical condition					0	0	0	1
Skin color	Reddening, Perigenital					1	0	0	0
Staining	Abnormal color, Brown, Dorsal surface					0	1	0	0
	Abnormal color, Brown, Ears					0	1	0	0
	Abnormal color, Brown, Forelimbs					2	1	2	0
	Abnormal color, Brown, Head					0	1	0	0
	Abnormal color, Brown, Hindlimbs					2	4	5	6
	Abnormal color, Brown, Perigenital					1	0	1	1
	Abnormal color, Brown, Tail					5	4	8	8

TABLE 11.1 (cont) Clinical signs - group distribution of observations

Request ID: 5376705

Dose Group	Control	Sodium Trifluoroacetate			Number of animals affected			
	1	2	3	4				
Dose (mg/kg/day)	0	180	375	750				
Category	Observation				Group/Sex:			
					Initial no:			
Staining	Abnormal color, Red, Muzzle				1F	2F	3F	4F
	Abnormal color, Red, Perigenital				24	24	24	24
	Abnormal color, Yellow, Dorsal surface				1	0	0	0
	Abnormal color, Yellow, Forelimbs				0	0	1	1
	Abnormal color, Yellow, Hindlimbs				0	0	1	0
	Abnormal color, Yellow, Tail				0	3	0	0
	Abnormal color, Yellow, Tail				3	2	1	2
					1	2	2	3



TABLE 11.2 Body weight and body weight change - group mean values (kg) during gestation

Request ID: 5377602

Dose Group		Control	Sodium Trifluoroacetate											
Dose (mg/kg/day)		1	2	3	4									
		0	180	375	750									
Group /Sex	Day	1	3	6	7	8	9	10	11	12	13	14	15	16
Statistics test		Av	Av	Av	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	3.54	3.54	3.53	3.51	3.50	3.49	3.48	3.46	3.47	3.52	3.56	3.59	3.59
	SD	0.462	0.452	0.463	0.453	0.450	0.443	0.439	0.431	0.439	0.448	0.457	0.461	0.454
	N	19	19	19	19	19	19	19	19	19	19	19	19	19
2F	Mean	3.51	3.54	3.54	3.51	3.49	3.50	3.50	3.49	3.49	3.52	3.54	3.57	3.57
	SD	0.421	0.387	0.395	0.392	0.378	0.383	0.375	0.368	0.371	0.376	0.370	0.368	0.362
	N	21	21	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	3.44	3.46	3.43	3.38	3.38	3.39	3.38	3.38	3.38	3.41	3.44	3.46	3.47
	SD	0.409	0.366	0.373	0.380	0.362	0.347	0.345	0.339	0.331	0.339	0.336	0.333	0.328
	N	24	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	3.36	3.35	3.35	3.32	3.33	3.30	3.32	3.32	3.32	3.33	3.37	3.39	3.41
	SD	0.508	0.508	0.508	0.498	0.480	0.471	0.478	0.458	0.463	0.449	0.436	0.433	0.427
	N	23	23	23	23	23	23	23	23	23	23	23	23	23

TABLE 11.2 (cont) Body weight and body weight change - group mean values (kg) during gestation

Request ID: 5377602

Dose Group		Control	Sodium Trifluoroacetate											
Dose (mg/kg/day)		1	2	3	4									
		0	180	375	750									
Group /Sex		Day 17	18	19	20	21	22	23	24	25	26	27	28	29
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	3.59	3.58	3.60	3.60	3.61	3.62	3.64	3.66	3.70	3.73	3.74	3.75	3.76
	SD	0.447	0.426	0.429	0.425	0.428	0.428	0.425	0.418	0.421	0.415	0.410	0.399	0.395
	N	19	19	19	19	19	19	19	19	19	19	19	18	18
2F	Mean	3.59	3.60	3.59	3.61	3.62	3.64	3.64	3.68	3.71	3.74	3.76	3.78	3.81
	SD	0.358	0.357	0.360	0.353	0.343	0.344	0.326	0.335	0.331	0.340	0.337	0.340	0.317
	N	21	21	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	3.48	3.49	3.51	3.52	3.52	3.53	3.56	3.58	3.59	3.61	3.65	3.67	3.71
	SD	0.326	0.320	0.315	0.326	0.334	0.321	0.322	0.337	0.326	0.330	0.328	0.326	0.325
	N	24	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	3.43	3.43	3.44	3.44	3.45	3.45	3.47	3.48	3.50	3.52	3.55	3.56	3.59
	SD	0.453	0.454	0.456	0.454	0.433	0.426	0.417	0.426	0.416	0.391	0.424	0.412	0.399
	N	22	23	23	23	23	23	23	23	23	23	23	23	23

TABLE 11.2 (cont) Body weight and body weight change - group mean values (kg) during gestation

Request ID: 5377602

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex		Change 1-6	Change 6-7	Change 6-8	Change 6-9	Change 6-10	Change 6-11	Change 6-12	Change 6-13	Change 6-14	Change 6-15	Change 6-16	Change 6-17	Change 6-18
Statistics test		KW	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Sh	Wi	Wi
1F	Mean	-0.01	-0.02	-0.03	-0.04	-0.05	-0.07	-0.06	-0.01	0.03	0.06	0.06	0.06	0.05
	SD	0.052	0.028	0.045	0.062	0.062	0.060	0.070	0.074	0.078	0.072	0.056	0.051	0.058
	N	19	19	19	19	19	19	19	19	19	19	19	19	19
2F	Mean	0.03	-0.03	-0.05	-0.05	-0.05	-0.05	-0.05	-0.03	0.00	0.02	0.03	0.04	0.05
	SD	0.087	0.039	0.052	0.045	0.048	0.060	0.049	0.053	0.077	0.067	0.068	0.078	0.083
	N	21	21	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	-0.01	-0.04	-0.04	-0.03	-0.04	-0.04	-0.04	-0.02	0.01	0.04	0.04	0.05	0.06
	SD	0.105	0.040	0.052	0.057	0.083	0.090	0.093	0.082	0.095	0.099	0.094	0.101	0.110
	N	24	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	-0.01	-0.03	-0.02	-0.04	-0.02	-0.02	-0.03	-0.01	0.02	0.04	0.06	0.07	0.08
	SD	0.118	0.035	0.054	0.064	0.057	0.073	0.069	0.079	0.101	0.107	0.123	0.104	0.109
	N	23	23	23	23	23	23	23	23	23	23	23	22	23

TABLE 11.2 (cont) Body weight and body weight change - group mean values (kg) during gestation

Request ID: 5377602

Dose Group		Control	Sodium Trifluoroacetate									
Dose (mg/kg/day)		1	2	3	4							
		0	180	375	750							
Group /Sex		Change 6-19	Change 6-20	Change 6-21	Change 6-22	Change 6-23	Change 6-24	Change 6-25	Change 6-26	Change 6-27	Change 6-28	Change 6-29
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	0.07	0.07	0.08	0.09	0.11	0.13	0.17	0.20	0.22	0.24	0.25
	SD	0.073	0.073	0.074	0.091	0.096	0.096	0.094	0.103	0.094	0.128	0.131
	N	19	19	19	19	19	19	19	19	19	18	18
2F	Mean	0.05	0.06	0.08	0.09	0.10	0.14	0.16	0.19	0.22	0.24	0.26
	SD	0.083	0.085	0.095	0.103	0.118	0.097	0.101	0.088	0.098	0.107	0.122
	N	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	0.08	0.09	0.09	0.11	0.13	0.15	0.17	0.19	0.22	0.24	0.28
	SD	0.128	0.120	0.129	0.132	0.138	0.137	0.147	0.147	0.160	0.157	0.167
	N	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	0.09	0.09	0.10	0.11	0.12	0.13	0.16	0.17	0.20	0.21	0.24
	SD	0.099	0.100	0.108	0.110	0.136	0.137	0.141	0.162	0.134	0.150	0.157
	N	23	23	23	23	23	23	23	23	23	23	23

TABLE 11.3 Gravid uterine weight, adjusted body weight and adjusted body weight change - group mean values (kg) on Day 29 of gestation

Request ID: 5376714

Dose Group		TFA					
Dose (mg/kg/day)		1	2	3	4		
		0	180	375	750		
Group /Sex		Body weight Day 6	Terminal body weight Day 29	Body weight change 6-29	Gravid uterine weight	Adjusted body weight Day 29	Adjusted body weight change 6-29
Statistics test		Av	Wi	Wi	Wi	Wi	Wi
1F	Mean	3.52	3.76	0.25	0.498	3.27	-0.25
	SD	0.475	0.393	0.130	0.1116	0.354	0.160
	N	18	18	18	18	18	18
2F	Mean	3.54	3.81	0.26	0.461	3.35	-0.20
	SD	0.395	0.314	0.124	0.0825	0.289	0.163
	N	21	21	21	21	21	21
3F	Mean	3.43	3.70	0.28	0.407*	3.29	-0.13*
	SD	0.373	0.327	0.163	0.1215	0.290	0.117
	N	24	24	24	24	24	24
4F	Mean	3.35	3.59	0.24	0.352**	3.24	-0.11**
	SD	0.508	0.402	0.154	0.1348	0.331	0.206
	N	23	23	23	23	23	23

TABLE 11.4 Food consumption - group mean values (g/animal/day) during gestation

Request ID: 5376715

Dose Group		Control	Sodium Trifluoroacetate											
Dose (mg/kg/day)		1	2	3	4									
		0	180	375	750									
Group /Sex		Day 2	3	4	5	6	7	8	9	10	11	12	13	14
Statistics test		Av	Av	Av	Av	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	104	127	128	123	115	104	94	88	87	98	111	111	114
	SD	27.9	30.3	26.8	23.2	25.6	22.5	30.8	21.4	22.7	27.8	21.9	26.0	29.2
	N	19	19	19	19	19	19	19	19	19	19	19	19	19
2F	Mean	103	137	141	134	103	92	85	86	97	98	97*	96	97*
	SD	43.3	33.8	27.7	30.0	21.8	19.7	28.7	21.2	20.3	20.2	18.9	23.1	22.1
	N	21	21	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	107	132	124	113	78**	74**	68**	71*	79	85	93**	97	97*
	SD	32.2	32.1	30.5	33.2	31.6	29.1	23.8	27.0	32.0	29.3	27.0	25.4	27.4
	N	24	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	103	125	133	118	83**	72**	66**	68*	70*	81*	85**	85**	84**
	SD	37.1	31.3	32.6	35.5	32.6	26.9	27.6	23.8	25.7	21.5	21.0	24.2	27.1
	N	23	23	23	23	23	23	23	23	23	23	23	23	23

TABLE 11.4 (cont) Food consumption - group mean values (g/animal/day) during gestation

Request ID: 5376715

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Statistics test		Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi	Wi
1F	Mean	111	107	103	106	111	103	105	97	94	97	94	93	96	89
	SD	21.5	23.3	25.9	26.1	28.1	25.4	21.0	16.7	17.5	18.6	21.6	28.2	30.6	25.2
	N	19	19	19	19	19	19	19	19	19	19	19	19	18	18
2F	Mean	98	106	111	113	115	110	105	107	102	105	112	109*	114*	111**
	SD	20.7	17.6	26.1	24.2	23.0	22.6	17.9	14.7	13.3	14.6	14.1	19.1	17.8	23.9
	N	21	21	21	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	94*	98	104	106	107	100	104	103	102	103	106	110*	114*	110**
	SD	25.9	27.3	26.5	24.8	23.2	28.1	20.9	17.4	20.0	19.3	21.3	22.5	20.5	19.9
	N	24	24	24	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	85**	90*	98	98	103	100	96	98	96	97	101	106*	111*	109**
	SD	28.4	26.5	28.0	23.7	21.7	24.2	21.0	23.3	21.8	20.0	19.0	22.7	27.7	21.4
	N	23	23	23	23	23	23	23	23	23	23	23	23	23	23



TABLE 11.5 Liver weight - group mean absolute and adjusted values (g) on Day 29 of gestation

Request ID: 5376716

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate		
	1 0	2 180	3 375	4 750

Group /Sex		Terminal Body weight	Liver
Statistics test		Wi	
1F	Mean	3765	102.332
	SD	393	13.700
	N	18	18
2F	Mean	3807	111.812
	SD	314	13.214
	N	21	21
3F	Mean	3702	115.638
	SD	327	14.160
	N	24	24
4F	Mean	3589	114.303
	SD	402	16.105
	N	23	23

Statistics test		Wi
1F	Adjusted Mean	101.410
2F	Adjusted Mean	110.173*
3F	Adjusted Mean	115.780**
4F	Adjusted Mean	116.373**

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TABLE 11.6 Histopathology - group distribution of findings

Request ID: 5388621

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate						
	1	2	3	4				
	0	180	375	750				
					Number of animals affected			
Tissue/Organ and Findings	Group/Sex No. of animals				1F	2F	3F	4F
					24	24	24	24
Liver	No. examined				24	24	24	24
Microvacuolation, Cytoplasmic, Hepatocellular, Generalized	Minimal				1	0	0	0
	Slight				1	0	0	0
	Total				2	0	0	0
Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal	Minimal				2	1	0	0
	Total				2	1	0	0
Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal	Minimal				2	2	1	0
	Total				2	2	1	0

TABLE 11.6 (cont) Histopathology - group distribution of findings

Request ID: 5388621

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			Tissue/Organ and Findings	Group/Sex No. of animals	Number of animals affected			
	1 0	2 180	3 375	4 750			1F 24	2F 24	3F 24	4F 24
Liver					No. examined		24	24	24	24
Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized					Minimal		2	0	0	1
					Total		2	0	0	1
Hyperplasia/Fibrosis, Bile Ducts					Minimal		0	3	2	6
					Slight		0	0	3	3
					Moderate		0	0	1	2
					Total		0	3	6	11
Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized					Minimal		0	1	2	1
					Total		0	1	2	1
Necrosis, Hepatocellular, Focal					Minimal		0	0	1	0
					Total		0	0	1	0

TABLE 11.6 (cont) Histopathology - group distribution of findings

Request ID: 5388621

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate						
	1 0	2 180	3 375	4 750				
					Number of animals affected			
					1F 24	2F 24	3F 24	4F 24
Tissue/Organ and Findings	Group/Sex No. of animals							
Liver	No. examined				24	24	24	24
Hyperplasia, Oval Cell	Minimal				1	3	2	0
	Slight				1	0	0	0
	Total				2	3	2	0
Hypertrophy, Hepatocellular, Generalized	Minimal				0	6	8	9
	Total				0	6	8	9
Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized	Minimal				2	2	2	3
	Total				2	2	2	3
Major Factor(s) contributing to death	No. examined				1	0	0	1
Accidental Death	Total				1	0	0	0
Suspected Abortion	Total				0	0	0	1

TABLE 11.7 Litter data - group mean values on Day 29 of gestation

Request ID: 5376717

		Control	Sodium Trifluoroacetate									
Dose Group		1	2	3	4							
Dose (mg/kg/day)		0	180	375	750							
Group /Sex		Corpora lutea	Implantations	Early	Resorptions Late	Total	Implantation loss (%)		Male	Live young Female	Total	Sex ratio (%M)
Statistics test		Wi	Wi				Wi	Wi			Wi	Wi
1F	Mean	10.4	9.1	0.6	0.2	0.8	12.6	10.2	4.4	3.9	8.3	51.8
	SD	2.06	2.00	0.85	0.38	0.94	13.48	13.10	1.92	1.57	2.47	14.93
	N	18	18	18	18	18	18	18	18	18	18	18
2F	Mean	9.6	8.5	0.7	0.3	1.0	11.1	10.1	3.3	4.2	7.5	43.6
	SD	2.29	2.09	1.11	0.56	1.07	15.41	10.34	1.96	1.66	1.78	22.18
	N	21	21	21	21	21	21	21	21	21	21	21
3F	Mean	9.6	8.0	0.4	0.4	0.8	17.8	10.7	3.7	3.5	7.2	49.6
	SD	1.64	2.71	0.65	0.77	0.99	22.96	14.50	2.14	1.67	2.77	24.39
	N	24	24	24	24	24	24	24	24	24	24	24
4F	Mean	8.3**	7.2*	0.7	0.3	1.1	15.7	14.9	3.0	3.1	6.1**	50.8
	SD	2.48	2.67	0.86	0.57	1.04	17.93	14.57	1.64	1.94	2.59	22.66
	N	23	23	23	23	23	23	23	23	23	23	23

TABLE 11.8 Placental, litter and fetal weights - group mean values (g) on Day 29 of gestation

Request ID: 5376718

Dose Group Dose (mg/kg/day)		Control 1 0	Sodium Trifluoroacetate 2 180      3 375      4 750			
Group /Sex		Placental weight	Total litter weight	Male fetal weight	Female fetal weight	Overall fetal weight
Statistics test		Wi	Wi	Wi	Wi	Wi
1F	Mean	5.4	330.3	41.3	40.2	40.6
	SD	0.89	83.93	5.40	4.38	4.45
	N	18	18	18	18	18
2F	Mean	5.2	299.1	39.8	40.5	40.3
	SD	0.56	57.29	5.14	3.93	3.77
	N	21	21	20	21	21
3F	Mean	5.2	256.0**	36.2**	37.5	37.4
	SD	0.91	87.85	6.03	6.97	7.13
	N	24	24	22	23	24
4F	Mean	5.0	217.6**	36.7**	36.0*	36.6*
	SD	0.76	89.24	5.55	3.90	4.58
	N	23	23	23	21	23

Regulation (EC) No 1049/2001.

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TABLE 11.9 Fetal examinations - major abnormality findings - group incidences

Request ID: 5375760

		Control	Sodium Trifluoroacetate										
Dose Group		1	2	3	4								
Dose (mg/kg/day)		0	180	375	750								
		Fetuses				Litters							
Group		1	2	3	4	1	2	3	4				
Number Examined		150	158	173	140	18	21	24	23				
Total Number Affected		2	3	16	16	2	3	10	9				
Head													
Visceral													
	Multiple folded retina	0	1	5	9	0	1	4	8				
	Absent aqueous/vitreous humour	0	1	6	8	0	1	4	6				
	Brain discrete area of amorphous tissue at position of optic nerve	0	0	1	0	0	0	1	0				
	Retina ruptured into surrounding tissue	0	0	1	1	0	0	1	1				
	Small/misshapen lens	0	0	1	1	0	0	1	1				
	Absent lens	0	0	0	1	0	0	0	1				
	Microphthalmia	0	1	1	1	0	1	1	1				
	Narrow optic nerve	0	0	1	0	0	0	1	0				
	Cleft palate	0	0	0	1	0	0	0	1				

Note: Individual fetuses/litters may occur in more than one category.



TABLE 11.9 (cont) Fetal examinations - major abnormality findings - group incidences

Request ID: 5375760

		Control		Sodium Trifluoroacetate											
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
		Fetuses				Litters									
Group		1	2	3	4	1	2	3	4						
Number Examined		150	158	173	140	18	21	24	23						
Total Number Affected		2	3	16	16	2	3	10	9						
Cervical/Thoracic Skeletal	Thoracic scoliosis	0	0	0	1	0	0	0	1						
	Cervical/thoracic hemivertebra	1	0	1	1	1	0	1	1						
	Multiple cervical vertebral abnormalities	0	0	1	0	0	0	1	0						
	Multiple thoracic vertebral/rib abnormalities	0	0	0	2	0	0	0	2						
	Distorted rib cage	0	0	0	1	0	0	0	1						
Visceral	Dorsoventral distortion of sternum	0	0	1	0	0	0	1	0						
	Narrow ascending aorta/aortic arch	0	0	1	0	0	0	1	0						
	Dilated ascending aorta/aortic arch	0	0	1	0	0	0	1	0						
	Dilated/dorsally displaced pulmonary trunk	0	0	1	0	0	0	1	0						
	Transposition of ascending aorta with pulmonary trunk	1	2	1	2	1	2	1	1						
	Truncus arteriosus	0	1	0	0	0	1	0	0						
	Membranous ventricular septal defect	0	1	1	0	0	1	1	0						
	Muscular ventricular septal defect	1	0	0	1	1	0	0	1						
	Double outlet ventricle(s)	0	1	1	0	0	1	1	0						

Note: Individual fetuses/litters may occur in more than one category.

TABLE 11.9 (cont) Fetal examinations - major abnormality findings - group incidences

Request ID: 5375760

	Control	Sodium Trifluoroacetate											
Dose Group	1	2	3	4									
Dose (mg/kg/day)	0	180	375	750									
Group					Fetuses				Litters				
	1	2	3	4	1	2	3	4					
Number Examined	150	158	173	140	18	21	24	23					
Total Number Affected	2	3	16	16	2	3	10	9					
Lumbar (and abdominal)/Sacral/Caudal													
Skeletal	Lumbar scoliosis				0	0	0	1	0	0	0	1	
	Lumbar hemivertebra				0	0	1	1	0	0	1	1	
	Fused/partially fused/misshapen disorganised sacral/caudal vertebrae				0	0	2	1	0	0	2	1	
	Brachyury				0	0	1	1	0	0	1	1	
External	Gastroschisis				0	0	1	1	0	0	1	1	
	Omphalocele				0	0	2	0	0	0	2	0	
Visceral	Displaced kidney(s)				0	1	0	0	0	1	0	0	
	Fused/caudally displaced kidney(s)				0	0	0	1	0	0	0	1	
	Absent kidney(s)				0	0	1	0	0	0	1	0	
	Absent ureter(s)				0	0	1	0	0	0	1	0	

Note: Individual fetuses/litters may occur in more than one category.

TABLE 11.10 Fetal examinations - minor skeletal abnormality findings - group incidences

Request ID: 5375913

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
		Fetuses				Litters								
Group		1	2	3	4	1	2	3	4					
Number Examined		150	158	173	140	18	21	24	23					
Number Intact		72	73	81	67	18	21	24	23					
Minor skeletal abnormalities														
Cranial	unossified area(s)	0	1	1	1	0	1	1	1					
	additional suture(s)	1	0	0	0	1	0	0	0					
	fissured interparietal	1	2	3	1	1	1	3	1					
	absent supraorbital notch(es)	0	0	0	1	0	0	0	1					
	bent cornu(a) of hyoid	0	0	1	0	0	0	1	0					
Vertebral element abnormalities	small 1st cervical vertebral arch(es)	1	1	0	0	1	1	0	0					
	cervical	0	0	4	3	0	0	4	3					
	thoracic	0	0	3	4	0	0	3	3					
	lumbar	0	0	1	1	0	0	1	1					
	sacral/caudal	0	0	2	1	0	0	2	1					
Ribs	misaligned	0	0	1	0	0	0	1	0					
	nodulated	0	0	1	0	0	0	1	0					
	branched with additional costal cartilage	0	0	2	1	0	0	2	1					
	absent	1	0	1	1	1	0	1	1					
	fused/partially fused	0	1	4	8	0	1	3	6					
	interrupted ossification 1st	0	0	3	0	0	0	1	0					
	medially thickened/kinked	0	0	0	1	0	0	0	1					

Note: Individual fetuses/litters may occur in more than one category.

TABLE 11.10 (cont) Fetal examinations - minor skeletal abnormality findings - group incidences

Request ID: 5375913

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
		Fetuses				Litters								
Group		1	2	3	4	1	2	3	4					
Number Examined		150	158	173	140	18	21	24	23					
Number Intact		72	73	81	67	18	21	24	23					
Minor skeletal abnormalities														
Sternebrae		partially fused	3	1	3	5	3	1	3	3				
		hemisternebra	0	0	1	2	0	0	1	1				
		bipartite ossified	0	0	0	1	0	0	0	1				
		misaligned ossification sites	2	0	0	0	2	0	0	0				
		misaligned hemicentres	1	0	5	5	1	0	5	3				
		misshapen	0	0	1	1	0	0	1	1				
Costal cartilage		fused/partially fused	0	0	0	3	0	0	0	3				
		misaligned	1	0	5	6	1	0	5	3				
		7th not connected to sternum	1	0	3	0	1	0	3	0				
Appendicular		long acromion/metacromion process	0	0	1	0	0	0	1	0				
Total affected by one or more of the above			9	6	24	16	7	5	13	7				

Note: Individual fetuses/litters may occur in more than one category.

TABLE 11.10 (cont) Fetal examinations - minor skeletal abnormality findings - group incidences

Request ID: 5375913

	Control	Sodium Trifluoroacetate			
Dose Group	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group	Fetuses				Litters			
	1	2	3	4	1	2	3	4
Number Examined	150	158	173	140	18	21	24	23
Number Intact	72	73	81	67	18	21	24	23

Rib and vertebral configuration									
Cervical rib	short supernumerary	5	0	1	1	4	0	1	1
	full supernumerary	0	0	0	1	0	0	0	1
Number of 13th ribs	short supernumerary	51	38	56	32	18	18	19	16
	full supernumerary	46	31	46	28	11	12	16	13
	total	83	61	91	56	18	19	21	18
Thoracolumbar vertebrae	18	0	0	1	2	0	0	1	2
	20	5	11	18	11	3	8	11	6
Pelvic girdle	unilateral caudal shift	5	5	7	4	4	5	6	4

Note: Individual fetuses/litters may occur in more than one category.

TABLE 11.10 (cont) Fetal examinations - minor skeletal abnormality findings - group incidences

Request ID: 5375913

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
		Fetuses				Litters								
Group		1	2	3	4	1	2	3	4					
Number Examined		150	158	173	140	18	21	24	23					
Number Intact		72	73	81	67	18	21	24	23					
Delayed/incomplete ossification/unossified														
Cranial	large posterior fontanelle	0	0	1	2	0	0	1	2					
	large lacrimal fossa	0	1	0	0	0	1	0	0					
	cranial centres	1	1	1	2	1	1	1	1					
Sternebrae	5th	17	47	55	39	12	17	17	14					
	1st to 4th, 6th	12	3	10	4	5	3	6	1					
	total	25	49	61	41	13	17	18	14					
Vertebrae	cervical (includes odontoid process)	1	1	8	8	1	1	6	6					
	thoracic	2	1	7	11	2	1	6	6					
	sacral/caudal	0	0	1	0	0	0	1	0					
Appendicular	epiphyses	1	6	22	18	1	4	10	8					
	metacarpals/phalanges	3	4	13	14	2	3	8	9					
	metatarsals/ phalanges	0	0	0	3	0	0	0	2					
Increased ossification														
Cranial	partially fused jugal to maxilla	0	0	0	2	0	0	0	1					

Note: Individual fetuses/litters may occur in more than one category.

TABLE 11.11 Fetal examinations - minor visceral abnormality and necropsy findings - group incidences

Request ID: 5375762

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
						Fetuses				Litters				
Group		1	2	3	4	1	2	3	4					
Number Examined		150	158	173	140	18	21	24	23					
Number of Heads Examined at Detailed Visceral Examination		78	85	92	73	18	21	22	22					
Head abnormalities (fixed visceral)														
Eyes	folded retina	0	1	0	3	0	1	0	3					
	haemorrhage aqueous/vitreous humour	0	0	1	2	0	0	1	2					
	haemorrhage harderian gland	0	0	1	1	0	0	1	1					
	dilated orbital sinus	0	0	0	2	0	0	0	2					
	small eye(s)	0	0	2	3	0	0	2	3					
	small lens	0	0	1	0	0	0	1	0					
Brain	subdural haemorrhage	1	0	2	0	1	0	2	0					
	dilated interventricular foramen	0	1	0	0	0	1	0	0					
Total affected by one or more of the above		1	2	6	7	1	2	6	6					
Necropsy observations (fresh visceral)														
Eye(s)	small	0	1	4	2	0	1	4	2					
Lungs	absent accessory lobe	0	0	6	0	0	0	2	0					
Ovary(s)	cyst(s)	0	0	0	1	0	0	0	1					
Ureter(s)	dilated	0	0	0	1	0	0	0	1					
Total affected by one or more of the above		0	1	10	4	0	1	6	4					

Note: Individual fetuses/litters may occur in more than one category.



TABLE 11.11 (cont) Fetal examinations - minor visceral abnormality and necropsy findings - group incidences

Request ID: 5375762

	Control	Sodium Trifluoroacetate											
Dose Group	1	2	3	4									
Dose (mg/kg/day)	0	180	375	750									
					Fetuses				Litters				
Group					1	2	3	4		1	2	3	4
Number Examined					150	158	173	140		18	21	24	23
Number of Heads Examined at Detailed Visceral Examination					78	85	92	73		18	21	22	22
Necropsy observations (external)													
Limb(s)			flexure forepaw(s)		0	0	3	4		0	0	3	3
Tail			hooked tip		0	0	1	0		0	0	1	0
			shortened		0	0	1	0		0	0	1	0
Total affected by one or more of the above					0	0	5	4		0	0	5	3

Note: Individual fetuses/litters may occur in more than one category.

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## 12. APPENDICES

Regulation (EC) No 1049/2001.

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## APPENDIX 12.1 Signs associated with dosing - individual observations

Request ID: 5376650

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
3F	0056	29	Behavior Eyes	Decreased activity Pupil dilated, Right	27-28 27-28
4F	0078AB	27	Abnormal gait Breathing	Unsteady Irregular	7 7

AB - Suspected Abortion

Only animals with observations are presented

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## APPENDIX 12.2 Clinical signs - individual observations

Request ID: 5376651

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
1F	0001	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0002N	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0003	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0004	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0005	29	Normal Staining	Within normal limits Abnormal color, Yellow, Tail	1 6, 12, 18, 24, 29
	0006N	29	Normal Build (Deformity) Skin color	Within normal limits Swollen area, Perigenital Reddening, Perigenital	1, 6, 12, 18, 24 29 29
	0007	29	Normal Excreta Staining	Within normal limits Fecal pellets reduced in size Abnormal color, Brown, Tail	1, 6, 12, 18, 24 29 29

N - Not pregnant

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
1F	0008DD	27	Normal	Within normal limits	12, 18, 24
			Muscle reaction	Convulsion, 1 - 2 minutes	27
			Staining	Abnormal color, Brown, Tail	1, 6
				Abnormal color, Red, Muzzle	27
	0009	29	Normal	Within normal limits	1, 6, 12, 18, 24
			Excreta	Fecal pellets reduced in size	29
	0010	29	Staining	Abnormal color, Brown, Forelimbs	1, 6, 12, 18, 24, 29
				Abnormal color, Brown, Hindlimbs	1, 6, 12, 18, 24, 29
				Abnormal color, Brown, Tail	1, 6
	0011	29	Normal	Within normal limits	1, 6, 12, 18, 24
			Excreta	Reduced urine output	29
	0012	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0013	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29

DD - Found dead after dosing

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
1F	0014	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0015	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0016	29	Normal Excreta	Within normal limits Decreased fecal pellets	1, 6, 12, 18, 24, 29 9
	0017	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0018	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0019N	29	Normal Staining	Within normal limits Abnormal color, Brown, Tail	1, 6, 18, 24 12, 29
	0020N	29	Normal Excreta Staining	Within normal limits Decreased fecal pellets Reduced urine output Abnormal color, Yellow, Hindlimbs	1, 18, 24 3, 6, 12 3, 6, 12 29

N - Not pregnant

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
1F	0021N	29	Normal Build Conformation Coat	Within normal limits Thin Hair loss, Whole body, No obvious bald patches, however displaying nesting behavior	1, 6, 12, 24 29 18-19
			Staining	Abnormal color, Yellow, Hindlimbs	29
	0022	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0023	29	Normal Staining	Within normal limits Abnormal color, Brown, Perigenital	1, 6, 12, 18, 24 29

N - Not pregnant

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
1F	0024	29	Normal Staining	Within normal limits	1, 6
				Abnormal color, Brown, Forelimbs	29
				Abnormal color, Brown, Hindlimbs	29
				Abnormal color, Brown, Tail	29
				Abnormal color, Yellow, Hindlimbs	12, 18, 24
2F	0025	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0026	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0027N	29	Normal Build Conformation	Within normal limits	1, 6, 12, 18, 24
				Thin	29
	0028	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0029	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29

N - Not pregnant



## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
2F	0030	29	Normal Coat	Within normal limits Hair loss, Hindlimbs, right hindlimb	1, 6, 12, 18, 24 29
	0031	29	Normal Staining	Within normal limits Abnormal color, Brown, Tail	1, 6, 12, 18, 24 29
	0032	29	Normal Staining	Within normal limits Abnormal color, Brown, Dorsal surface Abnormal color, Brown, Ears Abnormal color, Brown, Head Abnormal color, Brown, Hindlimbs Abnormal color, Yellow, Forelimbs Abnormal color, Yellow, Tail	1, 6, 12 24, 29 29 29 18, 24, 29 29 18, 24, 29
	0033	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
2F	0034	29	Normal Staining	Within normal limits	12, 18, 24, 29
				Abnormal color, Brown, Forelimbs	1, 6
				Abnormal color, Brown, Hindlimbs	1, 6
				Abnormal color, Brown, Tail	1, 6
	0035U	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0036	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0037	29	Normal Staining	Within normal limits	18, 24, 29
				Abnormal color, Brown, Hindlimbs	1, 6, 12
				Abnormal color, Brown, Tail	1, 6, 12
	0038	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0039	29	Normal Staining	Within normal limits	18, 24, 29
				Abnormal color, Brown, Hindlimbs	1, 6, 12
				Abnormal color, Brown, Tail	1, 6, 12

U - Unilateral implantation

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
2F	0040	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0041	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0042N	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0043	29	Normal Staining	Within normal limits Abnormal color, Yellow, Forelimbs Abnormal color, Yellow, Hindlimbs	1, 6, 12, 18, 24 29 29
	0044N	29	Normal Staining	Within normal limits Abnormal color, Yellow, Tail	1 6, 12, 18, 24, 29
	0045	29	Normal Staining	Within normal limits Abnormal color, Yellow, Forelimbs Abnormal color, Yellow, Hindlimbs	18, 24, 29 1, 6, 12 1, 6, 12

N - Not pregnant

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
2F	0046	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0047	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0048	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
3F	0049	29	Normal Staining	Within normal limits Abnormal color, Yellow, Tail	1, 12, 18, 24, 29 6
	0050	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0051	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0052	29	Normal Behavior Coat Excreta Staining	Within normal limits Decreased activity Hair loss, Hindlimbs, left hindlimb Feces loose Abnormal color, Brown, Perigenital Abnormal color, Brown, Tail	1, 6 10, 12 28-29 10, 12 10, 12, 18, 24, 28-29 10, 12, 18, 24, 28-29

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
3F	0053	29	Normal Staining	Within normal limits	1, 6, 12, 18, 24
				Abnormal color, Brown, Forelimbs	29
				Abnormal color, Brown, Hindlimbs	29
				Abnormal color, Brown, Tail	29
	0054	29	Normal Staining	Within normal limits	1, 6, 12, 18, 24
				Abnormal color, Brown, Forelimbs	29
				Abnormal color, Brown, Hindlimbs	29
				Abnormal color, Brown, Tail	29
	0055	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0056	29	Normal Staining	Within normal limits	1, 6, 12, 18, 24
				Abnormal color, Yellow, Dorsal surface	29

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
3F	0057	29	Normal Coat	Within normal limits	1, 6, 12, 18
				Hair loss, Dorsal surface	27, 29
			Staining	Hair loss, Ventral surface	29
				Abnormal color, Red, Perigenital, small amount off staining on under tray	24
	0058	29	Normal Staining	Within normal limits	12, 18, 24, 29
				Abnormal color, Brown, Hindlimbs	1, 6
				Abnormal color, Brown, Tail	1, 6
	0059	29	Normal Excreta Staining	Within normal limits	1, 6, 12
				Feces loose	17-18, 24
				Abnormal color, Brown, Tail	17-18, 24, 29
	0060U	29	Normal Staining	Within normal limits	12, 18, 24
				Abnormal color, Brown, Tail	1, 6
				Abnormal color, Yellow, Tail	29
	0061	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29

U - Unilateral implantation

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
3F	0062	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0063	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0064	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0065	29	Staining	Abnormal color, Brown, Tail	1, 6, 12, 18, 24, 29
	0066	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0067	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0068	29	Normal Staining	Within normal limits	1
				Abnormal color, Brown, Hindlimbs	6, 12, 18, 24, 29
				Abnormal color, Brown, Tail	6, 12, 18, 24, 29
	0069	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0070	29	Staining	Abnormal color, Yellow, Hindlimbs	1, 6, 12, 18, 24, 29

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
3F	0071	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0072	29	Normal Staining	Within normal limits Abnormal color, Brown, Hindlimbs	1, 6, 12, 18, 24 29
4F	0073	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0074	29	Normal Staining	Within normal limits Abnormal color, Red, Perigenital, Not noticeable on perigenital region, but found on undertray paper, paper was changed.	1, 6, 12, 18, 24, 29 24
	0075	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0076	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0077	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29



## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
4F	0078AB	27	Normal	Within normal limits	1, 6, 12, 18
			Reason for dispatch	General poor clinical condition, aborted 1 kit	27
			Staining	Abnormal color, Brown, Hindlimbs	24, 27
				Abnormal color, Brown, Tail	24, 27
	0079	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0080	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0081	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0082	29	Normal	Within normal limits	1, 6, 12, 18, 24
			Staining	Abnormal color, Yellow, Hindlimbs	29
				Abnormal color, Yellow, Tail	29
	0083	29	Normal	Within normal limits	1, 6, 12, 18, 24
			Staining	Abnormal color, Brown, Tail	29

AB - Suspected Abortion

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
4F	0084	29	Normal Staining	Within normal limits	1, 6, 18, 24
				Abnormal color, Brown, Tail	12
				Abnormal color, Yellow, Hindlimbs	29
				Abnormal color, Yellow, Tail	29
	0085	29	Staining	Abnormal color, Brown, Hindlimbs	1, 6, 12, 18, 24, 29
				Abnormal color, Brown, Tail	1, 6, 12, 18, 24, 29
	0086	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0087	29	Staining	Abnormal color, Brown, Hindlimbs	1, 6, 12, 18, 24, 29
				Abnormal color, Brown, Tail	1, 6, 12, 18, 24, 29
	0088	29	Staining	Abnormal color, Brown, Hindlimbs	1, 6, 12, 18, 24, 29
				Abnormal color, Brown, Tail	1, 6, 12, 18, 24, 29
	0089	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29

## APPENDIX 12.2 (cont) Clinical signs - individual observations

Request ID: 5376651

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day of Death	Category	Observation	Day(s) observed
4F	0090	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0091	29	Normal Staining	Within normal limits	1, 6, 12, 18, 24
				Abnormal color, Yellow, Tail	29
	0092	29	Normal Staining	Within normal limits	1
				Abnormal color, Brown, Hindlimbs	6, 12, 18, 24, 29
				Abnormal color, Brown, Tail	6, 12, 18, 24, 29
	0093	29	Normal Excreta Staining	Within normal limits	1, 6
				Feces loose	11-12, 18
				Feces mucoid	11-12, 18
				Abnormal color, Brown, Hindlimbs	11-12, 18, 24, 29
				Abnormal color, Brown, Tail	11-12, 18, 24, 29
	0094	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0095	29	Normal	Within normal limits	1, 6, 12, 18, 24, 29
	0096U	29	Normal Staining	Within normal limits	1, 6, 12, 18, 24
				Abnormal color, Brown, Perigenital	29

## APPENDIX 12.3 Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 1	3	6	7	8	9	10	11	12	13	14	15	16	
1F	0001	4.34	4.28	4.24	4.23	4.18	4.17	4.17	4.15	4.14	4.18	4.21	4.17	4.21	
	0002N	2.76	2.93	2.91	2.84	2.80	2.84	2.82	2.86	2.79	2.82	2.83	2.82	2.80	
	0003	4.52	4.43	4.57	4.49	4.43	4.41	4.39	4.37	4.40	4.52	4.61	4.68	4.67	
	0004	3.17	3.17	3.18	3.16	3.18	3.13	3.16	3.15	3.15	3.17	3.20	3.23	3.24	
	0005	4.26	4.32	4.31	4.27	4.35	4.18	4.20	4.14	4.15	4.19	4.24	4.31	4.29	
	0006N	2.87	2.91	2.86	2.83	2.89	2.87	2.89	2.84	2.85	2.89	2.88	2.86	2.80	
	0007	3.31	3.33	3.32	3.25	3.28	3.30	3.25	3.25	3.28	3.26	3.36	3.37	3.36	
	0008DD	3.70	3.76	3.71	3.70	3.67	3.76	3.65	3.62	3.64	3.67	3.69	3.73	3.75	
	0009	3.38	3.34	3.38	3.40	3.40	3.39	3.44	3.38	3.39	3.41	3.42	3.40	3.43	
	0010	3.17	3.12	3.07	3.07	3.06	3.02	3.01	3.05	3.03	3.08	3.13	3.14	3.14	
	0011	3.75	3.68	3.74	3.74	3.75	3.75	3.71	3.72	3.78	3.86	3.92	3.92	3.91	
	0012	3.27	3.28	3.20	3.23	3.26	3.27	3.22	3.20	3.23	3.29	3.30	3.32	3.28	
	0013	3.00	3.02	3.05	3.03	3.01	3.02	3.01	3.01	3.03	3.07	3.12	3.14	3.16	
	0014	3.19	3.20	3.17	3.15	3.12	3.06	3.05	3.05	3.00	3.01	3.03	3.08	3.12	
	0015	3.54	3.60	3.51	3.46	3.45	3.45	3.51	3.44	3.43	3.42	3.42	3.49	3.53	
	0016	3.58	3.58	3.53	3.53	3.47	3.43	3.36	3.40	3.49	3.57	3.60	3.66	3.62	
	0017	3.01	2.97	3.02	2.97	2.96	2.95	2.96	2.90	2.90	2.97	3.02	3.09	3.12	
	0018	3.13	3.11	3.11	3.10	3.12	3.12	3.09	3.10	3.14	3.18	3.19	3.16	3.19	
	0019N	3.31	3.42	3.46	3.49	3.45	3.45	3.33	3.30	3.30	3.37	3.38	3.31	3.24	
	0020N	3.06	3.16	3.10	3.09	3.08	3.09	3.03	3.06	2.97	2.96	3.00	2.95	2.85	
	0021N	3.15	3.20	3.15	3.15	3.11	3.12	3.10	3.08	3.10	3.03	2.98	2.88	2.82	
	0022	4.12	4.08	4.04	4.00	3.99	4.01	3.97	3.97	3.98	4.01	4.08	4.09	4.07	
	0023	3.45	3.53	3.53	3.51	3.54	3.58	3.55	3.52	3.54	3.60	3.59	3.65	3.65	
	0024	3.42	3.43	3.37	3.35	3.33	3.36	3.33	3.36	3.24	3.41	3.51	3.52	3.46	

DD - Found dead after dosing, N - Not pregnant

## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 17	18	19	20	21	22	23	24	25	26	27	28	29	
1F	0001	4.17	4.17	4.16	4.15	4.20	4.15	4.16	4.20	4.24	4.27	4.39	4.35	4.36	
	0002N	2.74	2.68	2.64	2.59	2.57	2.57	2.58	2.58	2.58	2.58	2.55	2.60	2.56	
	0003	4.60	4.55	4.57	4.59	4.60	4.65	4.63	4.65	4.63	4.65	4.61	4.54	4.50	
	0004	3.25	3.25	3.24	3.24	3.27	3.29	3.30	3.33	3.33	3.48	3.37	3.41	3.44	
	0005	4.41	4.27	4.29	4.31	4.32	4.33	4.35	4.37	4.45	4.46	4.47	4.50	4.53	
	0006N	2.79	2.74	2.70	2.69	2.68	2.69	2.71	2.74	2.75	2.77	2.77	2.80	2.78	
	0007	3.39	3.37	3.36	3.38	3.35	3.36	3.36	3.39	3.44	3.46	3.51	3.56	3.59	
	0008DD	3.75	3.75	3.77	3.77	3.79	3.83	3.83	3.79	3.90	3.93	3.89			
	0009	3.44	3.47	3.50	3.52	3.52	3.56	3.57	3.57	3.58	3.61	3.63	3.64	3.66	
	0010	3.12	3.17	3.19	3.17	3.20	3.27	3.28	3.34	3.36	3.38	3.41	3.49	3.49	
	0011	3.86	3.85	3.87	3.91	3.91	3.93	3.95	3.93	3.94	3.99	3.90	3.90	3.87	
	0012	3.28	3.28	3.31	3.35	3.38	3.41	3.40	3.41	3.47	3.52	3.55	3.59	3.55	
	0013	3.14	3.16	3.17	3.18	3.15	3.15	3.15	3.18	3.23	3.27	3.29	3.30	3.28	
	0014	3.13	3.13	3.15	3.16	3.16	3.14	3.17	3.19	3.21	3.19	3.27	3.24	3.31	
	0015	3.54	3.54	3.56	3.65	3.57	3.56	3.60	3.61	3.64	3.69	3.72	3.78	3.78	
	0016	3.59	3.58	3.60	3.59	3.64	3.62	3.63	3.67	3.71	3.73	3.73	3.72	3.73	
	0017	3.12	3.16	3.25	3.19	3.18	3.17	3.24	3.26	3.30	3.34	3.36	3.41	3.45	
	0018	3.22	3.18	3.18	3.25	3.33	3.38	3.43	3.46	3.50	3.49	3.54	3.60	3.60	
	0019N	3.15	3.11	3.12	3.14	3.15	3.15	3.13	3.11	3.18	3.22	3.26	3.27	3.28	
	0020N	2.79	2.77	2.77	2.80	2.85	2.85	2.91	2.95	2.98	3.06	3.07	3.11	3.10	
	0021N	2.82	2.83	2.85	2.86	2.88	2.90	2.93	2.88	2.88	2.89	2.86	2.84	2.86	
	0022	4.04	4.05	4.17	4.06	4.07	4.07	4.13	4.11	4.19	4.20	4.24	4.25	4.29	
	0023	3.63	3.59	3.54	3.54	3.53	3.58	3.63	3.63	3.69	3.71	3.74	3.75	3.78	
	0024	3.46	3.47	3.44	3.42	3.42	3.40	3.39	3.40	3.45	3.44	3.50	3.55	3.54	

DD - Found dead after dosing, N - Not pregnant

## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 1	3	6	7	8	9	10	11	12	13	14	15	16	
2F	0025	3.37	3.51	3.49	3.45	3.35	3.37	3.39	3.38	3.40	3.41	3.43	3.47	3.46	
	0026	3.25	3.25	3.21	3.20	3.18	3.16	3.19	3.15	3.13	3.14	3.18	3.28	3.29	
	0027N	2.79	2.72	2.67	2.61	2.60	2.62	2.62	2.58	2.58	2.56	2.49	2.54	2.48	
	0028	3.63	3.56	3.63	3.59	3.60	3.58	3.55	3.54	3.55	3.57	3.68	3.63	3.63	
	0029	3.51	3.48	3.61	3.53	3.51	3.54	3.52	3.46	3.48	3.48	3.43	3.56	3.59	
	0030	3.50	3.73	3.67	3.61	3.56	3.63	3.60	3.57	3.61	3.67	3.70	3.71	3.71	
	0031	4.00	3.93	3.89	3.83	3.84	3.81	3.82	3.80	3.83	3.87	3.93	3.97	3.98	
	0032	4.34	4.21	4.29	4.30	4.24	4.26	4.24	4.23	4.21	4.27	4.28	4.27	4.28	
	0033	2.85	3.05	3.00	2.95	2.96	2.93	2.94	2.95	2.98	3.01	3.06	2.99	3.01	
	0034	4.17	4.25	4.26	4.19	4.15	4.13	4.14	4.12	4.15	4.14	4.14	4.17	4.15	
	0035U	3.70	3.70	3.57	3.63	3.63	3.65	3.62	3.61	3.60	3.60	3.56	3.63	3.69	
	0036	2.86	2.90	2.92	2.91	2.94	2.94	2.98	2.98	2.97	2.98	3.07	3.10	3.08	
	0037	2.94	2.91	2.96	2.91	2.93	2.93	2.95	2.95	2.94	3.00	3.03	3.03	3.05	
	0038	3.23	3.34	3.19	3.17	3.20	3.16	3.18	3.22	3.19	3.20	3.23	3.22	3.27	
	0039	3.75	3.77	3.77	3.77	3.73	3.73	3.74	3.71	3.73	3.75	3.72	3.69	3.69	
	0040	4.16	4.11	4.10	4.02	4.04	4.03	4.04	4.04	3.99	4.04	4.07	4.13	4.12	
	0041	3.69	3.68	3.78	3.75	3.75	3.75	3.76	3.79	3.79	3.84	3.90	3.90	3.86	
	0042N	2.75	2.74	2.71	2.65	2.66	2.64	2.65	2.66	2.68	2.62	2.61	2.65	2.60	
	0043	3.16	3.21	3.24	3.18	3.18	3.17	3.16	3.17	3.16	3.21	3.26	3.30	3.33	
	0044N	3.29	3.31	3.28	3.26	3.23	3.23	3.23	3.20	3.19	3.19	3.15	3.16	3.07	
	0045	3.19	3.21	3.26	3.24	3.23	3.24	3.27	3.25	3.23	3.23	3.23	3.34	3.29	
	0046	3.58	3.57	3.55	3.59	3.54	3.52	3.49	3.48	3.52	3.50	3.53	3.55	3.58	
	0047	3.32	3.36	3.39	3.37	3.32	3.35	3.32	3.40	3.38	3.39	3.33	3.42	3.40	
	0048	3.49	3.63	3.65	3.55	3.51	3.56	3.56	3.52	3.56	3.58	3.58	3.57	3.61	

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex	Animal Number	Day 17	18	19	20	21	22	23	24	25	26	27	28	29
2F	0025	3.54	3.48	3.47	3.49	3.52	3.49	3.51	3.55	3.58	3.59	3.56	3.55	3.57
	0026	3.29	3.32	3.28	3.26	3.32	3.36	3.37	3.46	3.41	3.43	3.44	3.47	3.54
	0027N	2.48	2.46	2.48	2.45	2.43	2.44	2.44	2.43	2.41	2.41	2.36	2.39	2.40
	0028	3.64	3.64	3.68	3.72	3.67	3.70	3.71	3.69	3.70	3.73	3.78	3.78	3.88
	0029	3.60	3.63	3.63	3.70	3.64	3.66	3.67	3.68	3.76	3.82	3.86	3.86	3.95
	0030	3.71	3.72	3.74	3.75	3.74	3.76	3.78	3.78	3.77	3.86	3.86	3.87	3.85
	0031	3.99	4.03	4.04	4.02	4.06	4.04	4.05	4.09	4.11	4.11	4.10	4.13	4.17
	0032	4.25	4.22	4.22	4.20	4.17	4.18	4.02	4.21	4.26	4.28	4.29	4.29	4.31
	0033	3.03	3.05	3.04	3.08	3.10	3.10	3.16	3.14	3.23	3.22	3.27	3.29	3.33
	0034	4.20	4.24	4.23	4.24	4.21	4.26	4.26	4.31	4.35	4.40	4.46	4.47	4.31
	0035U	3.71	3.74	3.73	3.71	3.75	3.88	3.77	3.78	3.83	3.84	3.87	3.87	3.90
	0036	3.18	3.19	3.18	3.24	3.23	3.27	3.27	3.29	3.31	3.34	3.37	3.41	3.40
	0037	3.05	3.06	3.07	3.09	3.12	3.13	3.11	3.21	3.18	3.22	3.25	3.26	3.32
	0038	3.29	3.29	3.32	3.29	3.30	3.31	3.34	3.36	3.51	3.43	3.46	3.45	3.53
	0039	3.70	3.71	3.72	3.72	3.78	3.79	3.79	3.83	3.81	3.86	3.83	3.88	3.92
	0040	4.15	4.15	4.15	4.16	4.20	4.16	4.17	4.21	4.20	4.24	4.26	4.34	4.30
	0041	3.88	3.83	3.79	3.84	3.84	3.87	3.96	3.97	3.97	4.01	4.06	4.09	4.17
	0042N	2.60	2.58	2.56	2.58	2.51	2.59	2.62	2.62	2.65	2.57	2.54	2.54	2.55
	0043	3.28	3.26	3.29	3.34	3.39	3.38	3.43	3.48	3.53	3.55	3.57	3.65	3.66
	0044N	2.97	2.95	2.87	2.89	2.93	2.98	2.97	3.06	3.01	2.98	3.07	3.01	2.99
	0045	3.34	3.38	3.32	3.29	3.30	3.31	3.34	3.38	3.43	3.45	3.50	3.51	3.55
	0046	3.57	3.60	3.50	3.60	3.72	3.65	3.66	3.68	3.70	3.75	3.75	3.78	3.83
	0047	3.38	3.37	3.35	3.39	3.42	3.46	3.48	3.52	3.50	3.56	3.59	3.61	3.64
	0048	3.59	3.63	3.62	3.64	3.63	3.64	3.68	3.69	3.72	3.83	3.83	3.80	3.81

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 1	3	6	7	8	9	10	11	12	13	14	15	16	
3F	0049	3.38	3.44	3.38	3.34	3.35	3.37	3.38	3.37	3.37	3.43	3.46	3.47	3.43	
	0050	3.24	3.31	3.26	3.21	3.23	3.26	3.27	3.29	3.27	3.27	3.28	3.29	3.32	
	0051	3.42	3.44	3.36	3.39	3.39	3.42	3.43	3.44	3.44	3.44	3.48	3.52	3.52	
	0052	3.27	3.39	3.35	3.27	3.28	3.27	3.21	3.24	3.22	3.30	3.37	3.40	3.38	
	0053	3.48	3.53	3.59	3.49	3.47	3.57	3.51	3.52	3.55	3.59	3.66	3.67	3.66	
	0054	3.17	3.23	3.10	3.04	3.15	3.15	3.17	3.18	3.14	3.13	3.16	3.18	3.21	
	0055	2.85	3.02	2.91	2.84	2.86	2.88	2.83	2.85	2.84	2.88	2.95	2.98	2.92	
	0056	4.10	4.05	3.99	4.01	3.92	3.88	3.85	3.89	3.85	3.88	3.96	4.00	3.91	
	0057	3.31	3.45	3.37	3.34	3.32	3.31	3.34	3.30	3.29	3.31	3.37	3.43	3.42	
	0058	3.46	3.39	3.42	3.36	3.35	3.37	3.30	3.36	3.35	3.36	3.35	3.34	3.33	
	0059	3.41	3.32	3.33	3.30	3.32	3.34	3.35	3.32	3.31	3.31	3.32	3.36	3.37	
	0060U	3.04	3.09	3.06	3.02	3.00	3.03	3.01	3.03	3.02	3.01	3.03	3.03	3.00	
	0061	4.33	4.26	4.17	4.10	4.14	4.10	4.14	4.15	4.12	4.15	4.16	4.13	4.14	
	0062	2.81	2.83	2.79	2.73	2.79	2.81	2.87	2.90	2.95	2.95	2.95	2.96	3.05	
	0063	2.86	2.91	2.85	2.77	2.76	2.82	2.78	2.76	2.78	2.81	2.85	2.91	2.94	
	0064	3.39	3.27	3.34	3.25	3.23	3.23	3.28	3.26	3.32	3.36	3.41	3.42	3.46	
	0065	3.51	3.45	3.35	3.40	3.42	3.41	3.43	3.42	3.39	3.39	3.45	3.53	3.54	
	0066	4.11	3.85	3.84	3.78	3.73	3.72	3.65	3.62	3.62	3.62	3.68	3.68	3.78	
	0067	3.44	3.47	3.55	3.53	3.52	3.56	3.56	3.53	3.50	3.51	3.54	3.57	3.61	
	0068	3.45	3.58	3.59	3.56	3.51	3.47	3.43	3.41	3.44	3.51	3.56	3.57	3.59	
	0069	3.23	3.34	3.33	3.33	3.34	3.36	3.36	3.34	3.38	3.37	3.39	3.43	3.43	
	0070	3.93	3.92	3.81	3.80	3.78	3.80	3.80	3.81	3.85	3.88	3.95	3.96	3.86	
	0071	4.09	4.17	4.21	4.15	4.10	4.10	4.04	3.97	3.97	4.01	3.93	3.98	4.05	
	0072	3.24	3.30	3.31	3.23	3.22	3.24	3.24	3.21	3.23	3.26	3.25	3.26	3.27	

U - Unilateral implantation



## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex	Animal Number	Day 17	18	19	20	21	22	23	24	25	26	27	28	29
3F	0049	3.43	3.44	3.43	3.44	3.41	3.46	3.50	3.49	3.51	3.53	3.50	3.56	3.65
	0050	3.32	3.36	3.36	3.42	3.44	3.47	3.50	3.52	3.55	3.56	3.59	3.65	3.67
	0051	3.52	3.54	3.55	3.53	3.56	3.56	3.57	3.61	3.59	3.62	3.68	3.67	3.69
	0052	3.40	3.37	3.39	3.38	3.42	3.38	3.42	3.41	3.45	3.46	3.51	3.51	3.53
	0053	3.61	3.58	3.56	3.57	3.58	3.64	3.70	3.71	3.72	3.75	3.79	3.80	3.83
	0054	3.28	3.30	3.25	3.29	3.22	3.30	3.28	3.32	3.33	3.42	3.42	3.45	3.46
	0055	3.05	3.09	3.13	3.12	3.09	3.11	3.15	3.12	3.15	3.13	3.19	3.27	3.32
	0056	4.07	4.07	4.08	4.05	4.10	4.10	4.11	4.16	4.22	4.20	4.27	4.31	4.37
	0057	3.45	3.48	3.49	3.51	3.54	3.53	3.56	3.58	3.64	3.68	3.70	3.72	3.77
	0058	3.32	3.32	3.34	3.38	3.37	3.37	3.39	3.42	3.46	3.46	3.50	3.49	3.58
	0059	3.30	3.34	3.48	3.35	3.33	3.33	3.43	3.42	3.48	3.50	3.59	3.60	3.65
	0060U	3.03	3.04	3.03	3.02	3.01	3.03	3.03	3.04	3.05	3.05	3.10	3.12	3.13
	0061	4.11	4.11	4.11	4.15	4.27	4.21	4.18	4.23	4.21	4.24	4.28	4.27	4.33
	0062	2.98	3.04	3.15	3.10	3.16	3.18	3.19	3.21	3.30	3.27	3.33	3.33	3.38
	0063	2.91	2.89	2.88	2.90	2.90	2.96	2.93	2.94	2.94	2.94	3.01	2.99	3.06
	0064	3.46	3.52	3.55	3.57	3.57	3.61	3.67	3.65	3.67	3.72	3.72	3.80	3.83
	0065	3.54	3.55	3.60	3.57	3.60	3.61	3.64	3.65	3.67	3.71	3.76	3.77	3.81
	0066	3.75	3.75	3.74	3.86	3.75	3.76	3.78	3.79	3.79	3.80	3.81	3.93	3.85
	0067	3.65	3.67	3.73	3.82	3.71	3.72	3.74	3.76	3.78	3.81	3.82	3.85	3.92
	0068	3.64	3.59	3.62	3.60	3.56	3.60	3.56	3.57	3.61	3.64	3.65	3.67	3.71
	0069	3.47	3.44	3.47	3.48	3.55	3.54	3.58	3.72	3.63	3.65	3.66	3.64	3.68
	0070	3.87	3.89	3.93	3.93	3.93	3.97	4.01	4.03	4.06	4.06	4.17	4.11	4.16
	0071	4.00	4.01	4.00	4.00	4.00	4.00	4.02	4.11	4.04	4.06	4.03	4.05	4.06
	0072	3.27	3.31	3.35	3.36	3.32	3.36	3.41	3.43	3.43	3.48	3.47	3.48	3.52

U - Unilateral implantation

## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 1	3	6	7	8	9	10	11	12	13	14	15	16	
4F	0073	3.35	3.41	3.38	3.38	3.39	3.43	3.43	3.44	3.43	3.46	3.52	3.56	3.53	
	0074	2.82	2.79	2.87	2.84	2.85	2.82	2.87	2.88	2.88	2.93	2.97	3.00	3.10	
	0075	2.89	2.73	2.78	2.79	2.81	2.79	2.76	2.78	2.80	2.84	2.87	2.88	2.89	
	0076	3.63	3.76	3.69	3.63	3.58	3.58	3.57	3.58	3.58	3.63	3.63	3.62	3.60	
	0077	2.89	2.88	2.89	2.88	2.92	2.91	2.95	2.95	2.98	2.99	3.05	3.05	3.10	
	0078AB	3.21	3.30	3.40	3.28	3.28	3.28	3.31	3.31	3.31	3.33	3.32	3.31	3.31	
	0079	2.93	2.96	2.92	2.82	2.89	2.87	2.89	2.89	2.89	2.85	2.97	2.99	2.99	
	0080	2.47	2.42	2.39	2.41	2.39	2.44	2.43	2.46	2.45	2.50	2.55	2.61	2.63	
	0081	3.52	3.39	3.40	3.38	3.33	3.31	3.32	3.28	3.26	3.28	3.32	3.32	3.33	
	0082	3.52	3.28	3.25	3.24	3.32	3.27	3.27	3.28	3.23	3.25	3.29	3.33	3.32	
	0083	3.17	3.09	2.97	3.01	3.10	3.03	3.02	3.06	3.05	3.06	3.14	3.14	3.20	
	0084	3.75	3.79	3.92	3.86	3.87	3.77	3.86	3.85	3.86	3.86	3.95	3.94	3.99	
	0085	4.16	4.13	4.11	4.02	4.02	4.01	4.02	4.01	4.06	4.02	4.07	4.12	4.14	
	0086	4.00	3.88	3.85	3.78	3.80	3.74	3.81	3.80	3.74	3.72	3.73	3.77	3.65	
	0087	3.61	3.58	3.52	3.49	3.48	3.53	3.53	3.53	3.52	3.54	3.52	3.54	3.54	
	0088	3.31	3.46	3.53	3.47	3.45	3.43	3.46	3.43	3.43	3.44	3.39	3.48	3.50	
	0089	3.92	3.89	3.91	3.90	3.85	3.82	3.86	3.81	3.80	3.79	3.77	3.80	3.86	
	0090	2.73	2.74	2.75	2.73	2.77	2.80	2.85	2.86	2.84	2.81	2.91	2.96	3.02	
	0091	3.37	3.32	3.39	3.36	3.37	3.36	3.36	3.40	3.40	3.37	3.41	3.43	3.48	
	0092	4.44	4.46	4.49	4.49	4.45	4.41	4.42	4.34	4.36	4.34	4.35	4.36	4.39	
	0093	3.03	3.13	3.11	3.11	3.11	2.97	3.01	3.07	3.10	3.15	3.19	3.26	3.19	
	0094	3.68	3.73	3.66	3.60	3.60	3.57	3.58	3.58	3.61	3.63	3.67	3.61	3.65	
	0095	3.34	3.36	3.33	3.28	3.31	3.30	3.32	3.33	3.33	3.35	3.40	3.42	3.47	
	0096U	2.70	2.82	2.89	2.82	2.86	2.84	2.82	2.84	2.81	2.85	2.88	2.83	2.88	

AB - Suspected Abortion, U - Unilateral implantation

## APPENDIX 12.3 (cont) Body weight - individual values (kg) after mating

Request ID: 5377601

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 17	18	19	20	21	22	23	24	25	26	27	28	29	
4F	0073	3.57	3.52	3.49	3.54	3.55	3.54	3.58	3.59	3.66	3.63	3.68	3.68	3.70	
	0074	3.04	3.04	3.04	3.02	3.10	3.10	3.12	3.12	3.12	3.18	3.14	3.19	3.26	
	0075	2.89	2.89	2.86	2.88	2.94	2.97	3.01	3.01	3.06	3.10	3.12	3.15	3.19	
	0076	3.61	3.61	3.64	3.69	3.68	3.69	3.75	3.75	3.77	3.81	3.78	3.84	3.87	
	0077	3.09	3.11	3.08	3.08	3.09	3.09	3.14	3.11	3.10	3.16	3.18	3.20	3.22	
	0078AB	3.28	3.15	3.14	3.21	3.18	3.22	3.25	3.38	3.34	3.19				
	0079	2.99	3.01	2.99	3.01	3.08	3.06	3.08	3.08	3.14	3.23	3.14	3.13	3.20	
	0080	2.62	2.61	2.62	2.63	2.64	2.69	2.72	2.74	2.77	2.80	2.80	2.85	2.96	
	0081	3.32	3.35	3.37	3.37	3.39	3.39	3.35	3.36	3.39	3.40	3.41	3.37	3.43	
	0082	3.31	3.30	3.30	3.30	3.29	3.31	3.30	3.24	3.31	3.29	3.39	3.39	3.44	
	0083	2.55E	3.21	3.23	3.22	3.22	3.24	3.27	3.31	3.37	3.35	3.39	3.44	3.47	
	0084	3.98	4.04	4.04	4.02	4.02	4.03	4.06	4.06	4.08	4.14	4.10	4.13	4.14	
	0085	4.22	4.30	4.27	4.29	4.22	4.24	4.26	4.32	4.28	4.04	4.33	4.29	4.33	
	0086	3.76	3.77	3.79	3.77	3.77	3.74	3.76	3.74	3.84	3.77	3.81	3.84	3.89	
	0087	3.52	3.56	3.60	3.56	3.56	3.58	3.58	3.61	3.59	3.66	3.60	3.62	3.66	
	0088	3.52	3.46	3.53	3.55	3.55	3.58	3.59	3.65	3.67	3.72	3.79	3.73	3.75	
	0089	3.90	3.91	3.94	3.93	3.82	3.86	3.85	3.88	3.87	3.93	3.95	4.01	3.99	
	0090	3.03	3.04	3.06	3.05	3.07	3.00	3.16	3.16	3.19	3.23	3.19	3.21	3.22	
	0091	3.51	3.48	3.48	3.48	3.48	3.55	3.57	3.56	3.62	3.64	3.64	3.71	3.70	
	0092	4.44	4.43	4.44	4.43	4.44	4.38	4.36	4.39	4.40	4.40	4.51	4.44	4.44	
	0093	3.22	3.21	3.23	3.25	3.25	3.22	3.26	3.27	3.27	3.26	3.27	3.37	3.40	
	0094	3.67	3.68	3.68	3.68	3.73	3.72	3.66	3.69	3.67	3.66	3.70	3.72	3.77	
	0095	3.46	3.44	3.41	3.41	3.41	3.45	3.48	3.46	3.47	3.51	3.60	3.59	3.50	
	0096U	2.91	2.92	2.93	2.90	2.95	3.00	2.95	2.97	2.99	3.01	3.08	3.02	3.03	

AB - Suspected Abortion, U - Unilateral implantation, E - Excluded

## APPENDIX 12.4 Gravid uterine weight, adjusted body weight and adjusted body weight change - individual values (kg)

Request ID: 5376653

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		
Group /Sex	Animal Number	Body weight Day 6	Terminal body weight Day 29	Body weight change 6-29	Gravid uterine weight	Adjusted body weight Day 29	Adjusted body weight change 6-29
1F	0001	4.24	4.35	0.11	0.568	3.78	-0.46
	0002N	2.91	2.56	-0.35			
	0003	4.57	4.50	-0.07	0.563	3.93	-0.63
	0004	3.18	3.44	0.26	0.308	3.13	-0.05
	0005	4.31	4.53	0.21	0.534	3.99	-0.32
	0006N	2.86	2.78	-0.09			
	0007	3.32	3.59	0.27	0.566	3.03	-0.29
	0008DD	3.71					
	0009	3.38	3.66	0.28	0.626	3.04	-0.34
	0010	3.07	3.49	0.42	0.585	2.90	-0.16
	0011	3.74	3.87	0.13	0.571	3.30	-0.44
	0012	3.20	3.55	0.36	0.474	3.08	-0.12
	0013	3.05	3.28	0.23	0.265	3.01	-0.04
	0014	3.17	3.32	0.14	0.268	3.05	-0.12
	0015	3.51	3.78	0.27	0.425	3.35	-0.16
	0016	3.53	3.73	0.20	0.533	3.20	-0.33
	0017	3.02	3.45	0.43	0.564	2.88	-0.13
	0018	3.11	3.60	0.49	0.556	3.05	-0.07
	0019N	3.46	3.27	-0.19			
	0020N	3.10	3.11	0.02			
	0021N	3.15	2.83	-0.31			
	0022	4.04	4.29	0.25	0.532	3.76	-0.28
	0023	3.53	3.78	0.25	0.573	3.21	-0.32
	0024	3.37	3.57	0.19	0.454	3.11	-0.26

DD - Found dead after dosing, N - Not pregnant

## APPENDIX 12.4 (cont) Gravid uterine weight, adjusted body weight and adjusted body weight change - individual values (kg)

Request ID: 5376653

		Control	Sodium Trifluoroacetate					
Dose Group		1	2	3	4			
Dose (mg/kg/day)		0	180	375	750			
Group /Sex	Animal Number	Body weight Day 6	Terminal body weight Day 29	Body weight change 6-29	Gravid uterine weight	Adjusted body weight Day 29	Adjusted body weight change 6-29	
2F	0025	3.49	3.57	0.08	0.361	3.20	-0.28	
	0026	3.21	3.54	0.32	0.385	3.15	-0.06	
	0027N	2.67	2.40	-0.27				
	0028	3.63	3.88	0.25	0.477	3.40	-0.22	
	0029	3.61	3.95	0.34	0.592	3.36	-0.26	
	0030	3.67	3.85	0.18	0.552	3.30	-0.37	
	0031	3.89	4.17	0.28	0.533	3.63	-0.25	
	0032	4.29	4.31	0.02	0.419	3.89	-0.40	
	0033	3.00	3.36	0.36	0.444	2.91	-0.08	
	0034	4.26	4.30	0.04	0.565	3.74	-0.53	
	0035U	3.57	3.90	0.33	0.323	3.58	0.01	
	0036	2.92	3.41	0.49	0.387	3.02	0.10	
	0037	2.96	3.32	0.37	0.401	2.92	-0.04	
	0038	3.19	3.53	0.33	0.339	3.19	-0.01	
	0039	3.77	3.92	0.15	0.612	3.31	-0.46	
	0040	4.10	4.30	0.20	0.422	3.88	-0.22	
	0041	3.78	4.17	0.39	0.524	3.64	-0.14	
	0042N	2.71	2.55	-0.16				
	0043	3.24	3.65	0.41	0.433	3.22	-0.02	
	0044N	3.28	2.99	-0.29				
	0045	3.26	3.56	0.30	0.526	3.03	-0.23	
	0046	3.55	3.83	0.28	0.477	3.35	-0.20	
	0047	3.39	3.64	0.25	0.464	3.17	-0.22	
	0048	3.65	3.81	0.16	0.444	3.36	-0.28	

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.4 (cont) Gravid uterine weight, adjusted body weight and adjusted body weight change - individual values (kg)

Request ID: 5376653

Dose Group	Control	Sodium Trifluoroacetate					
	1	2	3	4			
Dose (mg/kg/day)	0	180	375	750			
Group /Sex	Animal Number	Body weight Day 6	Terminal body weight Day 29	Body weight change 6-29	Gravid uterine weight	Adjusted body weight Day 29	Adjusted body weight change 6-29
3F	0049	3.38	3.65	0.27	0.402	3.25	-0.13
	0050	3.26	3.67	0.41	0.428	3.24	-0.02
	0051	3.36	3.69	0.33	0.405	3.29	-0.07
	0052	3.35	3.53	0.18	0.352	3.18	-0.17
	0053	3.59	3.85	0.26	0.502	3.35	-0.25
	0054	3.10	3.46	0.36	0.330	3.13	0.03
	0055	2.91	3.31	0.40	0.478	2.83	-0.08
	0056	3.99	4.36	0.38	0.498	3.87	-0.12
	0057	3.37	3.76	0.39	0.556	3.20	-0.16
	0058	3.42	3.57	0.15	0.379	3.19	-0.23
	0059	3.33	3.65	0.32	0.496	3.15	-0.17
	0060U	3.06	3.13	0.07	0.109	3.02	-0.04
	0061	4.17	4.36	0.20	0.509	3.85	-0.31
	0062	2.79	3.38	0.59	0.461	2.92	0.13
	0063	2.85	3.06	0.21	0.180	2.88	0.03
	0064	3.34	3.83	0.49	0.523	3.31	-0.03
	0065	3.35	3.74	0.39	0.447	3.29	-0.06
	0066	3.84	3.85	0.01	0.366	3.48	-0.36
	0067	3.55	3.90	0.36	0.491	3.41	-0.13
	0068	3.59	3.68	0.09	0.331	3.35	-0.24
	0069	3.33	3.68	0.35	0.472	3.20	-0.12
	0070	3.81	4.16	0.35	0.526	3.63	-0.17
	0071	4.21	4.06	-0.14	0.132	3.93	-0.28
	0072	3.31	3.52	0.22	0.405	3.12	-0.19

U - Unilateral implantation

## APPENDIX 12.4 (cont) Gravid uterine weight, adjusted body weight and adjusted body weight change - individual values (kg)

Request ID: 5376653

		Control	Sodium Trifluoroacetate					
Dose Group		1	2	3	4			
Dose (mg/kg/day)		0	180	375	750			
Group /Sex	Animal Number	Body weight Day 6	Terminal body weight Day 29	Body weight change 6-29	Gravid uterine weight	Adjusted body weight Day 29	Adjusted body weight change 6-29	
4F	0073	3.38	3.70	0.32	0.263	3.44	0.06	
	0074	2.87	3.30	0.44	0.273	3.03	0.16	
	0075	2.78	3.19	0.40	0.356	2.83	0.05	
	0076	3.69	3.87	0.18	0.315	3.55	-0.14	
	0077	2.89	3.22	0.32	0.370	2.85	-0.05	
	0078AB	3.40						
	0079	2.92	3.20	0.28	0.258	2.94	0.02	
	0080	2.39	2.90	0.51	0.424	2.48	0.08	
	0081	3.40	3.44	0.04	0.148	3.29	-0.11	
	0082	3.25	3.44	0.19	0.188	3.25	0.01	
	0083	2.97	3.48	0.51	0.406	3.07	0.10	
	0084	3.92	4.14	0.22	0.631	3.51	-0.41	
	0085	4.11	4.33	0.23	0.605	3.73	-0.38	
	0086	3.85	3.89	0.04	0.430	3.46	-0.39	
	0087	3.52	3.66	0.15	0.339	3.32	-0.19	
	0088	3.53	3.75	0.23	0.394	3.36	-0.17	
	0089	3.91	3.99	0.09	0.476	3.51	-0.39	
	0090	2.75	3.22	0.46	0.249	2.97	0.21	
	0091	3.39	3.70	0.31	0.486	3.21	-0.18	
	0092	4.49	4.43	-0.06	0.490	3.94	-0.55	
	0093	3.11	3.40	0.29	0.245	3.16	0.05	
	0094	3.66	3.77	0.11	0.270	3.50	-0.17	
	0095	3.33	3.51	0.18	0.382	3.13	-0.21	
	0096U	2.89	3.03	0.14	0.094	2.93	0.05	

AB - Suspected Abortion, U - Unilateral implantation

## APPENDIX 12.5 Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex	Animal Number	Day 2	3	4	5	6	7	8	9	10	11	12	13	14
1F	0001	117	151	109	145	132	113	104	105	86	59	82	73	90
	0002N	115	105	78	90	62	66	84	62	52	75	84	113	96
	0003	87	125	133	166	120	121	133	103	86	105	157	166	171
	0004	99	109	123	122	112	88	85	106	108	103	130	120	123
	0005	148	148	133	160	124	109	69	84	51	98	127	132	153
	0006N	112	105	80	54	63	87	82	85	113	123	114	111	89
	0007	108	108	135	104	119	102	98	89	71	106	96	77	72
	0008DD	65	91	131	124	114	94	72	77	90	126	124	131	119
	0009	93	114	162	141	159	139	132	129	118	130	129	104	78
	0010	79	77	102	104	117	98	71	65	77	95	107	103	99
	0011	132	133	177	166	160	140	118	101	126	141	147	149	139
	0012	94	69	77	92	136	133	132	114	105	98	123	92	58
	0013	73	146	118	117	107	95	97	96	117	118	126	102	128
	0014	71	115	104	106	98	90	62	64	67	67	80	74	98
	0015	70	114	94	102	67	69	88	69	57	81	86	79	109
	0016	120	177	131	114	79	57	9	52	67	122	113	111	146
	0017	109	159	118	120	79	112	99	70	55	30	96	132	142
	0018	82	104	104	96	89	88	94	65	83	103	99	98	96
	0019N	73	89	145	128	121	104	71	1	41	85	112	123	95
	0020N	5	71	133	138	117	147	111	122	71	90	101	96	103
	0021N	91	116	122	99	101	95	87	78	79	91	71	43	17
	0022	148	150	167	135	121	106	85	76	111	121	112	138	123
	0023	143	162	159	121	144	132	136	117	87	102	90	114	107
	0024	138	160	153	103	106	95	96	84	96	62	95	111	122

DD - Found dead after dosing, N - Not pregnant



## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 15	16	17	18	19	20	21	22	23	24	25	26	27	
1F	0001	98	93	101	91	99	98	84	85	93	102	85	101	107	
	0002N	75	34	31	22	14	35	58	51	57	53	62	57	68	
	0003	147	82	109	134	142	131	137	82	75	58	56	11	17	
	0004	119	115	112	100	101	92	104	102	108	102	103	88	110	
	0005	135	139	101	105	132	120	135	122	123	137	128	111	101	
	0006N	64	56	21	31	30	44	60	62	67	57	81	59	77	
	0007	83	77	66	74	87	77	72	80	85	80	102	85	104	
	0008DD	131	125	119	120	101	114	108	103	117	103	88	55		
	0009	113	140	137	123	131	110	110	102	80	79	76	82	61	
	0010	110	106	113	113	115	112	109	102	105	94	95	101	117	
	0011	137	134	124	148	168	150	134	101	73	68	61	57	61	
	0012	86	96	114	121	131	122	115	84	81	104	100	115	120	
	0013	114	113	127	130	131	88	101	72	116	111	133	113	92	
	0014	106	93	103	101	105	95	96	100	93	87	66	112	107	
	0015	94	89	103	106	91	89	80	98	90	95	110	125	128	
	0016	98	101	74	103	118	96	106	80	105	96	104	96	101	
	0017	152	137	127	121	119	102	99	123	100	105	101	107	118	
	0018	77	54	37	53	90	140	135	122	107	117	117	126	124	
	0019N	45	4	31	59	46	69	67	78	71	91	116	116	123	
	0020N	7	20	34	60	78	91	96	121	119	128	141	135	122	
	0021N	19	30	44	44	47	55	64	71	62	62	59	52	54	
	0022	118	126	124	130	127	111	109	115	104	119	107	107	116	
	0023	98	110	62	52	35	38	82	105	65	101	94	75	42	
	0024	97	110	100	81	89	76	69	68	66	83	68	94	98	

DD - Found dead after dosing, N - Not pregnant

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day 28
1F	0001	91
	0002N	68
	0003	9
	0004	99
	0005	92
	0006N	72
	0007	72
	0008DD	
	0009	62
	0010	89
	0011	115
	0012	101
	0013	103
	0014	80
	0015	106
	0016	99
	0017	108
	0018	118
	0019N	107
	0020N	131
	0021N	56
	0022	103
	0023	71
	0024	79

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DD - Found dead after dosing, N - Not pregnant

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex	Animal Number	Day 2	3	4	5	6	7	8	9	10	11	12	13	14
2F	0025	164	171	149	158	105	79	61	96	109	111	126	110	125
	0026	68	88	80	98	78	72	74	91	77	50	68	82	94
	0027N	39	58	75	70	53	57	63	65	69	68	79	82	56
	0028	18	127	147	180	113	109	87	84	89	87	92	101	115
	0029	55	144	156	142	107	107	107	60	63	68	80	56	114
	0030	149	184	151	170	93	107	156	130	127	107	115	97	104
	0031	125	138	122	145	110	104	94	98	88	97	118	128	123
	0032	40	146	181	152	159	123	98	86	95	79	91	71	72
	0033	168	141	139	115	86	66	55	68	89	93	81	112	97
	0034	160	183	174	170	114	78	70	62	84	103	83	79	92
	0035U	115	117	156	120	100	76	98	74	88	75	111	112	107
	0036	55	59	100	88	82	91	80	73	83	93	92	111	107
	0037	77	92	112	122	88	70	57	75	99	95	102	115	112
	0038	93	115	83	58	48	69	56	58	78	94	57	63	50
	0039	122	146	140	159	121	105	75	77	75	109	96	58	50
	0040	61	149	153	128	91	105	118	124	108	87	93	128	120
	0041	85	164	163	143	128	135	139	119	110	135	134	121	84
	0042N	87	120	110	78	47	53	32	57	79	99	75	89	74
	0043	103	110	147	118	103	82	62	69	99	93	87	61	65
	0044N	61	123	127	96	103	72	52	53	98	94	96	88	75
	0045	129	123	130	116	103	104	110	110	135	115	113	104	86
	0046	127	123	142	121	118	98	84	93	97	120	90	97	92
	0047	95	165	174	159	106	69	66	97	146	132	110	109	115
	0048	147	189	158	146	115	79	47	66	101	108	90	99	102

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 15	16	17	18	19	20	21	22	23	24	25	26	27	
2F	0025	113	128	120	127	127	98	80	117	112	88	71	63	71	
	0026	90	102	91	77	86	124	104	127	101	100	124	119	143	
	0027N	25	34	44	40	36	29	54	52	41	58	63	63	56	
	0028	104	110	118	118	117	114	112	112	117	94	119	110	123	
	0029	122	96	112	102	126	80	98	85	84	105	116	119	127	
	0030	128	122	129	140	141	171	100	92	97	94	118	100	121	
	0031	118	113	116	112	134	112	122	121	105	99	114	117	127	
	0032	85	67	27	38	69	83	90	101	81	90	91	97	92	
	0033	99	112	109	127	125	117	110	107	110	110	131	151	122	
	0034	92	110	103	112	94	85	96	94	102	98	101	107	107	
	0035U	122	125	129	138	135	130	150	121	98	123	116	135	134	
	0036	92	106	116	125	141	113	123	100	98	115	110	108	110	
	0037	106	120	117	121	114	119	89	111	122	110	122	119	116	
	0038	74	102	105	123	72	77	94	89	87	92	113	106	105	
	0039	56	82	101	133	100	108	86	85	84	84	98	95	90	
	0040	129	127	131	140	118	105	116	111	108	85	110	98	101	
	0041	87	85	84	91	121	121	116	120	125	120	133	135	122	
	0042N	69	55	61	53	50	60	51	59	52	67	53	46	51	
	0043	90	129	149	142	148	131	114	103	102	113	111	107	126	
	0044N	0	10	17	12	32	49	55	61	49	66	64	56	59	
	0045	55	84	94	98	88	83	69	105	100	119	110	95	93	
	0046	95	84	94	94	102	89	98	95	78	100	98	86	102	
	0047	98	115	146	108	134	125	107	113	112	119	123	121	136	
	0048	113	116	137	130	132	125	124	142	113	139	118	93	120	

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day 28
2F	0025	94
	0026	118
	0027N	62
	0028	128
	0029	126
	0030	103
	0031	171
	0032	80
	0033	140
	0034	67
	0035U	123
	0036	124
	0037	118
	0038	101
	0039	82
	0040	97
	0041	122
	0042N	33
	0043	124
	0044N	55
	0045	86
	0046	86
	0047	123
	0048	120

Regulation (EC) No 1049/2001

Document disclosed in repl to an applica

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex	Animal Number	Day 2	3	4	5	6	7	8	9	10	11	12	13	14
3F	0049	109	157	117	132	101	99	83	91	102	106	109	95	98
	0050	142	141	118	134	79	78	88	116	131	120	113	120	109
	0051	127	135	108	108	68	87	80	104	151	144	126	129	117
	0052	96	129	125	120	55	54	43	55	53	56	104	128	129
	0053	106	118	135	157	87	101	86	98	110	106	104	118	111
	0054	54	122	96	104	48	75	52	81	81	83	70	52	47
	0055	86	60	79	66	53	41	53	33	43	54	71	93	99
	0056	121	135	179	115	119	97	52	65	98	122	139	132	130
	0057	131	127	114	110	65	40	54	69	74	89	113	129	121
	0058	91	114	140	148	104	74	72	88	91	86	73	65	61
	0059	64	117	151	127	81	77	87	89	68	85	85	87	71
	0060U	100	100	126	100	80	61	76	55	55	56	68	72	58
	0061	43	89	124	130	103	97	102	65	76	76	74	76	55
	0062	80	90	90	94	58	45	86	80	83	114	111	108	102
	0063	112	106	97	75	27	18	10	22	27	43	71	102	96
	0064	78	131	119	106	46	50	59	63	62	94	123	109	116
	0065	81	133	58	15	85	122	95	55	63	68	84	96	131
	0066	138	195	142	137	69	56	58	29	52	20	63	94	89
	0067	126	166	191	144	145	138	113	126	41	117	125	132	127
	0068	155	177	147	145	112	96	52	51	127	70	109	109	112
	0069	120	143	117	123	97	85	87	104	97	111	107	106	107
	0070	124	161	129	75	20	47	46	57	90	79	91	59	68
	0071	180	191	170	163	127	96	66	61	28	54	21	78	113
	0072	95	126	103	95	42	43	35	51	90	87	75	54	51

U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 15	16	17	18	19	20	21	22	23	24	25	26	27	
3F	0049	92	79	102	67	77	72	77	65	73	84	89	78	109	
	0050	102	117	132	122	137	147	141	140	133	124	123	120	122	
	0051	102	121	139	134	122	130	127	120	114	99	100	98	106	
	0052	111	103	97	94	87	101	94	94	94	88	84	114	112	
	0053	89	56	80	70	70	45	84	84	76	81	95	85	100	
	0054	62	101	94	87	109	119	144	121	136	119	127	146	161	
	0055	107	99	95	100	108	82	102	89	93	103	94	123	130	
	0056	111	121	101	112	112	103	113	117	120	118	90	146	125	
	0057	139	138	132	138	147	114	107	106	97	99	115	120	109	
	0058	85	80	113	121	130	98	103	101	117	96	96	116	107	
	0059	78	53	33	64	79	106	103	108	97	117	118	120	117	
	0060U	51	54	62	89	103	85	89	91	74	84	90	79	99	
	0061	58	74	96	97	109	60	79	79	102	83	101	100	81	
	0062	101	98	144	162	117	129	109	119	120	124	146	137	134	
	0063	82	80	75	71	52	59	57	92	72	91	76	63	87	
	0064	103	102	110	120	98	100	114	120	97	144	153	137	149	
	0065	115	111	113	127	129	124	114	107	100	109	124	108	114	
	0066	105	110	102	95	90	91	87	105	94	84	74	92	141	
	0067	123	132	146	118	130	127	120	107	117	103	105	102	113	
	0068	128	131	110	113	87	52	81	81	67	74	87	75	73	
	0069	81	95	104	135	122	128	125	117	123	116	124	122	102	
	0070	73	101	127	112	118	90	107	94	98	98	87	124	121	
	0071	117	139	112	92	124	136	123	123	130	145	129	119	97	
	0072	31	48	81	107	122	90	99	101	101	102	120	118	122	

U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day 28
3F	0049	101
	0050	130
	0051	105
	0052	104
	0053	97
	0054	146
	0055	126
	0056	138
	0057	101
	0058	114
	0059	122
	0060U	100
	0061	85
	0062	130
	0063	64
	0064	131
	0065	113
	0066	98
	0067	104
	0068	68
	0069	102
	0070	124
	0071	113
	0072	113

Regulation (EC) No 1049/2001

Document disclosed in repl to an applica

U - Unilateral implantation



## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate											
Dose Group		1	2	3	4									
Dose (mg/kg/day)		0	180	375	750									
Group /Sex	Animal Number	Day 2	3	4	5	6	7	8	9	10	11	12	13	14
4F	0073	95	139	141	118	89	83	79	89	108	125	116	120	126
	0074	80	107	121	125	72	53	55	40	43	73	111	118	136
	0075	-1	139	101	115	85	74	53	53	65	67	74	84	83
	0076	108	167	154	130	82	65	65	69	75	94	105	95	90
	0077	98	111	107	116	60	71	68	69	72	78	87	111	107
	0078AB	107	134	130	139	64	68	70	73	95	94	109	85	71
	0079	85	82	97	33	58	88	80	65	59	69	80	84	103
	0080	78	66	87	92	68	64	63	82	75	70	86	76	65
	0081	132	133	151	150	109	72	75	50	20	56	89	106	101
	0082	96	106	142	131	92	62	60	37	17	25	39	41	60
	0083	96	87	95	71	63	66	74	72	57	66	67	103	94
	0084	162	174	192	174	161	149	161	140	78	95	104	116	134
	0085	87	104	131	124	59	49	45	37	57	73	82	63	60
	0086	132	155	148	122	91	76	72	74	52	70	64	63	72
	0087	88	129	76	75	62	64	78	70	58	76	57	45	34
	0088	128	163	177	158	105	84	71	69	88	104	103	88	85
	0089	110	96	178	126	98	66	52	50	47	62	49	72	51
	0090	99	113	123	93	65	52	49	64	83	114	94	58	83
	0091	67	131	130	125	87	73	58	71	93	77	63	75	55
	0092	200	196	199	186	152	129	95	88	106	95	90	75	85
	0093	89	104	121	96	70	49	15	58	66	87	103	115	106
	0094	119	118	122	66	1	15	26	41	70	82	79	55	54
	0095	118	129	140	144	105	94	82	75	108	97	93	99	68
	0096U	113	130	134	139	70	56	51	110	111	107	113	105	90

AB - Suspected Abortion, U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

		Control	Sodium Trifluoroacetate												
Dose Group		1	2	3	4										
Dose (mg/kg/day)		0	180	375	750										
Group /Sex	Animal Number	Day 15	16	17	18	19	20	21	22	23	24	25	26	27	
4F	0073	114	118	83	82	124	130	117	132	125	138	126	128	138	
	0074	114	120	135	103	106	138	123	120	110	102	93	115	131	
	0075	78	90	74	75	92	100	101	105	103	92	118	99	156	
	0076	71	82	93	86	112	114	100	109	109	101	106	99	107	
	0077	106	108	111	79	101	115	110	105	99	84	114	118	138	
	0078AB	51	96	4	31	42	60	81	66	51	51	41	23		
	0079	102	95	103	93	114	107	106	100	104	106	101	125	109	
	0080	76	71	93	106	125	117	117	119	116	109	125	133	128	
	0081	110	112	112	107	103	92	78	76	84	83	82	58	72	
	0082	80	90	70	91	83	84	82	72	78	67	82	109	69	
	0083	122	123	118	113	114	101	96	102	117	108	101	115	140	
	0084	158	160	171	165	161	143	121	123	120	93	122	89	97	
	0085	58	66	95	89	90	80	87	98	90	113	117	140	151	
	0086	64	38	29	56	58	56	50	59	70	89	91	96	98	
	0087	43	60	79	95	98	87	71	69	58	81	69	63	62	
	0088	92	84	130	136	133	126	113	119	111	90	104	103	117	
	0089	35	69	93	95	90	83	75	86	82	78	85	84	101	
	0090	96	78	124	135	122	131	127	152	133	135	139	141	135	
	0091	79	91	111	108	112	97	108	97	103	119	112	114	111	
	0092	83	89	94	75	87	57	61	66	62	59	72	75	62	
	0093	88	98	87	105	101	90	86	90	100	121	110	123	123	
	0094	56	68	73	87	84	69	72	68	57	81	80	83	82	
	0095	51	59	76	73	76	85	104	104	76	85	81	110	105	
	0096U	80	93	93	99	94	97	103	95	106	105	100	110	117	

AB - Suspected Abortion, U - Unilateral implantation

## APPENDIX 12.5 (cont) Food consumption - individual values (g/animal/day) after mating

Request ID: 5376654

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day 28
4F	0073	126
	0074	121
	0075	125
	0076	116
	0077	103
	0078AB	
	0079	108
	0080	114
	0081	93
	0082	107
	0083	124
	0084	104
	0085	152
	0086	91
	0087	89
	0088	89
	0089	90
	0090	148
	0091	117
	0092	78
	0093	127
	0094	64
	0095	88
	0096U	122

Regulation (EC) No 1049/2001

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AB - Suspected Abortion, U - Unilateral implantation

## APPENDIX 12.6 Liver weight - individual values (g) on Day 29 after mating

Request ID: 5376655

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Terminal Body weight	Liver
1F	0001	4350	115.149
	0002N	2561	48.699
	0003	4496	138.976
	0004	3436	97.245
	0005	4528	120.687
	0006N	2775	61.385
	0007	3592	101.061
	0009	3661	96.264
	0010	3489	83.379
	0011	3867	83.795
	0012	3553	99.035
	0013	3276	108.585
	0014	3317	98.653
	0015	3779	108.145
	0016	3729	104.185
	0017	3449	107.305
	0018	3602	88.275
	0019N	3273	78.362
	0020N	3112	82.981
	0021N	2834	53.353
	0022	4291	100.830
	0023	3781	103.948
	0024	3565	86.466

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N - Not pregnant

## APPENDIX 12.6 (cont) Liver weight - individual values (g) on Day 29 after mating

Request ID: 5376655

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Terminal Body weight	Liver
2F	0025	3565	121.498
	0026	3536	114.994
	0027N	2399	61.913
	0028	3878	127.936
	0029	3949	134.939
	0030	3852	120.349
	0031	4167	111.033
	0032	4310	119.647
	0033	3355	87.160
	0034	4302	117.221
	0035U	3901	114.919
	0036	3411	109.539
	0037	3321	96.615
	0038	3525	87.698
	0039	3922	105.463
	0040	4299	113.984
	0041	4167	130.895
	0042N	2550	66.729
	0043	3651	105.362
	0044N	2987	74.899
	0045	3558	93.293
	0046	3826	100.276
	0047	3636	117.497
	0048	3809	117.741

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N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.6 (cont) Liver weight - individual values (g) on Day 29 after mating

Request ID: 5376655

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Terminal Body weight	Liver
3F	0049	3647	124.753
	0050	3672	110.944
	0051	3694	141.701
	0052	3528	100.999
	0053	3848	127.224
	0054	3462	121.442
	0055	3312	116.425
	0056	4363	126.011
	0057	3759	121.222
	0058	3567	100.476
	0059	3649	112.126
	0060U	3127	103.743
	0061	4362	130.170
	0062	3381	117.980
	0063	3056	104.218
	0064	3831	107.250
	0065	3736	126.202
	0066	3850	97.807
	0067	3904	113.530
	0068	3681	106.607
	0069	3676	99.171
	0070	4158	105.039
	0071	4060	154.476
	0072	3524	105.797

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U - Unilateral implantation

## APPENDIX 12.6 (cont) Liver weight - individual values (g) on Day 29 after mating

Request ID: 5376655

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Terminal Body weight	Liver
4F	0073	3703	145.907
	0074	3300	99.897
	0075	3188	125.162
	0076	3865	136.777
	0077	3218	95.192
	0079	3196	121.055
	0080	2900	90.049
	0081	3439	107.562
	0082	3438	126.570
	0083	3475	126.460
	0084	4143	95.292
	0085	4333	112.956
	0086	3885	119.833
	0087	3663	117.539
	0088	3754	123.442
	0089	3991	109.790
	0090	3215	129.400
	0091	3700	117.787
	0092	4428	128.654
	0093	3402	106.739
	0094	3769	112.650
	0095	3507	76.879
	0096U	3027	103.366

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U - Unilateral implantation

## APPENDIX 12.7 Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0001	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0002N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0003	29 (5)	Gestation	Liver: No macropathology findings	Liver: Microvacuolation, Cytoplasmic, Hepatocellular, Generalized, slight

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0004	29 (5)	Gestation	Uterus: Serosal cyst(s), left, clear, 10-19mm, 1 (one)	Not Applicable

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0005	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0006N	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

N - Not pregnant

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0007	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0008DD	27 (4)	Gestation	Adipose Tissue: Abnormal contents, retroperitoneal, gas, right	Not Applicable
				Adipose Tissue: Abnormal contents, retroperitoneal, fluid, right, red	Not Applicable
				Lungs and Bronchi: Dark area(s), all lobes, 2-9mm, 5+ (many)	Not Applicable
					Major Factor(s) contributing to death: Accidental Death, present
				Trachea: Perforated, middle	Not Applicable

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

DD - Found dead after dosing

APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0009	29 (5)	Gestation	Liver: No macropathology findings	Liver: Microvacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0010	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0011	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0012	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0013	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0014	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0015	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized, minimal, generalized hepatocytes

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0016	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized, minimal, periportal hepatocytes

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0017	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0018	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0019N	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

N - Not pregnant

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0020N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0021N	29 (5)	Gestation	Kidneys: Cyst(s), bilateral, clear, 2-9mm, 2-5 (few)  Liver: No macropathology findings	Not Applicable  Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0022	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0023	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0024	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0025	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0026	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hyal ertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0027N	29 (5)	Gestation	Liver: No macropathology findings	Liver: H perplasia, Oval Cell, minimal, multifocal Liver: H pertrophy, Hepatocellular, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0028	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0029	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

Regulation (EC) No 1049/2001

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0030	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0031	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0032	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0033	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001



APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0034	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal, minimal Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0035U	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

U - Unilateral implantation

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0036	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0037	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0038	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0039	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0040	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0041	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0042N	29 (5)	Gestation	Liver: No macropathology findings	<p>Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal</p> <p>Liver: Hypertrophy, Hepatocellular, Generalized, minimal</p> <p>Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal</p>

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0043	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0044N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0045	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0046	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0047	29 (5)	Gestation	Kidneys: Cyst(s), bilateral, clear, 2-9mm, 2-5 (few)	Not Applicable

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0048	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal
Tissues without comments under macropathology findings were within normal limits at necropsy.					

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0049	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001



## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0050	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0051	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0052	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0053	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hyal ertrophy, Hepatocellular, Generalized, minimal

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Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0054	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0055	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0056	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0057	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001



## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0058	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0059	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0060U	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

U - Unilateral implantation

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0061	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0062	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0063	29 (5)	Gestation	Liver: Irregular Surface, all lobes	Liver: Hypertrophy/Fibrosis, Bile Ducts, moderate, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

= - correlation of macropathology to histopathology finding

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0064	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0065	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001



## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0066	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0067	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0068	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal Liver: Necrosis, Hepatocellular, Focal, minimal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0069	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0070	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0071	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0072	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0073	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal
Tissues without comments under macropathology findings were within normal limits at necropsy.					

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Regulation (EC) No 1049/2001



## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0074	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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Regulation (EC) No 1049/2001

APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0075	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0076	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001

## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0077	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0078AB	27 (4)	Gestation	Liver: No macropathology findings  Spleen: Enlarged, noted	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal  Major Factor(s) contributing to death: Suspected Abortion, present  Not Applicable

Tissues without comments under macropathology findings were within normal limits at necropsy.

AB - Suspected Abortion

APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0079	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0080	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0081	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1049/2001



APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0082	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, moderate, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0083	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0084	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0085	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal
Tissues without comments under macropathology findings were within normal limits at necropsy.					

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0086	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hyal ertrophy, Hepatocellular, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0087	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, moderate, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0088	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0089	29 (5)	Gestation	Liver: No macropathology findings	Liver: H pertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0090	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized, minimal, centrilobular hepatocytes Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0091	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0092	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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## APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0093	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Regulation (EC) No 1049/2001

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0094	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0095	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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APPENDIX 12.7 (cont) Macropathology and histopathology - individual findings

Request ID: 5389297

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0096U	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyal erplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

U - Unilateral implantation

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Regulation (EC) No 1049/2001

## APPENDIX 12.8 Litter data - individual values

Request ID: 5376657

Dose Group	Control	Sodium Trifluoroacetate		
	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group /Sex	Animal Number	Corpora lutea	Implantations	Resorptions			Implantation loss (%)		Male	Live young		Sex ratio (%M)
				Early	Late	Total	Pre-	Post-		Female	Total	
1F	0001	9	9	0	0	0	0.0	0.0	7	2	9	77.8
	0002N	-	-	-	-	-	-	-	-	-	-	-
	0003	10	10	0	0	0	0.0	0.0	6	4	10	60.0
	0004	10	6	2	0	2	40.0	33.3	2	2	4	50.0
	0005	13	11	1	0	1	15.4	9.1	6	4	10	60.0
	0006N	-	-	-	-	-	-	-	-	-	-	-
	0007	11	10	0	0	0	9.1	0.0	6	4	10	60.0
	0008DD	11	7	0	0	0	36.4	0.0	-	-	7a	-
	0009	10	10	0	0	0	0.0	0.0	5	5	10	50.0
	0010	11	10	0	0	0	9.1	0.0	4	6	10	40.0
	0011	10	10	0	0	0	0.0	0.0	7	3	10	70.0
	0012	8	8	0	1	1	0.0	12.5	3	4	7	42.9
	0013	8	7	3	0	3	12.5	42.9	1	3	4	25.0
	0014	7	4	1	0	1	42.9	25.0	1	2	3	33.3
	0015	9	7	1	0	1	22.2	14.3	4	2	6	66.7
	0016	12	11	0	0	0	8.3	0.0	4	7	11	36.4
	0017	15	12	1	1	2	20.0	16.7	7	3	10	70.0
	0018	10	10	1	0	1	0.0	10.0	5	4	9	55.6
	0019N	-	-	-	-	-	-	-	-	-	-	-
	0020N	-	-	-	-	-	-	-	-	-	-	-
	0021N	-	-	-	-	-	-	-	-	-	-	-
	0022	10	9	0	0	0	10.0	0.0	5	4	9	55.6
	0023	11	10	0	0	0	9.1	0.0	3	7	10	30.0
	0024	14	10	1	1	2	28.6	20.0	4	4	8	50.0

DD - Found dead after dosing, N - Not pregnant, a - Includes 7 unsexed fetus(es)



## APPENDIX 12.8 (cont) Litter data - individual values

Request ID: 5376657

		Control	Sodium Trifluoroacetate									
Dose Group		1	2	3	4							
Dose (mg/kg/day)		0	180	375	750							
Group /Sex	Animal Number	Corpora lutea	Implantations	Early	Resorptions Late	Total	Implantation loss (%) Pre-	Post-	Male	Live young Female	Total	Sex ratio (%M)
2F	0025	5	5	0	0	0	0.0	0.0	1	4	5	20.0
	0026	10	7	1	0	1	30.0	14.3	1	5	6	16.7
	0027N	-	-	-	-	-	-	-	-	-	-	-
	0028	11	8	1	0	1	27.3	12.5	4	3	7	57.1
	0029	11	11	0	0	0	0.0	0.0	6	5	11	54.5
	0030	11	11	0	0	0	0.0	0.0	6	5	11	54.5
	0031	11	11	0	1	1	0.0	9.1	7	3	10	70.0
	0032	14	11	4	0	4	21.4	36.4	2	5	7	28.6
	0033	7	7	0	0	0	0.0	0.0	4	3	7	57.1
	0034	12	10	0	1	1	16.7	10.0	6	3	9	66.7
	0035U	10	4	0	0	0	60.0	0.0	3	1	4	75.0
	0036	7	7	0	1	1	0.0	14.3	1	5	6	16.7
	0037	7	7	0	0	0	0.0	0.0	5	2	7	71.4
	0038	8	8	2	0	2	0.0	25.0	4	2	6	66.7
	0039	11	11	0	2	2	0.0	18.2	3	6	9	33.3
	0040	8	7	0	0	0	12.5	0.0	3	4	7	42.9
	0041	12	9	1	0	1	25.0	11.1	3	5	8	37.5
	0042N	-	-	-	-	-	-	-	-	-	-	-
	0043	6	7	0	0	0	0.0@	0.0	1	6	7	14.3
	0044N	-	-	-	-	-	-	-	-	-	-	-
	0045	10	9	0	1	1	10.0	11.1	4	4	8	50.0
	0046	11	9	1	0	1	18.2	11.1	2	6	8	25.0
	0047	11	11	3	0	3	0.0	27.3	0	8	8	0.0
	0048	9	8	1	0	1	11.1	12.5	4	3	7	57.1

@ - Number of implantations exceed number of corpora lutea; pre-implantation loss considered to be zero

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.8 (cont) Litter data - individual values

Request ID: 5376657

		Control	Sodium Trifluoroacetate									
Dose Group		1	2	3	4							
Dose (mg/kg/day)		0	180	375	750							
Group /Sex	Animal Number	Corpora lutea	Implantations	Early	Resorptions Late	Total	Implantation loss (%) Pre-	Post-	Male	Live young Female	Total	Sex ratio (%M)
3F	0049	10	9	0	1	1	10.0	11.1	4	4	8	50.0
	0050	10	9	0	0	0	10.0	0.0	4	5	9	44.4
	0051	8	7	0	0	0	12.5	0.0	5	2	7	71.4
	0052	8	8	0	0	0	0.0	0.0	4	4	8	50.0
	0053	13	11	0	0	0	15.4	0.0	6	5	11	54.5
	0054	8	6	1	0	1	25.0	16.7	4	1	5	80.0
	0055	8	8	0	1	1	0.0	12.5	4	3	7	57.1
	0056	8	8	0	0	0	0.0	0.0	3	5	8	37.5
	0057	10	8	0	0	0	20.0	0.0	2	6	8	25.0
	0058	9	8	0	3	3	11.1	37.5	2	3	5	40.0
	0059	11	9	0	0	0	18.2	0.0	7	2	9	77.8
	0060U	11	1	0	0	0	90.9	0.0	0	1	1	0.0
	0061	12	11	0	2	2	8.3	18.2	4	5	9	44.4
	0062	10	10	0	0	0	0.0	0.0	6	4	10	60.0
	0063	7	4	1	0	1	42.9	25.0	0	3	3	0.0
	0064	13	12	1	0	1	7.7	8.3	6	5	11	54.5
	0065	9	8	0	0	0	11.1	0.0	1	7	8	12.5
	0066	8	6	0	0	0	25.0	0.0	2	4	6	33.3
	0067	10	8	0	0	0	20.0	0.0	5	3	8	62.5
	0068	8	7	1	1	2	12.5	28.6	2	3	5	40.0
	0069	11	10	2	0	2	9.1	20.0	4	4	8	50.0
	0070	10	11	0	0	0	0.0@	0.0	8	3	11	72.7
	0071	9	2	1	0	1	77.8	50.0	1	0	1	100.0
	0072	10	10	2	1	3	0.0	30.0	5	2	7	71.4

@ - Number of implantations exceed number of corpora lutea; pre-implantation loss considered to be zero

U - Unilateral implantation

## APPENDIX 12.8 (cont) Litter data - individual values

Request ID: 5376657

		Control	Sodium Trifluoroacetate									
Dose Group		1	2	3	4							
Dose (mg/kg/day)		0	180	375	750							
Group /Sex	Animal Number	Corpora lutea	Implantations	Early	Resorptions Late	Total	Implantation loss (%)		Male	Live young Female	Total	Sex ratio (%M)
							Pre-	Post-				
4F	0073	9	8	3	1	4	11.1	50.0	1	3	4	25.0
	0074	6	6	1	1	2	0.0	33.3	1	3	4	25.0
	0075	7	7	0	1	1	0.0	14.3	4	2	6	66.7
	0076	9	7	1	0	1	22.2	14.3	4	2	6	66.7
	0077	7	6	0	0	0	14.3	0.0	3	3	6	50.0
	0078AB	8	2	1	0	2a	75.0	100.0	-	-	-	-
	0079	7	5	1	0	1	28.6	20.0	4	0	4	100.0
	0080	8	8	1	0	1	0.0	12.5	4	3	7	57.1
	0081	4	2	0	0	0	50.0	0.0	1	1	2	50.0
	0082	7	5	2	0	2	28.6	40.0	1	2	3	33.3
	0083	8	7	0	0	0	12.5	0.0	3	4	7	42.9
	0084	11	11	0	2	2	0.0	18.2	5	4	9	55.6
	0085	12	11	0	0	0	8.3	0.0	6	5	11	54.5
	0086	10	8	0	0	0	20.0	0.0	5	3	8	62.5
	0087	11	7	0	1	1	36.4	14.3	2	4	6	33.3
	0088	8	8	0	1b	1	0.0	12.5	6	1	7	85.7
	0089	10	9	1	0	1	10.0	11.1	1	7	8	12.5
	0090	7	7	2	1	3	0.0	42.9	2	2	4	50.0
	0091	12	12	2	0	2	0.0	16.7	4	6	10	40.0
	0092	12	11	1	0	1	8.3	9.1	3	7	10	30.0
	0093	5	5	1	0	1	0.0	20.0	2	2	4	50.0
	0094	9	6	0	0	0	33.3	0.0	3	3	6	50.0
	0095	9	8	1	0	1	11.1	12.5	2	5	7	28.6
	0096U	3	1	0	0	0	66.7	0.0	1	0	1	100.0

AB - Suspected Abortion, U - Unilateral implantation, a - Includes 1 aborted fetus(es), b - Includes 1 dead fetus(es)

## APPENDIX 12.9 Placental, litter and fetal weights - individual litter mean values (g)

Request ID: 5376658

		Control	Sodium Trifluoroacetate							
Dose Group		1	2	3	4					
Dose (mg/kg/day)		0	180	375	750					
Group /Sex	Animal Number	Placental weight Mean	SD	Total litter weight	Male fetal weight Mean	SD	Female fetal weight Mean	SD	Overall fetal weight Mean	SD
1F	0001	5.9	0.82	364.0	40.3	4.27	40.9	4.31	40.4	4.01
	0002N	-	-	-	-	-	-	-	-	-
	0003	4.8	0.72	361.2	36.9	6.02	34.9	6.50	36.1	5.94
	0004	6.2	1.11	194.5	51.4	0.85	45.9	1.77	48.6	3.40
	0005	4.0	0.50	360.4	36.4	4.15	35.5	3.34	36.0	3.68
	0006N	-	-	-	-	-	-	-	-	-
	0007	4.5	1.20	381.9	38.3	6.10	38.0	8.30	38.2	6.60
	0008DD	-	-	-	-	-	-	-	-	-
	0009	5.7	0.67	440.5	44.2	3.48	43.9	7.62	44.1	5.59
	0010	5.4	0.70	392.8	38.6	2.55	39.7	2.75	39.3	2.59
	0011	6.1	0.62	382.8	38.8	3.65	37.0	3.21	38.3	3.46
	0012	5.4	0.72	296.0	42.1	3.12	42.4	4.75	42.3	3.82
	0013	5.5	0.91	168.9	47.1	-	40.6	8.52	42.2	7.68
	0014	7.6	1.17	151.1	53.7	-	48.7	2.69	50.4	3.46
	0015	5.6	0.60	268.5	43.2	2.53	47.8	5.23	44.8	3.86
	0016	4.4	0.86	358.0	31.3	7.84	33.3	3.23	32.5	5.08
	0017	4.7	0.50	386.6	38.4	5.49	39.2	3.38	38.7	4.77
	0018	6.4	1.00	381.6	42.3	7.34	42.6	2.91	42.4	5.49
	0019N	-	-	-	-	-	-	-	-	-
	0020N	-	-	-	-	-	-	-	-	-
	0021N	-	-	-	-	-	-	-	-	-
	0022	4.8	0.53	368.7	42.8	2.99	38.7	2.43	41.0	3.35
	0023	5.0	0.50	395.5	39.7	4.59	39.5	4.78	39.6	4.47
	0024	4.5	1.01	293.1	37.8	4.46	35.5	4.47	36.6	4.30

DD - Found dead after dosing, N - Not pregnant

## APPENDIX 12.9 (cont) Placental, litter and fetal weights - individual litter mean values (g)

Request ID: 5376658

		Control	Sodium Trifluoroacetate							
Dose Group		1	2	3	4					
Dose (mg/kg/day)		0	180	375	750					
Group /Sex	Animal Number	Placental weight Mean	SD	Total litter weight	Male fetal weight Mean	SD	Female fetal weight Mean	SD	Overall fetal weight Mean	SD
2F	0025	5.9	1.02	226.0	50.9	-	43.8	3.47	45.2	4.38
	0026	4.6	0.88	235.7	30.3	-	41.1	3.39	39.3	5.35
	0027N	-	-	-	-	-	-	-	-	-
	0028	5.7	0.54	298.3	43.0	4.43	42.1	8.10	42.6	5.65
	0029	5.5	0.56	406.5	36.9	3.24	37.1	1.38	37.0	2.46
	0030	4.5	0.53	379.9	35.1	6.11	33.9	6.32	34.5	5.92
	0031	4.7	0.87	358.5	35.6	5.63	36.5	4.74	35.9	5.13
	0032	5.1	0.51	238.9	32.4	1.34	34.8	1.23	34.1	1.67
	0033	5.0	0.68	307.2	43.2	4.68	44.8	2.85	43.9	3.79
	0034	6.1	0.49	363.9	40.3	3.71	40.6	0.67	40.4	2.95
	0035U	6.7	1.00	199.6	49.6	2.98	50.7	-	49.9	2.49
	0036	5.0	0.39	254.6	40.4	-	42.8	1.50	42.4	1.67
	0037	4.8	0.51	271.3	38.3	2.69	39.9	1.13	38.8	2.37
	0038	5.2	0.54	214.2	36.1	2.43	34.9	0.64	35.7	2.02
	0039	4.5	0.77	356.6	40.9	4.64	39.0	4.22	39.6	4.17
	0040	5.3	0.65	276.7	39.7	5.80	39.4	5.95	39.5	5.38
	0041	5.5	0.68	342.9	39.3	3.49	45.0	5.57	42.9	5.48
	0042N	-	-	-	-	-	-	-	-	-
	0043	4.6	0.69	301.0	44.9	-	42.7	4.57	43.0	4.26
	0044N	-	-	-	-	-	-	-	-	-
	0045	5.3	0.93	319.3	39.2	6.30	40.6	4.06	39.9	4.96
	0046	5.1	1.11	321.8	36.4	3.32	41.5	3.79	40.2	4.19
	0047	4.8	0.61	315.0	-	-	39.4	4.42	39.4	4.42
	0048	5.1	0.50	293.2	43.0	2.40	40.4	5.78	41.9	4.00

N - Not pregnant, U - Unilateral implantation

## APPENDIX 12.9 (cont) Placental, litter and fetal weights - individual litter mean values (g)

Request ID: 5376658

Dose Group	Control	Sodium Trifluoroacetate								
	1	2	3	4						
Dose (mg/kg/day)	0	180	375	750						
Group /Sex	Animal Number	Placental weight Mean	SD	Total litter weight	Male fetal weight Mean	SD	Female fetal weight Mean	SD	Overall fetal weight Mean	SD
3F	0049	5.1	0.70	227.9	26.2	4.68	30.8	3.87	28.5	4.67
	0050	4.1	0.48	293.8	31.6	4.73	33.5	2.73	32.6	3.63
	0051	4.7	0.47	282.6	40.0	2.33	41.3	4.03	40.4	2.59
	0052	4.3	1.08	222.5	27.0	6.38	28.7	4.73	27.8	5.27
	0053	4.8	0.73	306.7	27.2	2.02	28.7	4.98	27.9	3.54
	0054	6.5	0.90	206.1	40.9	2.77	42.5	-	41.2	2.50
	0055	4.7	0.82	267.5	37.6	1.34	39.0	7.09	38.2	4.26
	0056	5.9	0.86	325.6	38.4	4.44	42.1	3.52	40.7	4.04
	0057	5.6	0.73	363.3	48.7	0.57	44.3	5.67	45.4	5.21
	0058	4.5	0.93	200.7	36.6	2.76	42.5	2.58	40.1	4.00
	0059	4.8	0.98	328.3	35.2	6.82	40.8	9.90	36.5	7.29
	0060U	7.5	-	59.2	-	-	59.2	-	59.2	-
	0061	4.4	1.06	301.5	34.6	9.35	32.7	4.17	33.5	6.52
	0062	4.3	0.94	310.8	30.8	5.89	31.5	8.67	31.1	6.67
	0063	4.7	1.10	96.8	-	-	32.3	6.47	32.3	6.47
	0064	4.4	0.73	349.5	32.5	3.30	30.9	6.25	31.8	4.67
	0065	5.1	1.02	293.8	40.8	-	36.1	6.89	36.7	6.59
	0066	6.4	0.81	234.3	39.2	1.91	39.0	6.32	39.1	4.97
	0067	5.0	0.65	327.6	41.0	4.43	40.8	3.43	41.0	3.82
	0068	4.9	0.59	191.1	35.8	5.59	39.9	0.84	38.2	3.64
	0069	5.2	1.08	315.3	38.1	7.02	40.7	3.36	39.4	5.28
	0070	4.9	0.71	344.6	32.3	2.47	28.8	2.58	31.3	2.86
	0071	7.2	-	48.6	48.6	-	-	-	48.6	-
	0072	4.8	0.64	246.2	34.4	4.14	37.0	3.68	35.2	3.90

U - Unilateral implantation

## APPENDIX 12.9 (cont) Placental, litter and fetal weights - individual litter mean values (g)

Request ID: 5376658

		Control	Sodium Trifluoroacetate							
Dose Group		1	2	3	4					
Dose (mg/kg/day)		0	180	375	750					
Group /Sex	Animal Number	Placental weight Mean	SD	Total litter weight	Male fetal weight Mean	SD	Female fetal weight Mean	SD	Overall fetal weight Mean	SD
4F	0073	5.5	0.87	145.7	37.9	-	35.9	3.15	36.4	2.75
	0074	5.1	0.82	162.2	41.5	-	40.2	2.27	40.6	1.96
	0075	4.8	0.65	230.6	40.1	1.64	35.1	6.36	38.4	4.05
	0076	5.8	0.68	170.0	26.8	5.79	31.4	3.11	28.3	5.26
	0077	5.3	0.64	253.5	43.2	2.43	41.3	6.58	42.3	4.56
	0078AB	-	-	-	-	-	-	-	-	-
	0079	5.5	0.96	164.0	41.0	1.87	-	-	41.0	1.87
	0080	4.8	0.76	283.0	38.3	5.21	43.2	0.70	40.4	4.54
	0081	5.2	0.21	81.6	40.3	-	41.3	-	40.8	0.71
	0082	4.9	0.99	100.2	26.9	-	36.7	5.73	33.4	6.93
	0083	4.5	0.28	270.6	38.2	2.90	39.0	2.85	38.7	2.66
	0084	4.8	1.23	361.5	41.1	11.22	39.1	4.74	40.2	8.51
	0085	4.7	0.77	377.5	35.4	5.45	33.1	1.43	34.3	4.13
	0086	4.1	1.04	270.0	35.9	6.03	30.2	7.11	33.8	6.61
	0087	4.7	0.33	198.2	31.2	2.47	34.0	1.76	33.0	2.28
	0088	4.3	0.63	209.5	29.0	3.50	35.5	-	29.9	4.03
	0089	6.0	0.85	320.4	45.3	-	39.3	4.20	40.1	4.43
	0090	5.3	0.66	145.7	37.1	4.45	35.8	3.68	36.4	3.41
	0091	4.0	1.15	326.2	32.2	6.86	32.9	6.95	32.6	6.53
	0092	4.4	0.60	310.1	32.1	2.19	30.5	4.60	31.0	3.96
	0093	4.5	0.31	155.3	40.4	3.18	37.3	0.85	38.8	2.59
	0094	4.9	0.36	180.7	30.4	3.69	29.9	2.80	30.1	2.94
	0095	4.6	0.48	243.0	33.9	6.22	35.0	6.02	34.7	5.56
	0096U	7.6	-	45.7	45.7	-	-	-	45.7	-

AB - Suspected Abortion, U - Unilateral implantation

## APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities

Request ID: 5375792

Dose Group	Control		Sodium Trifluoroacetate				
	1	2	3	4			
Dose (mg/kg/day)	0	180	375	750			

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0001	4vk, 5vfk	2	M	34.4	vk	13th bilateral rib full supernumerary
			3	F	37.8	vfk	13th bilateral rib full supernumerary
			4	M	44.7	vk	13th bilateral rib full supernumerary, pelvic girdle unilateral caudal shift (left sided)
			5	M	43.4	vfk	13th bilateral rib full supernumerary
			7	F	43.9	vfk	13th bilateral rib short supernumerary
			8	M	41.6	vk	13th right rib full supernumerary, 5th sternebra unossified
			9	M	44.1	vfk	13th bilateral rib full supernumerary
	0003	5vk, 5vfk	2	M	33.2	vk	Parietal left additional suture(s)
			6	M	34.6	vk	13th bilateral rib short supernumerary
			7	F	26.1	vfk	13th bilateral rib short supernumerary
			8	F	34.7	vk	5th sternebra unossified
	0004	2vk, 2vfk	1	F	44.6	vk	13th left rib short supernumerary
			2	M	52.0	vk	13th left rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy



APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0005	5vk, 5vfk	1	M	42.7	vfk	13th left rib short supernumerary, 13th right rib full supernumerary
			2	F	31.7	vk	13th bilateral rib full supernumerary, 6th sternebra unossified
			3	F	33.6	vfk	13th left rib short supernumerary, 13th right rib full supernumerary, 20 thoracolumbar vertebrae
			4	M	32.5	vk	13th bilateral rib full supernumerary
			5	M	32.6	vfk	6th sternebra unossified
			6	M	38.7	vk	13th left rib short supernumerary, 13th right rib full supernumerary
			7	F	37.9	vfk	20 thoracolumbar vertebrae, rib(s) 12th left absent, THORACIC VERTEBRA(E) 12TH LEFT HEMIVERTEBRA, thoracic vertebral hemicentrum(a) 12th right incompletely ossified
			8	M	33.7	vk	13th bilateral rib full supernumerary, metacarpal/phalange(s) incompletely ossified/unossified left forepaw
			9	M	38.4	vfk	5th sternebra unossified
			10	F	38.6	vk	13th left rib short supernumerary
	0007	5vk, 5vfk	1	M	35.1	vfk	13th left rib short supernumerary
			2	M	37.0	vk	13th right rib short supernumerary
			3	M	43.9	vfk	5th sternebra unossified
			4	M	42.8	vk	13th bilateral rib short supernumerary, 5th sternebra unossified
			6	M	28.2	vk	13th right rib short supernumerary
			8	F	35.0	vk	5th sternebra unossified
			9	F	39.4	vfk	13th left rib short supernumerary, 13th right rib full supernumerary
			10	F	48.7	vk	13th bilateral rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0009	5vk, 5vfk	2	F	47.4	vk	13th bilateral rib short supernumerary
			3	F	53.6	vfk	13th bilateral rib full supernumerary
			4	M	43.5	vk	13th left rib full supernumerary
			5	F	39.5	vfk	13th left rib full supernumerary
			6	M	44.3	vk	13th bilateral rib full supernumerary
			7	M	38.7	vfk	13th bilateral rib short supernumerary
			9	F	33.7	vfk	4th sternebra incompletely ossified, 5th sternebra unossified, sternebra centre(s) 3rd to 4th partially fused
			10	F	45.5	vk	13th bilateral rib full supernumerary, 5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		
Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0010	5vk, 5vfk	1	M	40.4	vfk	13th bilateral rib full supernumerary
			2	F	35.5	vk	13th bilateral rib short supernumerary
			3	M	40.4	vfk	13th left rib short supernumerary
			4	F	38.5	vk	13th bilateral rib full supernumerary
			5	M	38.6	vfk	13th left rib full supernumerary, 13th right rib short supernumerary, 5th sternebra unossified, pelvic girdle (left sided) unilateral caudal shift
			6	F	40.5	vk	13th bilateral rib full supernumerary
			7	F	40.4	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			8	F	39.6	vk	13th bilateral rib full supernumerary
			9	F	43.9	vfk	13th bilateral rib full supernumerary
			10	M	35.0	vk	13th bilateral rib full supernumerary, costal cartilage(s) 2nd bilateral to 3rd misaligned, sternebral centre(s) 2nd misaligned hemicentres, sternebral centre(s) 3rd to 4th misaligned ossification sites, pelvic girdle (left sided) unilateral caudal shift
	0011	5vk, 5vfk	2	F	35.4	vk	13th bilateral rib short supernumerary, cervical rib short supernumerary left
			6	M	43.3	vk	5th sternebra unossified, cervical rib short supernumerary left
			10	M	41.0	vk	13th left rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0012	3vk, 4vfk	1	M	38.5	vfk	13th bilateral rib full supernumerary, thoracic vertebral centrum(a) 7th incompletely ossified
			2	F	42.0	vk	13th left rib short supernumerary, cervical rib short supernumerary bilateral
			5	F	46.5	vfk	13th left rib short supernumerary, 13th right rib full supernumerary
	0013	2vk, 2vfk	3	F	46.9	vfk	13th left rib short supernumerary
			4	F	30.9	vk	<i>VENTRICULAR SEPTUM MUSCULAR DEFECT, ASCENDING AORTA/PULMONARY TRUNK TRANSPOSITION</i> , sternebral centre(s) 1st to 5th partially fused, cervical vertebral arch(es) 1st left small, ventral arch incompletely ossified
	0014	1vk, 2vfk	2	M	53.7	vk	13th left rib short supernumerary
			3	F	50.6	vfk	6th sternebra unossified
	0015	3vk, 3vfk	1	M	42.3	vfk	13th left rib short supernumerary
			2	M	46.5	vk	13th bilateral rib short supernumerary
			3	M	43.6	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			4	F	44.1	vk	5th sternebra unossified, cervical rib short supernumerary bilateral
			5	F	51.5	vfk	<i>Cerebellum subdural haemorrhage</i> , 13th bilateral rib full supernumerary, pelvic girdle (right sided) unilateral caudal shift

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0016	5vk, 6vfk	1	F	34.2	vfk	13th bilateral rib short supernumerary
			2	M	39.3	vk	13th left rib full supernumerary
			3	F	39.4	vfk	13th bilateral rib short supernumerary, 6th sternebra unossified
			4	F	29.0	vk	13th left rib short supernumerary, 13th right rib full supernumerary, 6th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified left forepaw
			5	F	31.1	vfk	6th sternebra unossified
			6	M	21.4	vk	6th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			7	F	33.6	vfk	13th bilateral rib short supernumerary
			9	M	28.9	vfk	13th left rib short supernumerary, 5th sternebra unossified, 6th sternebra unossified
			10	F	32.3	vk	13th bilateral rib full supernumerary, 6th sternebra unossified
			11	F	33.4	vfk	13th left rib short supernumerary, pelvic girdle (left sided) unilateral caudal shift
	0017	5vk, 5vfk	3	M	29.6	vfk	13th bilateral rib short supernumerary, 20 thoracolumbar vertebrae
			5	M	44.9	vfk	13th bilateral rib short supernumerary
			10	M	41.9	vk	5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0018	4vk, 5vfk	1	F	43.8	vfk	13th bilateral rib short supernumerary
			3	F	43.8	vfk	5th sternebra unossified, sternebral centre(s) 4th misaligned ossification sites
			7	M	42.1	vfk	13th right rib short supernumerary
			9	M	54.3	vfk	Costal cartilage(s) 7th bilateral not connected to sternum
	0022	4vk, 5vfk	1	M	45.2	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			2	F	39.4	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			4	M	38.7	vk	13th left rib short supernumerary, 13th right rib full supernumerary
			5	F	39.5	vfk	13th bilateral rib full supernumerary
			8	F	40.8	vk	13th left rib short supernumerary, 13th right rib full supernumerary
	0023	5vk, 5vfk	1	F	35.1	vfk	13th bilateral rib full supernumerary
			2	F	32.6	vk	13th bilateral rib short supernumerary, interparietal incompletely ossified
			3	F	37.7	vfk	13th left rib short supernumerary, 13th right rib full supernumerary
			6	M	35.5	vk	13th bilateral rib short supernumerary, interparietal bipartite
			7	F	40.7	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			8	F	40.4	vk	13th bilateral rib full supernumerary
			9	M	39.0	vfk	13th bilateral rib full supernumerary
			10	M	44.6	vk	13th left rib short supernumerary, 13th right rib full supernumerary, sternebral centre(s) 3rd to 4th partially fused

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
1F	0024	4vk, 4vfk	1	F	28.9	vfk	13th bilateral rib full supernumerary
			2	F	37.0	vk	5th sternebra unossified, 6th sternebra unossified
			3	F	37.6	vfk	13th bilateral rib short supernumerary, 5th sternebra unossified, 6th sternebra unossified
			4	M	42.6	vk	13th bilateral rib full supernumerary
			6	M	35.1	vk	13th bilateral rib short supernumerary
			7	M	33.0	vfk	13th bilateral rib short supernumerary, 5th sternebra unossified
			8	F	38.6	vk	13th bilateral rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0025	2vk, 3vfk	1	F	39.7	vfk	13th left rib short supernumerary
			3	F	46.9	vfk	13th left rib full supernumerary, 5th sternebra unossified
			4	F	42.1	vk	5th sternebra unossified
			5	M	50.9	vfk	13th left rib short supernumerary
	0026	3vk, 3vfk	1	F	35.9	vfk	<i>KIDNEY RIGHT MEDIALY DISPLACED, ASCENDING AORTA/PULMONARY TRUNK TRANSPOSITION, AQUEOUS HUMOUR RIGHT ABSENT, EYE RIGHT MICROPHthalmia, RETINA RIGHT MULTIPLE FOLDED, VITREOUS HUMOUR RIGHT ABSENT, 20</i> thoracolumbar vertebrae, 5th sternebra unossified
			3	F	42.3	vfk	13th left rib short supernumerary, 13th right rib full supernumerary
			4	F	45.2	vk	Parietal right unossified area(s)
			5	F	40.4	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			6	M	30.3	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, 6th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy



APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0028	3vk, 4vfk	1	M	48.2	vfk	13th bilateral rib short supernumerary, cervical vertebral centrum(a) 3rd incompletely ossified
			2	M	38.0	vk	5th sternebra unossified
			3	F	39.6	vfk	13th left rib short supernumerary, rib(s) 2nd left to 3rd partially fused
			4	F	35.6	vk	<i>VENTRICULAR SEPTUM MEMBRANOUS DEFECT, ASCENDING AORTA/PULMONARY TRUNK TRUNCUS ARTERIOSUS</i> , 13th bilateral rib short supernumerary, epiphyses unossified
			6	M	44.7	vk	13th right rib short supernumerary, 5th sternebra unossified
			7	F	51.2	vfk	13th right rib short supernumerary, pelvic girdle (left sided) unilateral caudal shift
	0029	5vk, 6vfk	3	M	33.7	vfk	13th bilateral rib short supernumerary
			4	M	34.9	vk	13th bilateral rib short supernumerary
			5	F	38.3	vfk	<i>Interventricular foramen dilated</i> , 13th right rib short supernumerary, 20 thoracolumbar vertebrae, sternebra centre(s) 2nd to 3rd partially fused
			7	M	39.8	vfk	5th sternebra unossified
			9	F	37.4	vfk	13th bilateral rib short supernumerary
			11	M	41.8	vfk	5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0030	5vk, 6vfk	1	F	35.4	vfk	13th bilateral rib short supernumerary
			2	M	28.0	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			3	M	27.2	vfk	13th bilateral rib full supernumerary
			4	M	38.5	vk	5th sternebra unossified
			6	F	28.1	vk	13th left rib short supernumerary, 13th right rib full supernumerary, pelvic girdle (right sided) unilateral caudal shift
			7	F	26.6	vfk	13th left rib short supernumerary, 5th sternebra unossified, 6th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			8	F	37.9	vk	13th left rib short supernumerary, 5th sternebra unossified
			9	F	41.3	vfk	5th sternebra unossified
			11	M	40.4	vfk	13th left rib short supernumerary
	0031	5vk, 5vfk	1	M	30.2	vfk	13th left rib short supernumerary, 13th right rib full supernumerary, 5th sternebra unossified
			2	M	30.5	vk	Interparietal bipartite
			3	M	35.2	vfk	13th bilateral rib short supernumerary, 5th sternebra unossified
			4	M	29.7	vk	13th left rib full supernumerary, 13th right rib short supernumerary, interparietal bipartite
			6	F	38.4	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			7	M	43.4	vfk	13th bilateral rib full supernumerary
			8	F	40.0	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			10	M	40.3	vk	13th bilateral rib full supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0032	3vk, 4vfk	3	M	33.3	vfk	13th right rib short supernumerary, 5th sternebra unossified
			4	F	35.8	vk	5th sternebra unossified
			5	M	31.4	vfk	5th sternebra unossified
			6	F	35.2	vk	13th right rib full supernumerary, 20 thoracolumbar vertebrae
			7	F	32.7	vfk	5th sternebra unossified
	0033	3vk, 4vfk	3	M	38.0	vfk	13th bilateral rib short supernumerary
			5	M	47.3	vfk	5th sternebra unossified
			6	M	40.5	vk	5th sternebra unossified
			7	F	45.4	vfk	5th sternebra unossified
	0034	4vk, 5vfk	2	M	37.5	vk	13th right rib short supernumerary
			3	F	39.9	vfk	5th sternebra unossified
			6	M	45.0	vk	5th sternebra unossified
			7	M	41.3	vfk	5th sternebra unossified
			8	M	42.8	vk	5th sternebra unossified
			9	F	41.2	vfk	5th sternebra unossified
	0035	2vk, 2vfk	1	M	46.2	vfk	13th bilateral rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0036	3vk, 3vfk	1	M	40.4	vfk	5th sternebra unossified
			2	F	44.2	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			3	F	41.9	vfk	5th sternebra unossified
			4	F	40.8	vk	13th bilateral rib short supernumerary
			5	F	43.0	vfk	13th bilateral rib full supernumerary, 5th sternebra unossified
			6	F	44.3	vk	13th left rib full supernumerary, 13th right rib short supernumerary
	0037	3vk, 4vfk	1	M	38.0	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			2	M	40.4	vk	13th bilateral rib full supernumerary
			3	M	41.5	vfk	13th bilateral rib full supernumerary
			4	M	36.7	vk	13th bilateral rib full supernumerary
			5	M	34.9	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			6	F	39.1	vk	13th left rib full supernumerary, 13th right rib short supernumerary
			7	F	40.7	vfk	13th bilateral rib short supernumerary
	0038	3vk, 3vfk	2	M	32.9	vk	5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			4	F	35.3	vk	13th left rib full supernumerary, 5th sternebra unossified, epiphyses unossified
			6	F	34.4	vk	13th bilateral rib short supernumerary, epiphyses unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0039	4vk, 5vfk	2	M	36.6	vk	5th sternebra unossified, epiphyses unossified
			3	F	36.6	vfk	5th sternebra unossified
			6	M	45.8	vk	13th left rib short supernumerary, 13th right rib full supernumerary
			7	F	42.6	vfk	5th sternebra unossified
			8	F	34.7	vk	5th sternebra unossified
			9	F	35.4	vfk	5th sternebra unossified
	0040	3vk, 4vfk	3	M	33.2	vfk	5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			5	M	44.4	vfk	5th sternebra unossified
			6	F	32.0	vk	<i>Eye bilateral small confirmed by mb.</i> , 13th bilateral rib full supernumerary, 6th sternebra unossified, interparietal incompletely ossified, lachrimal fossa bilateral large, cervical vertebral arch(es) 1st right small, thoracic vertebral centrum(a) 4th bipartite ossified, pelvic girdle unilateral caudal shift (left sided), metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
	0041	4vk, 4vfk	All fetuses within normal limits				

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0043	3vk, 4vfk	2	F	47.3	vk	13th bilateral rib full supernumerary
			4	F	34.4	vk	5th sternebra unossified
			7	M	44.9	vfk	<i>VENTRICLE LEFT DOUBLE OULET, ASCENDING AORTA/PULMONARY TRUNK TRANSPOSITION</i> , 13th left rib short supernumerary, pelvic girdle (left sided) unilateral caudal shift
	0045	4vk, 4vfk	2	M	46.9	vk	5th sternebra unossified
			3	F	39.4	vfk	5th sternebra unossified
			4	F	35.6	vk	13th bilateral rib short supernumerary, 5th sternebra unossified
			5	M	31.7	vfk	Epiphyses unossified
			6	M	40.4	vk	13th right rib short supernumerary, 5th sternebra unossified
			7	F	45.0	vfk	5th sternebra unossified
			8	F	42.5	vk	5th sternebra unossified
	0046	4vk, 4vfk	1	F	42.6	vfk	<i>Retina right folded</i>

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

			Control		Sodium Trifluoroacetate		
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
2F	0047	4vk, 4vfk	1	F	46.7	vfk	13th bilateral rib full supernumerary
			2	F	39.9	vk	13th bilateral rib full supernumerary
			3	F	34.5	vfk	5th sternebra unossified
			4	F	32.8	vk	13th left rib full supernumerary
			5	F	39.2	vfk	13th left rib short supernumerary
			6	F	39.6	vk	13th bilateral rib full supernumerary, pelvic girdle (left sided) unilateral caudal shift
			7	F	39.0	vfk	13th left rib short supernumerary
			8	F	43.3	vk	13th bilateral rib short supernumerary, 20 thoracolumbar vertebrae
	0048	3vk, 4vfk	4	F	33.7	vk	5th sternebra unossified
			5	F	43.9	vfk	13th left rib short supernumerary
			7	F	43.5	vfk	5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0049	4vk, 4vfk	1	F	31.1	vfk	5th sternebra unossified, 6th sternebra unossified
			2	F	35.7	vk	5th sternebra unossified
			3	F	26.3	vfk	<i>AQUEOUS HUMOUR RIGHT ABSENT, eye right small, RETINA RIGHT MULTIPLE FOLDED, VITREOUS HUMOUR RIGHT ABSENT</i> , 5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			4	M	23.3	vk	5th sternebra unossified, posterior fontanelle large
			5	M	22.2	vfk	13th right rib short supernumerary, 5th sternebra unossified
			6	M	26.7	vk	4th sternebra incompletely ossified, 5th sternebra unossified
			8	F	30.0	vk	5th sternebra unossified
			0050	4vk, 5vfk	1	M	36.0
	2	F			36.1	vk	13th bilateral rib short supernumerary
	3	M			27.0	vfk	13th bilateral rib short supernumerary
	4	F			35.1	vk	13th bilateral rib full supernumerary, pelvic girdle (left sided) unilateral caudal shift
	5	M			35.3	vfk	13th left rib short supernumerary
	6	F			31.9	vk	13th left rib short supernumerary, 13th right rib full supernumerary, pelvic girdle (right sided) unilateral caudal shift
	7	M			28.0	vfk	<i>KIDNEY LEFT ABSENT, URETER LEFT ABSENT</i> , 13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
	8	F			34.9	vk	13th bilateral rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy



APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0051	3vk, 4vfk	3	M	43.6	vfk	13th bilateral rib short supernumerary, cervical vertebral centrum(a) 4th incompletely ossified
			4	M	40.0	vk	13th left rib short supernumerary
			7	F	38.4	vfk	Cervical vertebral centrum(a) 2nd hemicentric, epiphyses unossified
	0052	4vk, 4vfk	1	F	24.9	vfk	<i>BRAIN DISCRETE AREA OF AMORPHOUS TISSUE AT POSITION OF OPTIC CHIASMA</i> , 13th left rib short supernumerary, 6th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			2	M	22.4	vk	13th left rib short supernumerary, 20 thoracolumbar vertebrae, CERVICAL REGION MULTIPLE VERTEBRAL ABNORMALITIES, cervical vertebral arch(es) 4th left small, cervical vertebral centrum(a) 3rd hemicentric, cervical vertebral centrum(a) 4th absent, cervical vertebral centrum(a) 7th incompletely ossified, rib(s) 11th left nodulated, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			3	M	25.1	vfk	13th left rib short supernumerary, 13th right rib full supernumerary, 6th sternebra unossified, epiphyses unossified
			4	M	24.0	vk	13th left rib short supernumerary, thoracic vertebral centrum(a) 7th incompletely ossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			5	F	24.8	vfk	13th left rib short supernumerary, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			6	M	36.4	vk	13th bilateral rib short supernumerary, metacarpal/phalange(s) incompletely ossified/unossified left forepaw
			7	F	34.6	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			8	F	30.3	vk	6th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0053	5vk, 6vfk	1	F	21.6	vfk	Metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			3	M	30.0	vfk	5th sternebra unossified
			5	F	31.7	vfk	13th bilateral rib full supernumerary, rib(s) 10th left absent, rib(s) 9th left branched with additional costal cartilage, THORACIC VERTEBRA(E) 10TH LEFT HEMIVERTEBRA, thoracic vertebra(e) 9th bilateral to 10th misaligned, thoracic vertebral centrum(a) 9th right to 10th partially fused, thoracic vertebral hemicentrum(a) 9th right to 10th partially fused
			6	M	26.1	vk	13th left rib short supernumerary
			7	M	28.0	vfk	6th sternebra unossified, epiphyses unossified
			9	M	27.4	vfk	5th sternebra unossified
			10	M	27.8	vk	Epiphyses unossified
	0054	2vk, 3vfk	1	M	43.5	vfk	20 thoracolumbar vertebrae, 5th sternebra unossified, costal cartilage(s) 7th bilateral not connected to sternum
			2	M	41.8	vk	5th sternebra unossified
			3	F	42.5	vfk	13th bilateral rib full supernumerary, pelvic girdle (left sided) unilateral caudal shift
			4	M	41.3	vk	13th bilateral rib full supernumerary, costal cartilage(s) 4th bilateral to 5th misaligned, sternebral centre(s) 4th misaligned hemicentres
			5	M	37.0	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0055	3vk, 4vfk	1	M	37.2	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			2	F	44.5	vk	13th bilateral rib full supernumerary, interparietal unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			3	M	36.2	vfk	13th bilateral rib full supernumerary
			4	F	41.5	vk	13th right rib short supernumerary, frontal bilateral unossified area(s), parietal bilateral unossified area(s)
			5	M	39.4	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			6	M	37.7	vk	Cervical vertebral centrum(a) 4th hemicentric
			7	F	31.0	vfk	13th left rib short supernumerary
	0056	4vk, 4vfk	3	F	42.0	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			4	M	43.5	vk	13th left rib short supernumerary, 13th right rib full supernumerary
			6	F	43.7	vk	13th bilateral rib full supernumerary
			8	F	36.9	vk	5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0057	4vk, 4vfk	1	M	49.1	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			2	F	43.1	vk	13th right rib short supernumerary, 5th sternebra unossified
			3	F	47.6	vfk	13th bilateral rib short supernumerary
			4	F	48.2	vk	13th right rib short supernumerary
			5	F	42.6	vfk	<i>Aqueous humour right haemorrhage(s), harderian gland right haemorrhage, RETINA RIGHT MULTIPLE FOLDED, vitreous humour right haemorrhage(s), 13th left rib short supernumerary, 13th right rib full supernumerary</i>
			7	M	48.3	vfk	<i>VENTRICLE LEFT DOUBLE OULET, ASCENDING AORTA/AORTIC ARCH NARROW, PULMONARY TRUNK DILATED DORSALLY DISPLACED</i>
			8	F	34.4	vk	<i>Eye bilateral small, VENTRICULAR SEPTUM MEMBRANOUS DEFECT, ASCENDING AORTA/AORTIC ARCH DILATED, ASCENDING AORTA/PULMONARY TRUNK</i>
							<i>TRANSPOSITION, tail short, ABDOMEN OMPHALOCELE, 13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified, costal cartilage(s) 3rd to 5th misaligned, sternebra centre(s) 3rd to 4th misaligned hemicentres, interparietal fissure(s), cervical vertebral centrum(a) 3rd incompletely ossified, cervical vertebral centrum(a) 5th asymmetrically ossified, rib(s) 6th left to 7th partially fused, thoracic vertebral centrum(a) 1st hemicentric, thoracic vertebral centrum(a) 5th incompletely ossified, thoracic vertebral centrum(a) 7th dumbell ossified, acromion process bilateral long, metacromion process right long, caudal vertebra(e) 10th to 11th unossified, caudal vertebra(e) 15th to 16th fused, CAUDAL VERTEBRA(E) 6TH TO 9TH MISSHAPEN PARTIALLY FUSED</i>

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0058	2vk, 3vfk	1	M	34.6	vfk	13th right rib short supernumerary, 5th sternebra unossified
			2	F	40.8	vk	13th left rib short supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified
			3	F	41.3	vfk	<i>Cerebellum subdural haemorrhage</i> , 13th bilateral rib full supernumerary
			4	F	45.5	vk	20 thoracolumbar vertebrae
			5	M	38.5	vfk	<i>Accessory lung lobe absent</i>
	0059	4vk, 5vfk	1	M	33.1	vfk	Sternebral centre(s) 1st to 5th misshapen partially fused, STERNUM DORSOVENTRAL DISTORTION
			2	M	30.1	vk	13th bilateral rib short supernumerary, 5th sternebra unossified, pelvic girdle (right sided) unilateral caudal shift
			3	F	33.8	vfk	13th bilateral rib short supernumerary, 5th sternebra unossified
			4	M	37.8	vk	<i>Eye right small</i> , 13th bilateral rib short supernumerary, 5th sternebra unossified, cervical vertebral centrum(a) 4th asymmetrically ossified
			5	M	46.2	vfk	13th bilateral rib short supernumerary
			6	M	24.9	vk	<i>Forepaw(s) left flexure</i> , 13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified, 6th sternebra unossified, rib(s) 8th right to 9th fused, thoracic vertebral centrum(a) 6th incompletely ossified, thoracic vertebral centrum(a) 7th bipartite ossified
			7	M	35.6	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			8	M	39.0	vk	18 thoracolumbar vertebrae, rib(s) 11th bilateral branched with additional costal cartilage
			9	F	47.8	vfk	13th left rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0060	1vk					All fetuses within normal limits
	0061	4vk, 5vfk	1	F	32.1	vfk	<i>Cerebellum subdural haemorrhage</i> , 13th bilateral rib short supernumerary
			2	M	35.4	vk	5th sternebra unossified
			3	M	39.2	vfk	6th sternebra unossified
			4	F	37.4	vk	13th right rib short supernumerary, costal cartilage(s) 7th bilateral not connected to sternum
			5	M	42.4	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			6	F	26.2	vk	6th sternebra unossified, interparietal fissure(s)
			7	F	34.9	vfk	5th sternebra unossified
			8	F	32.7	vk	13th left rib short supernumerary, 5th sternebra unossified
			9	M	21.2	vfk	5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
	0062	5vk, 5vfk	1	M	23.0	vfk	5th sternebra unossified, epiphyses unossified
			3	M	33.2	vfk	13th bilateral rib short supernumerary
			4	M	23.9	vk	5th sternebra unossified, 6th sternebra unossified, epiphyses unossified
			6	F	35.0	vk	5th sternebra unossified
			8	F	19.3	vk	5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			10	M	36.3	vk	13th bilateral rib short supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0063	1vk, 2vfk	1	F	37.4	vfk	<i>Forepaw(s) left flexure</i>
			2	F	25.0	vk	13th bilateral rib full supernumerary, costal cartilage(s) 4th bilateral to 5th misaligned, sternebral centre(s) 3rd to 4th partially fused, sternebral centre(s) 4th misaligned hemicentres, epiphyses unossified
			3	F	34.4	vfk	<i>AQUEOUS HUMOUR LEFT ABSENT, lens left small, OPTIC NERVE LEFT NARROW, RETINA LEFT MULTIPLE FOLDED, VITREOUS HUMOUR LEFT ABSENT</i> , 13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, cervical vertebral centrum(a) 4th incompletely ossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0064	5vk, 6vfk	1	M	32.5	vfk	<i>Accessory lung lobe absent, AQUEOUS HUMOUR BILATERAL ABSENT, VITREOUS HUMOUR BILATERAL ABSENT</i> , 13th bilateral rib full supernumerary
			2	F	27.8	vk	<i>Accessory lung lobe absent, ABDOMEN GASTROSCHISIS</i> , 13th left rib full supernumerary, 13th right rib short supernumerary, 5th sternbra unossified, cervical vertebral arch(es) 2nd left incompletely ossified, cervical vertebral centrum(a) 2nd to 3rd misaligned, rib(s) 5th right to 6th partially fused
			3	M	29.7	vfk	<i>Accessory lung lobe absent</i> , 13th bilateral rib full supernumerary, rib(s) 1st bilateral interrupted ossification
			4	F	23.2	vk	13th left rib short supernumerary, rib(s) 1st left interrupted ossification, epiphyses unossified
			5	F	40.1	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, RETINA BILATERAL MULTIPLE FOLDED, VITREOUS HUMOUR BILATERAL ABSENT</i> , 13th bilateral rib full supernumerary, rib(s) 1st left interrupted ossification
			6	M	34.3	vk	13th bilateral rib full supernumerary
			7	F	32.5	vfk	13th bilateral rib full supernumerary, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			8	M	36.3	vk	13th left rib full supernumerary
			9	F	30.8	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			10	M	34.7	vk	<i>Accessory lung lobe absent</i> , 13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, cervical vertebral centrum(a) 7th asymmetrically ossified, thoracic vertebral centrum(a) 2nd incompletely ossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy



APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0064	5vk, 6vfk	11	M	27.6	vfk	continued from previous page <i>Accessory lung lobe absent, ABDOMEN OMPHALOCELE, eye left small, EYE RIGHT MICROPTHALMIA, RETINA RIGHT MULTIPLE FOLDED, VITREOUS HUMOUR LEFT ABSENT</i> , 13th bilateral rib full supernumerary, costal cartilage(s) 1st bilateral to 2nd misaligned, sternbral centre(s) 1st to 2nd partially fused, sternbral centre(s) 2nd misaligned hemicentres, sternbral centre(s) 3rd to 4th partially fused, cervical vertebral centrum(a) 4th incompletely ossified, rib(s) 3rd right to 4th partially fused, thoracic vertebral centrum(a) 6th incompletely ossified, CAUDAL VERTEBRA(E) 4TH TO 12TH FUSED, MISSHAPEN AND DISORGANISED, TAIL BRACHYURY
	0065	4vk, 4vfk	1	F	27.9	vfk	Epiphyses unossified
			2	M	40.8	vk	5th sternbra unossified
			4	F	42.8	vk	5th sternbra unossified, epiphyses unossified
			7	F	33.1	vfk	5th sternbra unossified
			8	F	40.9	vk	5th sternbra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0066	3vk, 3vfk	1	M	37.8	vfk	<i>Eye bilateral small</i> , 13th right rib short supernumerary, 5th sternebra unossified
			2	F	29.7	vk	13th bilateral rib full supernumerary, costal cartilage(s) 2nd bilateral to 6th misaligned, sternebral centre(s) 2nd hemisternebra, sternebral centre(s) 4th misaligned hemicentres, interparietal fissure(s), thoracic vertebral centrum(a) 7th dumbell ossified, pelvic girdle (right sided) unilateral caudal shift, epiphyses unossified
			3	M	40.5	vfk	13th right rib short supernumerary, 5th sternebra unossified
			4	F	40.4	vk	13th bilateral rib full supernumerary
			6	F	43.3	vk	13th bilateral rib short supernumerary, 5th sternebra unossified, hyoid cornua bent inwards bilateral
	0067	4vk, 4vfk	2	M	44.8	vk	5th sternebra unossified
			4	F	37.9	vk	13th left rib short supernumerary, 5th sternebra unossified
			5	M	37.4	vfk	5th sternebra unossified
			6	M	40.6	vk	13th left rib full supernumerary, 13th right rib short supernumerary
			7	F	40.0	vfk	13th bilateral rib short supernumerary, 5th sternebra unossified
			8	F	44.6	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified, LUMBAR VERTEBRA(E) 7TH RIGHT HEMIVERTEBRA, lumbar vertebral hemicentrum(a) 7th left absent, sacral vertebra(e) 1st bilateral to 2nd misaligned, pelvic girdle unilateral caudal shift (right sided)

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

		Control	Sodium Trifluoroacetate				
Dose Group		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0068	2vk, 3vfk	1	F	40.3	vfk	Thoracic vertebral centrum(a) 4th to 5th incompletely ossified, thoracic vertebral centrum(a) 6th dumbbell ossified, epiphyses unossified
			2	F	38.9	vk	13th bilateral rib short supernumerary, 5th sternebra unossified
			3	M	31.8	vfk	5th sternebra unossified, epiphyses unossified
			4	F	40.4	vk	Epiphyses unossified
	0069	4vk, 4vfk	1	M	28.9	vfk	<i>Tail tip hooked</i> , 13th bilateral rib short supernumerary, 5th sternebra unossified
			3	F	41.8	vfk	5th sternebra unossified
			4	F	35.7	vk	13th bilateral rib short supernumerary
			7	F	42.8	vfk	5th sternebra unossified
			8	M	43.6	vk	5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0070	5vk, 6vfk	1	F	31.8	vfk	13th right rib short supernumerary, 5th sternebra unossified
			2	F	27.1	vk	<i>Eye left small</i> , 13th right rib short supernumerary, 5th sternebra unossified, cervical rib short supernumerary left, epiphyses unossified
			3	M	28.5	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, LENS LEFT MISSHAPEN, RETINA LEFT RUPTURED INTO SPACE IN SURROUNDING TISSUE, VITREOUS HUMOUR BILATERAL ABSENT</i> , 13th bilateral rib full supernumerary
			4	M	35.4	vk	13th right rib short supernumerary, 5th sternebra unossified
			6	F	27.6	vk	5th sternebra unossified, epiphyses unossified
			7	M	31.3	vfk	5th sternebra unossified, epiphyses unossified
			8	M	29.5	vk	13th bilateral rib short supernumerary
			9	M	32.1	vfk	13th bilateral rib full supernumerary, rib(s) 10th right misaligned, thoracic vertebra(e) 8th bilateral to 10th misaligned, thoracic vertebral centrum(a) 10th hemicentric
			10	M	35.1	vk	5th sternebra unossified
			11	M	32.6	vfk	13th bilateral rib short supernumerary, costal cartilage(s) 7th bilateral not connected to sternum, epiphyses unossified
	0071	1vk					All fetuses within normal limits

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
3F	0072	3vk, 4vfk	1	F	39.6	vfk	13th right rib short supernumerary
			2	M	29.9	vk	13th bilateral rib full supernumerary
			4	F	34.4	vk	5th sternebra unossified
			5	M	33.8	vfk	13th left rib full supernumerary, 13th right rib short supernumerary
			6	M	41.1	vk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			7	M	32.7	vfk	<i>Forepaw(s) left flexure</i> , 13th bilateral rib full supernumerary, pelvic girdle (left sided) unilateral caudal shift

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0073	2vk, 2vfk	1	M	37.9	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, orbital sinus bilateral dilated, RETINA BILATERAL MULTIPLE FOLDED, VITREOUS HUMOUR BILATERAL ABSENT</i> , 13th bilateral rib full supernumerary, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			2	F	35.9	vk	5th sternebra unossified, rib(s) 6th right to 7th partially fused
			3	F	32.8	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, RETINA BILATERAL MULTIPLE FOLDED, RETINA BILATERAL RUPTURED INTO SPACE IN SURROUNDING TISSUE, VITREOUS HUMOUR BILATERAL ABSENT</i> , 13th right rib short supernumerary
			4	F	39.1	vk	13th bilateral rib short supernumerary, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
	0074	2vk, 2vfk	2	F	40.6	vk	13th bilateral rib full supernumerary, 5th sternebra unossified
			4	M	41.5	vk	13th left rib short supernumerary, 13th right rib full supernumerary, 5th sternebra unossified
	0075	3vk, 3vfk	1	M	40.4	vfk	5th sternebra unossified
			2	M	38.8	vk	5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0076	3vk, 3vfk	1	M	19.8	vk	<i>ABDOMEN GASTROSCHISIS</i> , 13th bilateral rib full supernumerary, 5th sternebra unossified, costal cartilage(s) 1st bilateral to 5th misaligned, sternebal centre(s) 1st hemisternebra, sternebal centre(s) 2nd to 4th bipartite ossified misaligned hemicentres, cervical vertebral centrum(a) 3rd misaligned, RIB CAGE DISTORTED, rib(s) 12th left to 13th partially fused, rib(s) 4th left to 8th medially thickened and kinked, rib(s) 4th right to 7th medially thickened and kinked, thoracic vertebral centrum(a) 12th bipartite misaligned, thoracic vertebral centrum(a) 5th dumbell ossified, thoracic vertebral centrum(a) 7th dumbell ossified, thoracic vertebral centrum(a) 8th incompletely ossified, epiphyses unossified
			2	F	29.2	vfk	<i>AQUEOUS HUMOUR RIGHT ABSENT</i> , eye right small, retina left folded, <i>RETINA RIGHT MULTIPLE FOLDED</i> , <i>VITREOUS HUMOUR RIGHT ABSENT</i> , 13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified, epiphyses unossified
			3	M	29.9	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, epiphyses unossified
			4	F	33.6	vk	5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified left forepaw, epiphyses unossified
			5	M	32.9	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, costal cartilage(s) 2nd to 5th misaligned, sternebal centre(s) 2nd to 4th misaligned hemicentres, sternebal centre(s) 3rd to 5th partially fused, thoracic vertebral centrum(a) 8th incompletely ossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0076	3vk, 3vfk	6	M	24.6	vk	continued from previous page
							13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae, costal cartilage(s) 1st left to 2nd fused, costal cartilage(s) 4th bilateral to 6th misaligned, sternebral centre(s) 4th to 5th hemisternebra, interparietal bipartite, rib(s) 10th left to 11th partially fused, rib(s) 4th left to 9th partially fused, rib(s) 4th right to 7th partially fused, THORACIC REGION SCOLIOSIS, THORACIC REGION MULTIPLE THORACIC VERTEBRAL AND RIB ABNORMALITIES, thoracic vertebral arch(es) 4th left to 8th partially fused small, thoracic vertebral arch(es) 4th right to 5th partially fused, thoracic vertebral arch(es) 6th right absent, thoracic vertebral arch(es) 7th right to 8th partially fused, thoracic vertebral centrum(a) 10th hemicentric, thoracic vertebral centrum(a) 5th hemicentric, thoracic vertebral centrum(a) 6th dumbell ossified, thoracic vertebral centrum(a) 7th hemicentric, thoracic vertebral centrum(a) 8th dumbell ossified, epiphyses unossified
	0077	3vk, 3vfk	3	M	40.4	vfk	Epiphyses unossified
			4	F	45.1	vk	13th bilateral rib short supernumerary
			5	M	44.5	vfk	Epiphyses unossified
	0079	2vk, 2vfk	3	M	42.1	vfk	5th sternebra unossified
			4	M	38.3	vk	13th right rib short supernumerary
	0080	3vk, 4vfk					
			All fetuses within normal limits				

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy



APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0081	1vk, 1vfk	2	F	41.3	vk	Cervical vertebral centrum(a) 4th asymmetrically ossified
			1	F	40.7	vfk	13th right rib short supernumerary
	0082	1vk, 2vfk	2	M	26.9	vk	Metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			3	F	32.6	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, RETINA BILATERAL MULTIPLE FOLDED, VITREOUS HUMOUR BILATERAL ABSENT</i> , metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
	0083	3vk, 4vfk	1	M	35.0	vfk	13th left rib short supernumerary
			2	F	42.7	vk	13th bilateral rib full supernumerary
			3	F	37.2	vfk	13th bilateral rib full supernumerary, 20 thoracolumbar vertebrae
			4	F	39.8	vk	13th left rib short supernumerary, 13th right rib full supernumerary
			5	M	38.8	vfk	13th bilateral rib short supernumerary
			6	M	40.7	vk	13th bilateral rib short supernumerary, 20 thoracolumbar vertebrae
			7	F	36.4	vfk	13th right rib short supernumerary, pelvic girdle left unilateral caudal shift

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0084	4vk, 5vfk	2	F	35.4	vk	5th sternebra unossified, cervical vertebral centrum(a) 3rd asymmetrically ossified
			3	M	46.7	vfk	5th sternebra unossified
			4	M	23.5	vk	5th sternebra unossified, posterior fontanelle large, metacarpal/phalange(s) incompletely ossified/unossified left forepaw
			6	F	41.8	vk	5th sternebra unossified
	0085	5vk, 6vfk	2	F	32.2	vk	Thoracic vertebral centrum(a) 3rd hemicentric
			4	M	32.1	vk	Cervical rib short supernumerary right
			6	F	31.2	vk	Epiphyses unossified
			9	M	35.0	vfk	Cervical vertebral centrum(a) 3rd hemicentric
			11	M	45.9	vfk	13th left rib short supernumerary
	0086	4vk, 4vfk	1	M	41.2	vfk	13th bilateral rib short supernumerary, pelvic girdle (left sided) unilateral caudal shift
			2	M	29.4	vk	13th right rib short supernumerary, 5th sternebra unossified
			3	F	24.9	vfk	<i>Forepaw(s) bilateral flexure</i> , cervical rib full supernumerary right
			4	M	30.4	vk	<i>Forepaw(s) left flexure</i> , 13th bilateral rib short supernumerary, 5th sternebra unossified
			5	M	35.7	vfk	13th bilateral rib full supernumerary
			6	F	38.3	vk	13th bilateral rib short supernumerary
			7	F	27.5	vfk	13th left rib short supernumerary
			8	M	42.6	vk	13th bilateral rib full supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0087	3vk, 3vfk	1	F	33.4	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, RETINA BILATERAL MULTIPLE FOLDED, VITREOUS HUMOUR BILATERAL ABSENT</i>
			2	F	36.3	vk	<i>Forepaw(s) bilateral flexure</i>
			3	F	34.1	vfk	13th right rib short supernumerary
			4	F	32.1	vk	Maxilla/jugal bilateral partially fused, cervical vertebral centrum(a) 2nd asymmetrically ossified, cervical vertebral centrum(a) 4th asymmetrically ossified
			6	M	29.4	vk	Maxilla/jugal left partially fused, cervical vertebral centrum(a) 5th asymmetrically ossified
	0088	3vk, 4vfk	1	M	24.1	vfk	<i>Forepaw(s) right flexure</i> , 5th sternebra unossified, 6th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw
			2	M	26.2	vk	6th sternebra unossified, posterior fontanelle large
			3	M	30.2	vfk	5th sternebra unossified
			4	M	29.3	vk	5th sternebra unossified
			5	F	35.5	vfk	13th left rib full supernumerary, 5th sternebra unossified
			6	M	34.2	vk	6th sternebra unossified
			7	M	30.0	vfk	<i>Aqueous humour haemorrhage(s) left, eye bilateral small, harderian gland left haemorrhage, RETINA BILATERAL MULTIPLE FOLDED, vitreous humour left haemorrhage(s), 5th sternebra unossified, 6th sternebra unossified</i>

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group	Control		Sodium Trifluoroacetate				
	1	2	3	4			
Dose (mg/kg/day)	0	180	375	750			

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0089	4vk, 4vfk	1	F	31.8	vfk	13th left rib full supernumerary, 13th right rib short supernumerary, 5th sternebra unossified
			3	F	41.2	vfk	13th left rib short supernumerary, thoracic vertebral centrum(a) 7th incompletely ossified
			4	F	39.5	vk	13th bilateral rib short supernumerary
			5	F	43.7	vfk	5th sternebra unossified
			6	F	39.3	vk	Thoracic vertebral centrum(a) 3rd asymmetrically ossified
			8	F	43.4	vk	13th right rib full supernumerary
	0090	2vk, 2vfk	1	M	33.9	vfk	13th bilateral rib short supernumerary, 20 thoracolumbar vertebrae, 5th sternebra unossified
			2	F	33.2	vk	5th sternebra unossified
			3	M	40.2	vfk	13th bilateral rib full supernumerary, pelvic girdle (right sided) unilateral caudal shift
			4	F	38.4	vk	<i>Ovary bilateral cyst(s)</i> , 5th sternebra unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0091	5vk, 5vfk	1	M	34.1	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, retina bilateral folded, VITREOUS HUMOUR BILATERAL ABSENT</i> , 13th bilateral rib full supernumerary, 5th sternebra unossified, epiphyses unossified
			2	M	40.5	vk	13th left rib short supernumerary
			3	F	24.2	vfk	<i>AQUEOUS HUMOUR BILATERAL ABSENT, RETINA BILATERAL MULTIPLE FOLDED, VITREOUS HUMOUR BILATERAL ABSENT</i> , costal cartilage(s) 2nd bilateral to 5th misaligned, costal cartilage(s) 2nd left to 3rd partially fused, sternebral centre(s) 2nd to 3rd partially fused, sternebral centre(s) 3rd misaligned hemicentres, cervical vertebral centrum(a) 7th hemicentric, rib(s) 2nd left to 3rd partially fused, rib(s) 2nd right to 3rd partially fused, rib(s) 4th left to 5th partially fused, rib(s) 7th right to 8th partially fused, thoracic vertebral centrum(a) 6th incompletely ossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, metatarsal/phalange(s) incompletely ossified/unossified bilateral hindpaw
			4	M	24.3	vk	13th bilateral rib full supernumerary, epiphyses unossified
			5	F	30.3	vfk	18 thoracolumbar vertebrae
			6	F	34.4	vk	13th bilateral rib full supernumerary, epiphyses unossified
			7	F	27.5	vfk	13th bilateral rib full supernumerary
			8	M	29.7	vk	13th left rib full supernumerary, 20 thoracolumbar vertebrae, cervical vertebral centrum(a) 4th incompletely ossified, rib(s) 5th left to 6th partially fused, LUMBAR REGION SCOLIOSIS, lumbar vertebra(e) 1st bilateral to 3rd misaligned, LUMBAR VERTEBRA(E) 2ND RIGHT HEMIVERTEBRA
			9	F	38.5	vfk	Costal cartilage(s) bilateral misaligned, sternebral centre(s) 4th misaligned hemicentres
			10	F	42.7	vk	<i>Eye right small</i> , 13th bilateral rib full supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0092	5vk, 5vfk	1	F	24.6	vfk	5th sternebra unossified, rib(s) 10th right to 11th partially fused, thoracic vertebral centrum(a) 10th incompletely ossified, metacarpal/phalange(s) incompletely ossified/unossified left forepaw
			2	F	32.6	vk	13th right rib short supernumerary, 5th sternebra unossified
			3	M	34.6	vfk	<i>Retina bilateral folded</i>
			4	F	36.4	vk	5th sternebra unossified
			5	M	31.2	vfk	13th left rib short supernumerary, 5th sternebra unossified
			6	F	33.1	vk	5th sternebra unossified
			7	M	30.5	vfk	<i>RETINA RIGHT MULTIPLE FOLDED</i> , 13th right rib short supernumerary, 5th sternebra unossified, cervical vertebral centrum(a) 6th incompletely ossified
			8	F	25.0	vk	20 thoracolumbar vertebrae, 5th sternebra unossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			9	F	28.3	vfk	13th bilateral rib full supernumerary, 5th sternebra unossified
			10	F	33.8	vk	5th sternebra unossified
	0093	2vk, 2vfk	1	M	38.1	vfk	13th bilateral rib full supernumerary
			3	F	36.7	vfk	13th left rib short supernumerary
			4	F	37.9	vk	13th bilateral rib full supernumerary

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

	Control	Sodium Trifluoroacetate		
Dose Group	1	2	3	4
Dose (mg/kg/day)	0	180	375	750

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0094	3vk, 3vfk	1	F	26.8	vfk	13th bilateral rib short supernumerary, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, metatarsal/phalange(s) incompletely ossified/unossified bilateral hindpaw, epiphyses unossified
			2	M	26.4	vk	<i>Eye left small, ASCENDING AORTA/PULMONARY TRUNK TRANSPOSITION</i> , 5th sternebra unossified, anterior supraorbital notch bilateral absent, frontal bilateral unossified area(s), interparietal incompletely ossified, jugal incompletely ossified bilateral, parietal bilateral unossified area(s), thoracic vertebral centrum(a) 3rd asymmetrically ossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, metatarsal/phalange(s) incompletely ossified/unossified bilateral hindpaw, epiphyses unossified
			3	M	33.7	vfk	13th bilateral rib short supernumerary, 20 thoracolumbar vertebrae, thoracic vertebral centrum(a) 5th asymmetrically ossified, epiphyses unossified
			4	F	32.3	vk	13th left rib full supernumerary, 13th right rib short supernumerary, 20 thoracolumbar vertebrae
			5	M	31.0	vfk	<i>VENTRICULAR SEPTUM MUSCULAR DEFECT, ASCENDING AORTA/PULMONARY TRUNK TRANSPOSITION</i> , 13th right rib short supernumerary, rib(s) 12th right to 13th partially fused, thoracic vertebral centrum(a) 12th bilateral bipartite ossified, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw, epiphyses unossified
			6	F	30.5	vk	5th sternebra unossified, jugal incompletely ossified bilateral

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0095	3vk, 4vfk	3	F	39.8	vfk	13th bilateral rib short supernumerary, cervical vertebral centrum(a) 3rd asymmetrically ossified
			4	F	37.4	vk	18 thoracolumbar vertebrae, sternebral centre(s) 4th to 5th partially fused, rib(s) 12th bilateral absent, rib(s) 7th right branched with additional costal cartilage
			5	F	24.6	vfk	<i>KIDNEY BILATERAL FUSED CAUDALLY DISPLACED, ureter left dilated, AQUEOUS HUMOUR BILATERAL ABSENT, eye left small, EYE RIGHT MICROPHthalmia, LENS LEFT ABSENT, RETINA BILATERAL MULTIPLE FOLDED, VITREOUS HUMOUR BILATERAL ABSENT, PALATE CLEFT</i> , 5th sternebra unossified, sternebral centre(s) 1st to 2nd misshapen, sternebral centre(s) 1st to 4th partially fused, SACRAL VERTEBRAL ARCHES RIGHT 1ST MISSHAPEN, sacral vertebral arches to 2nd bilateral 1st misaligned, pelvic girdle unilateral caudal shift (left sided), CAUDAL VERTEBRA(E) DISORGANISED PARTIALLY FUSED, TAIL BRACHYURY
			6	F	35.6	vk	Costal cartilage(s) 3rd bilateral to 5th misaligned, sternebral centre(s) 3rd to 5th misaligned hemicentres, sternebral centre(s) 3rd to 5th partially fused, cervical vertebral centrum(a) 2nd asymmetrically ossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy



APPENDIX 12.10 Fetal examinations - individual litter/fetal incidence of abnormalities  
(cont)

Request ID: 5375792

Dose Group		Control	Sodium Trifluoroacetate				
		1	2	3	4		
Dose (mg/kg/day)		0	180	375	750		

Group	Animal Number	Examined	Fetus Number	Sex	Weight (g)	Fate	Reportable abnormalities (only fetuses with reportable abnormalities are listed) major abnormalities in CAPITALS, necropsy and fixed visceral abnormalities in <i>italics</i>
4F	0095	3vk, 4vfk	7	M	29.5	vfk	continued from previous page <i>Aqueous humour haemorrhage(s) right, LENS LEFT MISSHAPEN, orbital sinus bilateral dilated, 13th bilateral rib full supernumerary, 5th sternebra unossified, costal cartilage(s) 5th right to 6th partially fused, rib(s) 5th left to 6th partially fused, rib(s) 5th right to 7th partially fused, THORACIC REGION MULTIPLE THORACIC VERTEBRAL AND RIB ABNORMALITIES, THORACIC VERTEBRA(E) 5TH RIGHT HEMIVERTEBRA, thoracic vertebral centrum(a) 3rd dumbell ossified, thoracic vertebral centrum(a) 6th hemicentric, thoracic vertebral centrum(a) 7th absent, metacarpal/phalange(s) incompletely ossified/unossified bilateral forepaw</i>
	0096	1vk	1	M	45.7	vk	Epiphyses unossified

vk - fresh visceral and skeletal examination, vfk - all examination types, including fixed visceral examination of fetal heads removed at necropsy

### 13. ATTACHMENTS

Regulation (EC) No 1049/2001.

Document disclosed in repl to an applica

**Attachment 13.1      Certificate of analysis**

Regulation (EC) No 1049/2001.

Document disclosed in repl to an applica

Certificate Of Analysis (C O A)

品名/PRODUCT: 三氟乙酸钠/Sodium trifluoroacetate

CAS 号/CAS NO: 2923-18-4

生产日期/MFGDATE: 2019.05.23

报告日期/REPORT DATE: 2019.05.31

批 号/Batch No.: 2019052304

批重量/Batch Weight: —

重 量/Weight: 35 磅

检验项目 Test Item	标准 Standard	检验结果 Test Result
外 观 Appearance	白色固体 White solid	白色固体 white solid
含 量 Purity	≥99%	99.90 %
	≤1.0%	
CONCLUSION (结论) <div style="text-align: center;">  </div>		

ANALYZED BY (检验): [REDACTED] CHECKED BY (复核): [REDACTED]

REVIEWED BY (审核): [REDACTED]

**Attachment 13.2      Formulation analysis report**

Regulation (EC) No 1049/2001.

Document disclosed in repl to an applica

## Formulation Analysis Contributing Report

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001

<b>Study Number:</b>	8437242
<b>Version ID:</b>	Final Report
<b>Issue Date:</b>	September 2021
<b>Contributing Scientist:</b>	
<b>Department:</b>	Dose Formulation Analysis

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Regulation (EC) No 1049/2001

**SIGNATURE PAGE****Formulation Analysis Contributing Report**

This is a true reflection of the work conducted and my interpretation of the results.

[Redacted Signature]

13 Sep 2021  
Date

Contributing Scientist

[Redacted] Early Development Laboratories Limited

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001



# 1 INTRODUCTION AND PURPOSE

## 1.1 Purpose

This report describes the analytical and sampling procedures used and details the results obtained for the determination of concentrations of Sodium Trifluoroacetate in test formulations analyzed during the study.

The formulations for this study were prepared by Pharmacy personnel at [REDACTED]. The analytical work was undertaken by Dose Formulation Analysis personnel.

## 1.2 Study Schedule

Analytical phase start date                      30 June 2020

Analytical phase completion date              21 July 2020

Regulation (EC) No 1049/2001

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## 2 MATERIALS AND TEST METHODS

### 2.1 Analytical Procedure

The samples were analyzed in accordance with the validated [REDACTED] Analytical Procedure (DFA/M021/20).

The analytical method involved extraction in and dilution in 25 mM sodium phosphate buffer pH 5.8 followed by reverse phase high performance liquid chromatographic analysis with ultra violet detection at 195 nm. Sample concentrations were determined with reference to external standards prepared in the concentration range 100 µg/mL to 1000 µg/mL.

### 2.2 Test Item and Supporting Information

Sponsor's identification	Sodium Trifluoroacetate
Batch No.	2019052304
CAS No.	2923-18-4
Purity	99.9%
Correction factor	Not required, used as supplied
Appearance	White solid
Expiry date	01 May 2021 (two years after analysis/issue date of Certificate of Analysis)
Storage conditions	At ambient temperature (15 to 25 °C)

### 2.3 Concentration of Dose Formulations

The formulations for First and Last preparation were sampled, 1 × 10 mL (accurately weighed), from the middle of the formulation by Pharmacy personnel.

Two aliquots from the sample were analyzed in accordance with the analytical procedure. The remainder of the samples were retained for contingency. Samples were disposed of once satisfactory results were achieved.

### 2.4 Major Computerized Systems

Chromatography data handling:	Waters Empower 2
Sample handling system:	Sample Registry System, [REDACTED]
Test item management:	Pristima, Xybion Medical Systems Corporation
Version numbers of the systems are maintained by	[REDACTED]

### 3 RESULTS AND CONCLUSION

The mean concentrations of Sodium Trifluoroacetate in test formulations analyzed during the study and the deviation of the mean result from the nominal value are detailed in [Table 1](#).

The mean concentrations were within 2% of the nominal concentration, confirming the accuracy of formulation. The difference from mean remained within 1%, confirming precise analysis.

Regulation (EC) No 1049/2001

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**Table 1 Analyzed Concentrations for Sodium Trifluoroacetate in Water**

Occasion	Group	Nominal concentration (mg/mL)	Analyzed concentration (mg/mL)			RME (%)	Difference from mean (%)
			Analysis 1	Analysis 2	Mean		
First preparation	1	0	ND	ND	-	-	-
	2	18	18.2	18.0	18.1	+0.6	±0.35
	3	37.5	38.1	37.7	37.9	+1.1	±0.50
	4	75	75.6	75.7	75.6	+0.8	±0.08
Last preparation	1	0	ND	ND	-	-	-
	2	18	18.3	18.2	18.3	+1.7	±0.38
	3	37.5	37.5	37.6	37.5	0.0	±0.10
	4	75	74.0	74.2	74.1	-1.2	±0.09

RME Relative mean error, representing the deviation from nominal

ND Not detected

Mean analyzed concentrations and difference from mean values were calculated using unrounded figures.

Regulation (EC) No 1049/2001

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**Attachment 13.3      Pathology report**

Regulation (EC) No 1049/2001.

Document disclosed in repl to an applica



# Final Anatomic Pathology Report

Study Title Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration

Contributing Scientist

Pathologist Manager

Test Facility

 Study Number

8437242

Co - Sponsors

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Report Issue Date

06 September 2021

Page Number

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Regulation (EC) No 1831/2003

## 1. SUMMARY

This report describes anatomic pathology findings for [REDACTED] Study 8437242. The purpose of this study was to assess the influence of Sodium Trifluoroacetate on embryo-fetal survival and development when administered during the organogenesis and fetal growth phases of pregnancy in the New Zealand White rabbit. Animals were administered 180, 375, or 750 mg/kg/day Sodium Trifluoroacetate.

No test article-related F0 mortality occurred.

Test article-related microscopic changes were seen in the liver of F0 females.

In the liver, bile duct hyperplasia/fibrosis was seen in females of all treated groups and demonstrated a dose relationship. Bile duct hyperplasia, is likely to reflect test article excretion in the bile, causing an insult to the bile duct epithelium ([Sahota et al., 2019](#)). Generalized hepatocellular hypertrophy was seen in females of all treated groups and exhibited a dose relationship. The hypertrophic changes noted in the liver were suggestive of an adaptive response to mixed function oxidase induction in the liver ([Cattley et al., 2002](#); [Maronpot et al., 2010](#); [Thoolan et al., 2010](#)) but the precise mechanism of hypertrophy cannot be determined by histopathological examination alone ([Sahota et al., 2019](#)). The hypertrophy identified in this study was of minimal severity and not accompanied by other changes in the liver (degeneration or necrosis for example). The findings of bile duct hyperplasia/fibrosis and or hepatocellular hypertrophy, which were both seen in the liver of some females, correlated with the higher than control mean body weight adjusted liver weights for females administered Sodium Trifluoroacetate.

At the macroscopic examination of Gestation Day 29 (GD 29) fetuses, eye abnormalities (such as combinations of folded retina, retinal rupture and/or absence of humors) were recorded.

Microscopic examination of histological sections was subsequently performed on the eyes from selected Gestation Day 29 (GD 29) fetuses with these eye abnormalities. The objective was to attempt and understand the nature/aetiology of the malformations. The folded retina and the absence of humor in most cases occurred in the same fetuses, and histopathological examination was performed to try and determine the possible pathogenesis of these abnormalities, and whether the absence of humor was the principal finding causing folded retina or that the folded retina resulted in the lack of humor.

Following histological examination of the fetal eye abnormalities, although some further information was gained about the histopathological changes associated with these lesion, the pathogenesis could not be established following examination of one section of the eyes from each of the selected GD 29 fetuses.



## 2. METHODS

New Zealand White rabbits were administered vehicle control or test article, Sodium Trifluoroacetate, once daily via oral gavage, as indicated in the following table. The vehicle control article was water.

Group	Treatment	Dose (mg/kg/day)	Number of animals
			Female
1	Control	0	24
2	Sodium Trifluoroacetate	180	24
3	Sodium Trifluoroacetate	375	24
4	Sodium Trifluoroacetate	750	24

At necropsy, macroscopic examinations were conducted. Study plan-specified organ weights were recorded at each scheduled sacrifice. Study plan-specified tissues (when present) were examined from each animal.

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### 3. RESULTS AND DISCUSSION

#### 3.1 Mortality

No test article-related mortality occurred.

There was an unscheduled death of a control female, and of a female that was administered 750 mg/kg/day that was not considered unrelated to treatment with Sodium Trifluoroacetate.

Control female No. 8, was found dead following dosing on Gestation Day 27. At necropsy, perforation of the mid trachea, dark areas on all lobes of the lungs and red fluid and gas in the right retroperitoneal adipose tissue were seen. There was no Study Plan requirement to examine these tissues microscopically, although the findings in the trachea and lungs at necropsy indicated an accidental death due to mis-dosing during the oral gavage administration procedure.

Female No. 78, administered 750 mg/kg/day, was killed on Gestation Day 27 due to suspected abortion. At necropsy, an enlarged spleen was noted. There was no Study Plan requirement to examine this tissue microscopically. At microscopic examination of the liver, slight multifocal bile duct hyperplasia/fibrosis and minimally decreased generalized hepatocyte cytoplasmic rarefaction in the liver were seen. Bile duct hyperplasia/fibrosis was seen as a test article related finding in other females of this dose group. These findings were not considered to have contributed to the death of this animal, with the main contributory factor being suspected abortion.

As both of these females died on Gestation Day 27, and the scheduled sacrifice of terminal females was on Gestation Day 29, the microscopic findings from the liver of these two animals were included with the terminal sacrifice animals.

All other F0 females survived to their scheduled sacrifice.

#### 3.2 Organ Weights

At the terminal sacrifice, mean body weight adjusted organ weight increases were noted for the liver of F0 females.

Mean body weight adjusted liver weights were statistically significantly higher in F0 females administered 180, 375 or 750 mg/kg/day (body weight adjusted: 109%, 114% and 115% respectively) when compared with controls.

**Text Table 3.1: Test Article-Related Effects in Organ Weight Parameters – Terminal Sacrifice on Day 29 of Gestation**

Group/Sex	Sodium Trifluoroacetate			
	1F	2F	3F	4F
Dose Level (mg/kg/day)	0	180	375	750
Liver				
Absolute Weight (g)	102	109	113	112
Body Weight Adjusted (g)	101	109*	114**	115**

\*/\*\* = Statistically significant difference (absolute or adjusted) compared with respective control mean value.

Note: Values for absolute weight and body weight adjusted organ weights for dosed groups expressed as percentage control mean value.

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: presence only in absolute weight or in body weight adjusted but not both; lack of a dose relationship or correlative findings; and/or the magnitude was considered small.

### 3.3 Macroscopic Observations

Macroscopic individual data are listed in [Table 6.1](#)

A Sodium Trifluoroacetate-related macroscopic finding was noted in one female at terminal sacrifice.

An irregular surface of the liver was seen in female No. 63, administered 375 mg/kg/day. Following microscopic examination of the liver, moderate multifocal bile duct hyperplasia/fibrosis accounted for the irregular surface. As bile duct hyperplasia/fibrosis was seen as a Sodium Trifluoroacetate-related finding in females of all treated groups, the macroscopic and microscopic findings in the liver of this female were considered related to treatment with the test article.

All other 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 female New Zealand White rabbits of this age. Consequently, they were considered not test article related.

### 3.4 Microscopic Observations

Microscopic observation data are summarized in [Table 5.1](#); individual data are listed in [Table 6.1](#)

Changes related to treatment with Sodium Trifluoroacetate were seen in the liver. Only the livers were required to be examined microscopically.

In the liver, minimal to moderate bile duct hyperplasia/fibrosis was seen in females of all treated groups and demonstrated a dose relationship. Bile duct hyperplasia can be a response to insult to the bile duct epithelium ([Sahota et al., 2019](#)), and is indicative of test article excretion in the bile. Minimal generalized hepatocellular hypertrophy was seen in females of all treated groups and exhibited a dose relationship. The hypertrophic changes noted in the liver were suggestive of an adaptive response to mixed function oxidase induction in the liver ([Cattley et al., 2002](#); [Maronpot et al., 2010](#); [Thoolan et al., 2010](#)) but the precise mechanism of hypertrophy cannot be determined by histopathological examination alone ([Sahota et al., 2019](#)). The change identified in this study was of minimal severity and not accompanied by other changes in the liver (degeneration or necrosis for example). The findings of bile duct hyperplasia/fibrosis and or hepatocellular hypertrophy correlated with the higher than control mean body weight adjusted liver weights for females administered Sodium Trifluoroacetate.

**Text Table 3.2: Incidence and Severity of Test Article-Related Microscopic Findings – Terminal Sacrifice on Day 29 of Gestation**

Group/Sex		Sodium Trifluoroacetate			
		1F	2F	3F	4F
Dose Level (mg/kg/day)		0	180	375	750
Liver					
	Number Examined	24	24	24	24
Hyperplasia/Fibrosis, Bile Ducts					
	Minimal	0	3	2	6
	Slight	0	0	3	3
	Moderate	0	0	1	2
Hypertrophy, Hepatocellular, Generalized					
	Minimal	0	6	8	9

**Histopathological Examination of Fetal Eye Abnormalities**

Fetal eye data are summarized in [Table 5.2](#); individual data are listed in [Table 6.2](#)

Initial microscopic examination of the head sections from four Control fetuses<sup>#</sup> was undertaken to assess the condition of the sectioned eyes from the Bouin's fixed tissue prior to the proposed histopathological examination of eye abnormalities in fetuses from treated groups. The tissue from all four fetuses had representative tissue morphology and architecture and good staining characteristics. Based on the condition of these Control sections, they were considered suitable to support the request to extend the microscopic examination to the eyes of affected treated fetuses.

<sup>#</sup> Litter No. 3; Fetus No. 7  
 Litter No. 5; Fetus No. 1  
 Litter No. 9; Fetus No. 3  
 Litter No. 16; Fetus No. 1

At the macroscopic examination of Gestation Day 29 (GD 29) fetuses, eye abnormalities (such as combinations of folded retina, retinal rupture and/or absence of humors) were recorded. Microscopic examination of histological sections was subsequently performed on the eyes from selected fetuses with these abnormalities.

The eyes were examined from 9 male and 11 female GD 29 fetuses from treated groups (Group 2: 1 female; Group 3: 4 males, 4 females and Group 4: 5 males, 6 females).

At microscopic examination, slight to marked retinal folds were seen in the majority (5 of 8) of animals whose dams were administered 375 mg/kg/day and in all animals (11 of 11) whose dams were administered 750 mg/kg/day and demonstrated a relationship to dose in terms of relative group incidences. Marked retinal folds were seen in the one female whose dam was administered 180 mg/kg/day. Lens degeneration was seen in several fetuses (6 of 20), and hemorrhage in the vitreous chamber was seen in a few fetuses (2 of 20), that had retinal folds. The majority of the fetuses that had retinal folds also had absence of aqueous and/or vitreous humor (13 of 20, generally bilateral) reported at macroscopic examination. The presence, or confirmation of the absence at initial gross fetal examination, of the aqueous and vitreous humors could not reliably be assessed at microscopic examination as they generally do not persist following tissue processing ([Ramos et al., 2021](#)).

At microscopy, structural (anatomical) disorganisation of the eyes was seen in one male and female of each treated group whose dams were administered 375 or 750 mg/kg/day. The retinal rupture through the vitreous chamber reported at macroscopic examination could not always be reliably identified and/or confirmed at microscopy.

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#### 4. ASSOCIATED STUDY INFORMATION

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#### 4.1 References

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Thoolen B., Maronpot R. R., Harada T., Nyska A., Rousseaux C., Nolte T., Malarkey D. E., Kaufmann W., Kuttler K., Deschl D., Nakae D., Gregson R., Vinlove M. P., Brix A. E., Singh B., Belpoggi F., And Ward J. M. (2010). Proliferative and Nonproliferative Lesions of the Rat and Mouse Hepatobiliary System. Toxicologic Pathology, 38: 5S-81S.

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## 4.2 Abbreviations

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

<i><b>Abbreviation</b></i>	<i><b>Definition</b></i>
<b>Neoplastic Findings</b>	
B	Primary, benign neoplasm
F	Infiltrating neoplasm
I	Locally invasive neoplasm
M	Primary, malignant neoplasm
N	Metastatic neoplasm
X	Other neoplasm
<b>Grades for Severity or Amount</b>	
1	Minimal - describes an inconspicuous change
2	Slight - referring to a noticeable but not prominent feature
3	Moderate - a prominent feature
4	Marked - a dominant but not overwhelming feature
5	Severe - implies an overwhelming condition
<b>Tissue Abbreviations</b>	
F	Female
M	Male

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### 4.3 Comments on the Data

The following comments on the data are used by [REDACTED] Some, but not necessarily all, of this information may be needed for this report.

Various models of calculators, computers, and computer programs were used to analyze data in this study. Values in some tables (e.g., means, standard deviations, or individual values) may differ slightly from those in other tables, from individually calculated data, or from statistical analysis data because different models round off or truncate numbers differently. Neither the integrity nor the interpretation of the data was affected by these differences.

The number of animals listed in the heading of the anatomic pathology summary tables indicates the number of animals assigned to each respective necropsy interval.

Data for replaced animals, removed from study, may appear in the individual animal data tables; however, are not discussed further in the study results.

Rabbits are clinically recorded to the tenth of a gram or ones of a gram, respectively, and appear this way throughout the tables.

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## 5. SUMMARY TABLES

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**Table 5.1: Histopathology - group distribution of findings**

TABLE 5.1 Histopathology - group distribution of findings

Request ID: 5388621

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
	1 0	2 180	3 375	4 750	

Tissue/Organ and Findings	Group/Sex No. of animals	Number of animals affected			
		1F 24	2F 24	3F 24	4F 24
Liver	No. examined	24	24	24	24
Microvacuolation, Cytoplasmic, Hepatocellular, Generalized	Minimal	1	0	0	0
	Slight	1	0	0	0
	Total	2	0	0	0
Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal	Minimal	2	1	0	0
	Total	2	1	0	0
Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal	Minimal	2	2	1	0
	Total	2	2	1	0

TABLE 5.1 (cont) Histopathology - group distribution of findings

Request ID: 5388621

Dose Group	Control	Sodium Trifluoroacetate			Regulation (EC) No 609/2001.	
Dose (mg/kg/day)	1	2	3	4		
	0	180	375	750		
Tissue/Organ and Findings	Group/Sex No. of animals	Number of animals affected				
		1F 24	2F 24	3F 24		4F 24
Liver	No. examined	24	24	24		24
Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized	Minimal	2	0	0		1
	Total	2	0	0		1
Hyperplasia/Fibrosis, Bile Ducts	Minimal	0	3	2		6
	Slight	0	0	3		3
	Moderate	0	0	1		2
	Total	0	3	6		11
Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized	Minimal	0	1	2	1	
	Total	0	1	2	1	
Necrosis, Hepatocellular, Focal	Minimal	0	0	1	0	
	Total	0	0	1	0	

TABLE 5.1 (cont) Histopathology - group distribution of findings

Request ID: 5388621

	Control	Sodium Trifluoroacetate			
Dose Group	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Tissue/Organ and Findings	Group/Sex No. of animals	Number of animals affected			
		1F	2F	3F	4F
		24	24	24	24
Liver	No. examined	24	24	24	24
Hyperplasia, Oval Cell	Minimal	1	3	2	0
	Slight	1	0	0	0
	Total	2	3	2	0
Hypertrophy, Hepatocellular, Generalized	Minimal	0	6	8	9
	Total	0	6	8	9
Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized	Minimal	2	2	2	3
	Total	2	2	2	3
Major Factor(s) contributing to death	No. examined	1	0	0	1
Accidental Death	Total	1	0	0	0
Suspected Abortion	Total	0	0	0	1

**Table 5.2: Histopathology – group distribution of fetal ocular findings**

TABLE 5.2 Histopathology – group distribution of fetal ocular findings

		Control	Sodium Trifluoroacetate							
Dose Group	1	2	3	4						
Dose (mg/kg/day)	0	180	375	750						
					Number of fetuses affected					
					1M/1F	2M/2F	3M/3F	4M/4F		
Tissue/Organ and Findings	Group/Sex No. of animals				150	158	173	140		
Eyes	No. examined (M/F)				1/3	0/1	4/4	5/6		
Structural Disorganisation	Present (M/F)				0/0	0/0	1/1	1/1		
	Combined Total				0	0	2	2		
Retinal Folds	Slight				0/0	0/0	0/0	4/1		
	Moderate				0/0	0/0	1/4	1/4		
	Marked				0/0	0/1	0/0	0/1		
	Total (M/F)				0/0	0/1	1/4	5/6		
	Combined Total				0	1	5	11		
Retinal Degeneration	Moderate (M/F)				0/0	0/0	0/1	0/0		
	Combined Total				0	0	1	0		
Lens Degeneration	Minimal				0/0	0/0	0/0	1/0		
	Slight				0/0	0/0	0/0	0/0		
	Moderate				0/0	0/0	1/0	0/0		
	Marked				0/0	0/0	0/1	1/1		
	Severe				0/0	0/0	0/0	0/1		
	Total (M/F)				0/0	0/0	1/1	2/2		
	Combined Total				0	0	2	4		
Lens Hemiation into Anterior Chamber	Present (M/F)				0/0	0/0	1/0	0/1		
	Combined Total				0	0	1	1		

TABLE 5.2 (cont.) Histopathology – group distribution of fetal ocular findings

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate		
	1 0	2 180	3 375	4 750

Tissue/Organ and Findings	Group/Sex No. of animals	Number of fetuses affected			
		1M/1F 150	2M/2F 158	3M/3F 173	4M/4F 140
Eyes	No. examined (M/F)	1/3	0/1	4/4	5/6
Hemorrhage	Minimal	0/0	0/0	1/1	0/0
	Slight	0/0	0/0	0/1	0/0
	Total (M/F)	0/0	0/0	1/2	0/0
	Combined Total	0	0	3	0
Retina Ruptured Proximally Through Vitreous Chamber	Present (M/F)	0/0	0/0	1/0	0/0
	Combined Total	0	0	1	0
Lens Fragmented; Fragments Embedded in Choroid/Sclera	Present (M/F)	0/0	0/0	0/0	0/1
	Combined Total	0	0	0	1
Lens Misshapen	Present (M/F)	0/0	0/0	0/0	1/0
	Combined Total	0	0	0	1

## 6. INDIVIDUAL ANIMAL DATA TABLES

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**Table 6.1: Macropathology and histopathology – individual animals**

TABLE 6.1 Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0001	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0002N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0003	29 (5)	Gestation	Liver: No macropathology findings	Liver: Microvacuolation, Cytoplasmic, Hepatocellular, Generalized, slight

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0004	29 (5)	Gestation	Uterus: Serosal cyst(s), left, clear, 10-19mm, 1 (one)	Not Applicable

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
		1	2	3	4
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0005	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0006N	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

N - Not pregnant

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0007	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0008DD	27 (4)	Gestation	Adipose Tissue: Abnormal contents, retroperitoneal, gas, right	Not Applicable
				Adipose Tissue: Abnormal contents, retroperitoneal, fluid, right, red	Not Applicable
				Lungs and Bronchi: Dark area(s), all lobes, 2-9mm, 5+ (many)	Not Applicable
					Major Factor(s) contributing to death: Accidental Death, present
				Trachea: Perforated, middle	Not Applicable
Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:					
Liver					

DD - Found dead after dosing



TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0009	29 (5)	Gestation	Liver: No macropathology findings	Liver: Microvacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0010	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0011	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0012	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0013	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0014	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0015	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized, minimal, generalized hepatocytes

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
		1	2	3	4	
		0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0016	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized, minimal, periportal hepatocytes

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003



TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0017	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0018	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0019N	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

N - Not pregnant

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0020N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal
Tissues without comments under macropathology findings were within normal limits at necropsy.					

N - Not pregnant

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			Phase	Macropathology findings	Histopathology findings
	1	2	3	4			
Dose (mg/kg/day)	0	180	375	750			
Group /Sex	Animal Number	Day (Week) of Death					
1F	0021N	29 (5)	Gestation		Kidneys: Cyst(s), bilateral, clear, 2-9mm, 2-5 (few)	Not Applicable	
					Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal	

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0022	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0023	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
1F	0024	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0025	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

		Control	Sodium Trifluoroacetate			
Dose Group		1	2	3	4	
Dose (mg/kg/day)		0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings		Histopathology findings
2F	0026	29 (5)	Gestation	Liver: No macropathology findings		Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
	1 0	2 180	3 375	4 750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0027N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0028	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0029	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0030	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0031	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0032	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003



TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0033	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0034	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Midzonal, minimal Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0035U	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

U - Unilateral implantation

TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0036	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0037	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0038	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0039	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0040	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
		1	2	3	4	
		0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0041	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0042N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0043	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0044N	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

N - Not pregnant

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Regulation (EC) No 1831/2003

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0045	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0046	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0047	29 (5)	Gestation	Kidneys: Cyst(s), bilateral, clear, 2-9mm, 2-5 (few)	Not Applicable

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
		1	2	3	4	
		0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
2F	0048	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0049	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0050	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0051	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0052	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0053	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0054	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0055	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0056	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0057	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0058	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0059	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0060U	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

U - Unilateral implantation

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0061	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0062	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0063	29 (5)	Gestation	Liver: Irregular Surface, all lobes	= Liver: Hyperplasia/Fibrosis, Bile Ducts, moderate, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

= - correlation of macropathology to histopathology finding

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0064	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0065	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
		1	2	3	4	
		0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0066	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0067	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Periportal, minimal Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0068	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal Liver: Necrosis, Hepatocellular, Focal, minimal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0069	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0070	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0071	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
3F	0072	29 (5)	Gestation	Liver: No macropathology findings	Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal Liver: Hyperplasia, Oval Cell, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0073	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0074	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0075	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:

Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0076	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0077	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group Dose (mg/kg/day)	Control	Sodium Trifluoroacetate			
	1 0	2 180	3 375	4 750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0078AB	27 (4)	Gestation	Liver: No macropathology findings  Spleen: Enlarged, noted	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal  Major Factor(s) contributing to death: Suspected Abortion, present  Not Applicable
Tissues without comments under macropathology findings were within normal limits at necropsy.					

AB - Suspected Abortion

TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0079	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0080	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0081	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0082	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, moderate, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0083	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0084	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0085	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0086	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0087	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, moderate, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0088	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, slight, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0089	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0090	29 (5)	Gestation	Liver: No macropathology findings	Liver: Rarefaction, Cytoplasmic, Hepatocyte, Increased, Generalized, minimal, centrilobular hepatocytes Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0091	29 (5)	Gestation	All tissues: No macropathology findings	All examined tissues: No histopathology findings

Tissues without comments under macropathology findings were within normal limits at necropsy. The following examined tissues had no histopathology findings, notes, or comments:  
Liver

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0092	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hypertrophy, Hepatocellular, Generalized, minimal Liver: Rarefaction, Cytoplasmic, Hepatocyte, Decreased, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0093	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal Liver: Macrovacuolation, Cytoplasmic, Hepatocellular, Generalized, minimal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0094	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont)      Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0095	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

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TABLE 6.1 (cont) Macropathology and histopathology - individual findings

Request ID: 5438412

Dose Group	Control	Sodium Trifluoroacetate			
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	
Group /Sex	Animal Number	Day (Week) of Death	Phase	Macropathology findings	Histopathology findings
4F	0096U	29 (5)	Gestation	Liver: No macropathology findings	Liver: Hyperplasia/Fibrosis, Bile Ducts, minimal, multifocal

Tissues without comments under macropathology findings were within normal limits at necropsy.

U - Unilateral implantation



**Table 6.2: Histopathology – individual litter/fetal ocular findings**

TABLE 6.2 Individual litter/fetal ocular histopathology findings

Dose Group	Dose (mg/kg/day)	Control	Sodium Trifluoroacetate		
		1	2	3	4
		0	180	375	750

Group	Animal Number	Fetus Number	Sex	Histopathology findings
2F	0026	1	F	Retinal folds, right eye, marked (correlated to fetal examination finding of right retina multiple folds) Right lens missing from section
3F	0049	3	F	Retinal folds, right eye, moderate (correlated to fetal examination finding of right retina multiple folds)
	0057	5	F	Structural disorganization, right eye, present Retinal folds, right eye, moderate (correlated to fetal examination finding of right retina multiple folds) Hemorrhage, vitreous chamber, right eye, slight (correlated to fetal examination finding of right vitreous humour hemorrhage)
	0063	3	F	Retinal folds, left eye, moderate (correlated to fetal examination finding of left retina multiple folds) Retinal degeneration, left eye, moderate, Lens degeneration, left eye, marked (correlated to fetal examination finding of left lens small)
	0064	1	M	Hemorrhage, vitreous chamber, bilateral, minimal Left lens missing from section
		5	F	Retinal folds, bilateral, moderate (correlated to fetal examination finding of bilateral retina multiple folds) Hemorrhage, vitreous chamber, left eye, minimal

TABLE 6.2 (cont) Individual litter/fetal ocular histopathology findings

Dose Group	Control		Sodium Trifluoroacetate		
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group	Animal Number	Fetus Number	Sex	Histopathology findings
3F	0064	11	M	Retinal folds, right eye, moderate (correlated to fetal examination finding of right retina multiple folds) Lens degeneration, left eye, moderate Right lens missing from section
	0066	1	M	Left retina missing from section
	0070	3	M	Structural disorganization, right eye, present Lens hemiation into anterior chamber, right eye, present Retina ruptured proximally through vitreous chamber, left eye, present
4F	0073	1	M	Retinal folds, bilateral, moderate (correlated to fetal examination finding of bilateral retina multiple folds)
		3	F	Retinal folds, bilateral, slight (correlated to fetal examination finding of bilateral retina multiple folds) Lens degeneration, bilateral, marked
	0076	2	F	Retinal folds, right eye, moderate (correlated to fetal examination finding of right retina multiple folds)

TABLE 6.2 (cont) Individual litter/fetal ocular histopathology findings

Dose Group	Control		Sodium Trifluoroacetate		
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group	Animal Number	Fetus Number	Sex	Histopathology findings
4F	0082	3	F	Retinal folds, right eye, moderate (partial correlate to fetal examination finding of bilateral retina multiple folds) Left lens missing from section
	0087	1	F	Retinal folds, bilateral, moderate (correlated to fetal examination finding of bilateral retina multiple folds)
	0088	7	M	Retinal folds, left eye, slight (partial correlate to fetal examination finding of bilateral retina multiple folds) Lens degeneration, right eye, minimal Right retina missing from section
	0091	1	M	Retinal folds, bilateral, slight (correlated to fetal examination finding of bilateral retina folds)
		3	F	Retinal folds, bilateral, moderate (correlated to fetal examination finding of bilateral retina multiple folds)
	0092	7	M	Retinal folds, right eye, slight (correlated to fetal examination finding of right retina multiple folds)

TABLE 6.2 (cont) Individual litter/fetal ocular histopathology findings

Dose Group	Control		Sodium Trifluoroacetate		
	1	2	3	4	
Dose (mg/kg/day)	0	180	375	750	

Group	Animal Number	Fetus Number	Sex	Histopathology findings
4F	0095	5	F	Structural disorganization, right eye, present Retinal folds, left eye, marked (partial correlate to fetal examination finding of bilateral retina multiple folds) Lens hemiation into anterior chamber, right eye, present Lens degeneration, right eye, severe Lens fragmented; fragments embedded in choroid/sclera, left eye, present (correlated to fetal examination finding of left lens absent)
		7	M	Structural disorganization, right eye, present Retinal folds, right eye, slight Lens degeneration, bilateral, marked Lens misshapen, left eye, present (correlated to fetal examination finding of left lens misshapen)

**7. REPORT SIGNATURE AND COMPLIANCE STATEMENT**

The pathologist's signature denotes that this report provides a true and accurate record of the results obtained and interpretation of those results. The histopathology evaluation and report were completed in accordance with Study plan-specified Good Laboratory Practice regulations.

  
  
Anatomic Pathologist

6<sup>th</sup> September 2021.  
Date

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001.

**Attachment 13.4      Historical control data**

Regulation (EC) No 1049/2001.

Document disclosed in repl to an applica

## Fetal examinations - major historical control data

Species/strain/source Rabbit/ New Zealand White  
 Necropsy date range Sept 2017 – Present  
 Number of studies 37  
 Study types Main

Group		8437242								HCD Range	
		Fetuses				Litters				Fetuses	Litters
Number Examined		1	2	3	4	1	2	3	4		
		150	158	173	140	18	21	24	23	5687	744
Head											
Visceral	Multiple folded retina	0	1	5	9	0	1	4	8	0-1	0-1
	Absent aqueous/vitreous humour	0	1	6	8	0	1	4	6	0-1	0-1
	Brain discrete area of amorphous tissue at position of optic nerve	0	0	1	0	0	0	1	0	0-0	0-0
	Retina ruptured into surrounding tissue	0	0	1	1	0	0	1	1	0-0	0-0
	Small/misshapen lens	0	0	1	1	0	0	1	1	0-1	0-1
	Absent lens	0	0	0	1	0	0	0	1	0-1	0-1
	Microphthalmia	0	1	1	1	0	1	1	1	0-1	0-1
	Narrow optic nerve	0	0	1	0	0	0	1	0	0-0	0-0
	Cleft palate	0	0	0	1	0	0	0	1	0-1	0-1

## Fetal examinations - major historical control data

Species/strain/source Rabbit/ New Zealand White  
 Necropsy date range Sept 2017 – Present  
 Number of studies 37  
 Study types Main

		8437242								HCD Range	
		Fetuses				Litters				Fetuses	Litters
		1	2	3	4	1	2	3	4		
Number Examined		150	158	173	140	18	21	24	23	5687	744
Cervical/Thoracic	Skeletal										
	Thoracic scoliosis	0	0	0	1	0	0	0	1	0-2	0-2
	Multiple cervical vertebral abnormalities	0	0	1	0	0	0	1	0	0-3	0-3
	Multiple thoracic vertebral/rib abnormalities	0	0	0	2	0	0	0	2	0-2	0-2
	Distorted rib cage	0	0	0	1	0	0	0	1	0-1	0-1
	Dorsoventral distortion of sternum	0	0	1	0	0	0	1	0	0-1	0-1
Visceral	Narrow ascending aorta/aortic arch	0	0	1	0	0	0	1	0	0-2	0-2
	Dilated ascending aorta/aortic arch	0	0	1	0	0	0	1	0	0-1	0-1
	Dilated/dorsally displaced pulmonary trunk	0	0	1	0	0	0	1	0	0-1	0-1
	Transposition of ascending aorta with pulmonary trunk	1	2	1	2	1	2	1	1	0-1	0-1
	Truncus arteriosus	0	1	0	0	0	1	0	0	0-1	0-1
	Membranous ventricular septal defect	0	1	1	0	0	1	1	0	0-2	0-1
	Muscular ventricular septal defect	1	0	0	1	1	0	0	1	0-2	0-2
	Double outlet ventricle(s)	0	1	1	0	0	1	1	0	0-0	0-0



## Fetal examinations - major historical control data

Species/strain/source Rabbit/ New Zealand White  
 Necropsy date range Sept 2017 – Present  
 Number of studies 37  
 Study types Main

Group Number Examined		8437242								HCD Range	
		Fetuses				Litters				Fetuses	Litters
		1 150	2 158	3 173	4 140	1 18	2 21	3 24	4 23	5687	744
Lumbar (and abdominal)/Sacral/Caudal Skeletal	Lumbar scoliosis	0	0	0	1	0	0	0	1	0-2	0-2
	Lumbar hemivertebra	0	0	1	1	0	0	1	1	0-1	0-1
	Fused/partially fused/misshapen disorganised sacral/caudal vertebrae	0	0	2	1	0	0	2	1	0-2	0-1
	Brachyury	0	0	1	1	0	0	1	1	0-2	0-1
External	Gastroschisis	0	0	1	1	0	0	1	1	0-1	0-1
	Omphalocele	0	0	2	0	0	0	2	0	0-2	0-2
Visceral	Displaced kidney(s)	0	1	0	0	0	1	0	0	0-0	0-0
	Fused/caudally displaced kidney(s)	0	0	0	1	0	0	0	1	0-0	0-0
	Absent kidney(s)	0	0	1	0	0	0	1	0	0-1	0-1
	Absent ureter(s)	0	0	1	0	0	0	1	0	0-1	0-1

## Fetal examinations - Visceral historical control data

Species/strain/source Rabbit/ New Zealand White  
 Necropsy date range Sept 2017 – Present  
 Number of studies 37  
 Study types Main

		8437242								HCD Range	
Group		Fetuses				Litters				Fetuses	Litters
		1	2	3	4	1	2	3	4		
Number Examined		150	158	173	140	18	21	24	23	5830	764
Number of Heads Examined at Detailed Visceral Examination		78	85	92	73	18	21	22	22	2600	762
Head abnormalities (fixed visceral)											
Eyes	folded retina	0	1	0	3	0	1	0	3	0-1	0-1
	haemorrhage aqueous/vitreous humour	0	0	1	2	0	0	1	2	0-0	0-0
	haemorrhage hardierian gland	0	0	1	1	0	0	1	1	0-0	0-0
	dilated orbital sinus	0	0	0	2	0	0	0	2	0-2	0-2
	small eye(s)	0	0	2	3	0	0	2	3	0-0	0-0
	small lens	0	0	1	0	0	0	1	0	0-0	0-0
Brain											
	dilated interventricular foramen	0	1	0	0	0	1	0	0	0-1	0-1
Necropsy observations (fresh visceral)											
Eye(s)	small	0	1	4	2	0	1	4	2	0-0	0-0
Lungs	absent accessory lobe	0	0	6	0	0	0	2	0	0-2	0-2
Ovary(s)	cyst(s)	0	0	0	1	0	0	0	1	0-1	0-1
Ureter(s)	dilated	0	0	0	1	0	0	0	1	0-0	0-0

## Fetal examinations - Visceral historical control data

Species/strain/source Rabbit/ New Zealand White [REDACTED]  
 Necropsy date range Sept 2017 – Present  
 Number of studies 37  
 Study types Main

		8437242								HCD Range	
Group		Fetuses				Litters				Fetuses	Litters
		1	2	3	4	1	2	3	4		
Number Examined		150	158	173	140	18	21	24	23	5830	764
Number of Heads Examined at Detailed Visceral Examination		78	85	92	73	18	21	22	22	2600	762
Necropsy observations (external)											
Limb(s)	flexure forepaw(s)	0	0	3	4	0	0	3	3	0-4	0-3
Tail	hooked tip	0	0	1	0	0	0	1	0	0-2	0-1
	shortened	0	0	1	0	0	0	1	0	0-0	0-0

## Fetal examinations - Skeletal historical control data

Species/strain/source Rabbit/ New Zealand White

Necropsy date range Sept 2017 – Present

Number of studies 37

Study types Main

		8437242								HCD Range	
Group		Fetuses				Litters				Fetuses	Litters
		1	2	3	4	1	2	3	4		
Number Examined		150	158	173	140	18	21	24	23	5836	765
Number Intact		72	73	81	67	18	21	24	23	3222	765
Minor skeletal abnormalities											
Cranial	unossified area(s)	0	1	1	1	0	1	1	1	0-5	0-4
	absent supraorbital notch(es)	0	0	0	1	0	0	0	1	0-1	0-1
	bent cornu(a) of hyoid	0	0	1	0	0	0	1	0	0-6	0-5
Vertebral element abnormalities	cervical	0	0	4	3	0	0	4	3	2-2	2-2
	thoracic	0	0	3	4	0	0	3	3	0-5	0-4
	lumbar	0	0	1	1	0	0	1	1	0-2	0-2
	sacral/caudal	0	0	2	1	0	0	2	1	0-2	0-2
Ribs	misaligned	0	0	1	0	0	0	1	0	0-1	0-1
	nodulated	0	0	1	0	0	0	1	0	0-1	0-1
	branched with additional costal cartilage	0	0	2	1	0	0	2	1	0-2	0-2
	fused/partially fused	0	1	4	8	0	1	3	6	0-4	0-3
	interrupted ossification 1st	0	0	3	0	0	0	1	0	0-0	0-0
	medially thickened/kinked	0	0	0	1	0	0	0	1	0-1	0-1

## Fetal examinations - Skeletal historical control data

Species/strain/source Rabbit/ New Zealand White

Necropsy date range Sept 2017 – Present

Number of studies 37

Study types Main

		8437242								HCD Range	
		Fetuses				Litters				Fetuses	Litters
		1	2	3	4	1	2	3	4		
Group		150	158	173	140	18	21	24	23	5836	765
Number Examined		72	73	81	67	18	21	24	23	3222	765
Number Intact											
Minor skeletal abnormalities											
Sternebrae	hemisternebra	0	0	1	2	0	0	1	1	0-1	0-1
	bipartite ossified	0	0	0	1	0	0	0	1	0-1	0-1
	misaligned hemicentres	1	0	5	5	1	0	5	3	0-3	0-3
	misshapen	0	0	1	1	0	0	1	1	0-1	0-1
Costal cartilage	fused/partially fused	0	0	0	3	0	0	0	3	0-2	0-2
	misaligned	1	0	5	6	1	0	5	3	0-3	0-3
Appendicular	long acromion/metacromion process	0	0	1	0	0	0	1	0	0-1	0-1
Rib and vertebral configuration											
Cervical rib	full supernumerary	0	0	0	1	0	0	0	1	0-2	0-2
Thoracolumbar vertebrae	18	0	0	1	2	0	0	1	2	0-3	0-3
	20	5	11	18	11	3	8	11	6	0-20	0-9

## Fetal examinations - Skeletal historical control data

Species/strain/source Rabbit/ New Zealand White  
 Necropsy date range Sept 2017 – Present  
 Number of studies 37  
 Study types Main

		8437242								HCD Range	
		Fetuses				Litters				Fetuses	Litters
		1	2	3	4	1	2	3	4		
Group		150	158	173	140	18	21	24	23	5836	765
Number Examined		72	73	81	67	18	21	24	23	3222	765
Number Intact											
Delayed/incomplete ossification/unossified											
Cranial	large posterior fontanelle	0	0	1	2	0	0	1	2	0-5	0-4
	large lacrimal fossa	0	1	0	0	0	1	0	0	0-1	0-1
Sternebrae	5th	17	47	55	39	12	17	17	14	7-62	4-24
Vertebrae	cervical (includes odontoid process)	1	1	8	8	1	1	6	6	0-9	0-5
	thoracic	2	1	7	11	2	1	6	6	0-5	0-4
	sacral/caudal	0	0	1	0	0	0	1	0	0-4	0-4
Appendicular	epiphyses	1	6	22	18	1	4	10	8	1-23	1-8
	metacarpals/phalanges	3	4	13	14	2	3	8	9	1-15	1-7
	metatarsals/ phalanges	0	0	0	3	0	0	0	2	0-7	0-7
Increased ossification											
Cranial	partially fused jugal to maxilla	0	0	0	2	0	0	0	1	0-4	0-3

**Attachment 13.5      Study plan amendment**

Regulation (EC) No 1049/2001.

Document disclosed in repl to an applica



## Study Plan Amendment 6

# Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration

**Study Number:**

8437242

**Sponsor Name:**

Bayer AG and Rhodia Operations - Solvay

**Version ID:**

Final Study Plan Amendment 6

**Issue Date:**

16 June 2021

**Study Director:**



**Test Facility:**





## Study Plan – Log of Revisions

<b>Final Study Plan</b>	<b>Issue date: 16 June 2020</b>
<b>Amendment No. 6</b>	<b>Issue date: 16 June 2021</b>
2.2	Reporting schedule updated
8.3.1	Fetus no. 6 from Group 2 litter no. 40 was observed at necropsy with small eyes. However, this fetus was subject to whole body skeletal examination and as such no bouins sections are available for histopathological examination; reference to this fetus is deleted.
<b>Amendment No. 5</b>	<b>Issue date: 11 June 2021</b>
2.2, 8.3.1 and 8.3.2	<p>Bouins sections from four Control animals were subject to histopathological examination. The tissue from all four fetuses had representative tissue morphology and architecture and good staining characteristics. Based on the condition of these Control sections, they were considered suitable to support microscopic examination of the abnormal eyes in the treated groups.</p> <p>The Sponsor has requested that histopathology is performed on all fetuses with eye abnormalities (multiple folded retina, absent humour, microphthalmia, retina ruptured). The objective of the additional examination is to try and understand the nature/aetiology of the malformations. The multiple folded retina and the absence of humor are in most cases occurring in the same fetuses and histopathological examination may determine whether the absence of humor is the principal finding causing multiple folded retina or that the multiple folded retina results in the lack of humor.</p> <p>Sections updated accordingly.</p>
<b>Amendment No. 4</b>	<b>Issue date: 12 May 2021</b>
8.3.1 and 8.3.2	<p>The Sponsor has asked whether the fetal eye abnormalities can undergo histopathological examination. In order to assess feasibility eye sections from four Control fetuses (four litters) will be subject to histopathological examination; study plan updated accordingly.</p> <p>If the sections prove to be suitable for microscopic examination a further amendment will be issued to initiate examination of the eye abnormalities.</p>
<b>Amendment No. 3</b>	<b>Issue date: 17 November 2020</b>
Page 1 and 16	Sponsor details are clarified and revised.

**Amendment No. 2      Issue date: 25 September 2020**

2.2 and 8.3      At the request of the Sponsor the livers retained from F0 females at scheduled termination on GD29 will be subject to histopathological examination; relevant sections updated accordingly.

**Amendment No. 1      Issue date: 07 August 2020**

Page 1, Section 16      A replacement Study Director is appointed because the original Study Director is commencing Maternity Leave.

Any changes to the study design after the date of this authorizing signature will be documented in further versions of the study plan as Study Plan Amendments. Modifications will be described in the above summary of changes, and within the body of the Study Plan Amendment any deleted statements are struck through and, with the exception of new sections, new statements are underlined and in bold. Any previous amendment changes are shown as clean text.

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001

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## 1. Introduction and Purpose

### 1.1 Purpose

Assessment of the influence of Sodium Trifluoroacetate on embryo-fetal survival and development when administered during the organogenesis and fetal growth phases of pregnancy in the New Zealand White rabbit.

### 1.2 Test System

New Zealand White rabbit (sexually mature, virgin), accepted by regulatory agencies, historical control data available.

### 1.3 Route of Administration

Oral Gavage, to simulate the conditions of possible human exposure.

### 1.4 Treatment Groups and Doses

Group	1	2	3	4
Compound	Control	Sodium Trifluoroacetate	Sodium Trifluoroacetate	Sodium Trifluoroacetate
Dose (mg/kg/day)	0	180	375	750

### 1.5 Rationale for Dose Level Selection

Dose levels for this study were chosen in conjunction with the Study Monitors based on the results of a preliminary embryo-fetal study in the New Zealand White rabbit with Sodium Trifluoroacetate in water at dose levels of 250, 500 or 750 (1000) mg/kg/day (Study Number YQ44HR).

In that study an initial dose at 1000 mg/kg/day resulted in four females found to be unsteady and/or underactive in their home cage. By Day 7 (following two doses at 1000 mg/kg/day) all females were unsteady and/or underactive with two females also observed to have impaired locomotion (limited use of limbs), and a further female shown to have rapid breathing, reduced body tone and flattened posture. Consequently, the decision was made to reduce this dose level to 750 mg/kg/day for the remainder of the treatment period; at 750 mg/kg/day these signs improved, until no longer present by Day 12. For females treated at 250 or 500 mg/kg/day, isolated incidences of unsteady gait and decreased activity were similarly observed however to a much lesser magnitude and as such were not considered to be adverse. Body weight and food consumption at doses up to and including 750 mg/kg/day were not adversely affected. Macroscopic examination revealed some abnormalities of the lungs and heart amongst fetuses from litters of females treated with Sodium Trifluoroacetate, however these were considered to be either non-adverse or, the incidence of the findings were within background Control data ranges. As such, a high dose level of 750 mg/kg/day was considered to be a suitable high dose for this main embryo-fetal development study. The low and intermediate dose levels of 180 and 375 mg/kg/day (respectively) have been selected to allow evaluation of any dose related trends.

## 2. Proposed Schedule

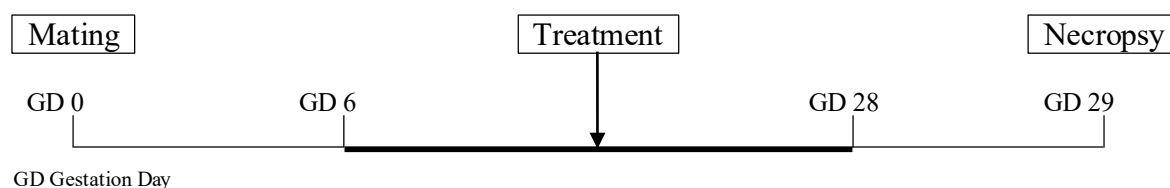
### 2.1 Duration of Treatment

Females Days 6 to 28 after mating.

### 2.2 Scheduled Time Plan

Experimental start date (animal arrival)	23 June 2020
Mating at suppliers (GD0)	22 – 25 June 2020
Animal arrival (GD1)	23 – 26 June 2020
Treatment to commence	28 June – 01 July 2020
Necropsy to commence	21 – 24 July 2020
Fetal pathology report due	28 August 2020
Histopathology report – Maternal	06 November 2020
Histopathology report – Maternal and Fetal	<b><u>14 July 2021</u></b> To be included
Experimental completion date	<b><u>July 2021</u></b> To be included
Audited Draft report to be issued	07 December 2020
Revised Draft report to be issued	<b><u>20 August 2021</u></b> To be included
Final report to be issued	<b><u>01 December 2021</u></b> 01 March 2021 (estimated)

#### 2.2.1 Study Design



### **3. Regulatory Information**

#### **3.1 Good Laboratory Practice**

The study will be conducted in compliance with principles of Good Laboratory Practice Standards as set forth in:

- 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 2004/10/EC

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

#### **3.2 Animal Welfare**

The in-life experimental procedures to be undertaken during the course of this study are subject to the provisions of:

United Kingdom Animals (Scientific Procedures) Act 1986 Amendment Regulations 2012 (the Act).

The number of animals used will be the minimum that is consistent with scientific integrity and regulatory acceptability, consideration having been given to the welfare of individual animals in terms of the number and extent of procedures to be carried out on each animal.

#### **3.3 Regulatory Testing Guidelines**

The study will be performed in accordance with the following guideline:

Current EU, OECD 414 and EPA (OPPTS 870.3700) Guidelines.

Japanese Ministry of Agriculture, Forestry and Fisheries, Test Data for Registration of Agricultural Chemicals, 12 Nohsan No. 8147, Agricultural Production Bureau, November 24, 2000.

#### 4. Test Item and Supporting Information

Test item	Sodium Trifluoroacetate.
Test item identity (including alternative names)	Trifluoroacetate (TFA)
Action of test item	Industrial chemical Metabolite
Batch number	2019052304
CAS No.	2923-18-4
Storage conditions	At ambient temperature (15 to 25 °C)
Certificate of analysis (or other appropriate documentation)	Composition and/or appropriate characteristics.
Purity	99.9 %
Correction	Not required, will be used as supplied
Appearance	White solid
Stability/expiry	01 May 2021 (two years after analysis/issue date of Certificate of Analysis)



## 5. Test Item Preparation, Analysis

### 5.1 Formulation

Treatment	Formulated concentration*
Group 1	
Group 2	Sodium Trifluoroacetate; 18 mg/mL.
Group 3	Sodium Trifluoroacetate; 37.5 mg/mL.
Group 4	Sodium Trifluoroacetate; 75 mg/mL.

\* As supplied

Dose Volume 10 ml/kg/day

Validated concentration range 2 mg/mL to 200 mg/mL.

Validation status GLP Study Reference [REDACTED] No. [LC59WX](#).

Correction factor None.

Vehicle Water.

Method of preparation The formulation procedure will be documented in the study data and included in the final report.

The required amount of test item will be ground in a mortar using a pestle and mixed with some vehicle to form a paste. Further amounts of vehicle will be gradually added and mixed to produce a smooth, pourable suspension. The suspension will be quantitatively transferred and diluted to volume and finally mixed using a high-shear mixer.

Frequency of preparation Weekly, and may be prepared in advance of the first day of dosing.

The homogeneity and stability of formulations during storage were determined as part of another study, [REDACTED] No. [LC59WX](#). In that study, formulations in the range 2 to 200 mg/mL were determined to be stable for

- 24 hours at ambient temperature (15 to 25°C)
- 15 days when stored refrigerated (2 to 8°C)

Expected appearance of formulation Clear colorless solution.

Storage and stability of formulations

	Storage conditions	Stability
Dose formulations and Liquid samples for achieved concentration analysis	Ambient (15 to 25°C) Refrigerated (2 to 8°C)	24 hours 15 Days

## 5.2 Formulation Analysis

Liquid formulation

At specified intervals during treatment, the test formulations will be analyzed for achieved concentration of the test item. Analysis for achieved concentration will be performed and reported according to GLP regulations as part of this current study.

Analysis

The method of analysis will be documented in the study data and a summary included in the final report.

The analytical method will involve the dilution of the test formulations with a suitable solvent followed by chromatographic assay.

The formulated samples will be analyzed using a method validated with respect to the determination of the specificity of analysis, limits of detection, linearity of detector response, repeatability, method accuracy and precision.

### Achieved concentration

Assay sampling

Test formulations will be analyzed for the occasions given below.

Sample storage

Stored samples will be retained refrigerated should any result require confirmation.

Sample Disposal

Samples (contingency/residual) will be disposed of once satisfactory results are obtained.

### Table of required achieved concentration samples

Occasion	Groups	Pharmacy		Dose Formulation Analysis	
		Sample volume (mL)	Samples taken	Samples assayed	Samples stored
First prep	All	10.0	1 (middle)	In duplicate	Remainder
Last prep	All	10.0	1 (middle)	In duplicate	Remainder

## 6. Test System

### 6.1 Animal Information

#### 6.1.1 Animals

Species	Rabbit.
Strain	New Zealand White.
Age ordered	18 – 22 weeks on arrival
Weight range ordered	2.5-4.5 kg
Number of animals ordered	96 time-mated females in total.
Supplier	

Animals will be supplied time mated to identified males of the same strain and source. Supplied in four deliveries on Day 1 after mating.

#### 6.1.2 Acclimatization

Duration	Minimum of 4 days from arrival on GD1 to the start of treatment on GD6
Husbandry conditions	Refer to Section 6.2
Animals that fail to acclimatize	Initially moistened diet and/or water bowls will be offered. Veterinary surgeon available to examine animals as necessary.

If necessary, administration of any veterinary preparations (such as a probiotic preparation for the maintenance of the rabbit gastrointestinal tract (for example 'Biolaxis') and/or metoclopramide), or other significant treatment may be administered; this will be documented in the raw data and included in the final report.

### 6.1.3 Mating

Method Natural mating with New Zealand White bucks of established fertility at the supplier's facility. Males and females not closely related. After mating, each female will be injected intravenously with 25 i.u. lutenising hormone.

Day 0 of gestation (GD0) Day of mating.

Delivery to [REDACTED] Day 1 after mating (GD1)

### 6.1.4 Allocation to Treatment Groups

Allocation On day of arrival.

Method Randomly to group and cage position. Females mated on any one day evenly distributed amongst the groups.

Possible exceptions Allocation will be controlled to prevent any stock male from providing more than 1 mated female in each treated group and to prevent more than 1 sibling female in each group, where possible.

Cage distribution Arrangement designed to minimize environmental variables.

### 6.1.5 Identification

Numbering Unique for each animal.

Method Microchip.

Cage labels Uniquely identifying the occupant.

## 6.2 Animals – Housing, Diet and Water Supply, and Environmental Enrichment

### 6.2.1 Environmental Control

Multispecies facility: Limited access – to minimize entry of external biological and chemical agents.

Air supply: Filtered, not recirculated.

Temperature: Monitored and maintained within the range of 15-21°C.

Relative humidity: Monitored and maintained within the range of 45-70%.

Excursions outside these ranges documented in the study data.

Lighting:	14 hours light : 10 hours dark.
Alarm systems:	Activated on ventilation failure and when temperature/humidity limits exceeded.
Electricity supply:	Public supply with automatic stand-by generators.

### 6.2.2 Animal Accommodation

One animal per cage. Females will be housed singly to permit collection of food consumption data individually for presumed pregnant females.

Suspended cages fitted with perforated floor panels and a raised area to allow the rabbits to lie, sit and easily move underneath are mounted in batteries. Undertray lined with absorbent paper which is changed at least 3 times a week. Precise details of caging will be included in the final report.

### 6.2.3 Diet and Water Supply

#### Diet supply

Diet name	Teklad 2930.
Diet type	Pelleted diet.
Availability	200 g/animal/day
Certification	A certificate of analysis will be available for each batch of diet used on the study. The diet will be analyzed for various nutritional components and chemical and microbiological contaminants.

This diet contains no added antibiotic or other chemotherapeutic or prophylactic agents.

Should an individual show a significant non-treatment related reduced food consumption, moistened diet (50 g pelleted diet moistened with 50 mL of water) will be offered; the consumption will be recorded.

In addition, a hay supplement will be given on a daily basis and a small amount of chopped fresh vegetables will be given twice weekly; consumption will be monitored qualitatively but not quantitatively.

#### Water supply

Supply	Potable water from the public supply.
Availability	Non-restricted via polycarbonate bottles with sipper tubes. Water bowls may also be used in addition to a bottle; this will be documented in the raw data.

Certification                      Certificates of analysis are routinely received from the supplier.

### **Environmental enrichment**

Each animal will have access to an Aspen chew block (soft white untreated wood block) at all times. Each block will be replaced as necessary. A stainless steel key ring is attached to the cage to provide further environmental enrichment.

From Day 20 after mating females will receive cage paper to allow expression of nesting behavior, paper will be replaced as necessary.

### **6.2.4 Contaminants Assay**

It is the Sponsor's responsibility to advise [REDACTED] of any specific contaminants likely to prejudice the outcome of the study. Analyses for such contaminants may be performed if requested by the Sponsor.

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### 6.3 Dose Administration

#### 6.3.1 Identity of Treatment Groups

Group	Treatment	Dose # mg/kg/day	Number of animals	Animal numbers
1	Control	0	24	1-24
2	Sodium Trifluoroacetate	180	24	25-48
3	Sodium Trifluoroacetate	375	24	49-72
4	Sodium Trifluoroacetate	750	24	73-96

# Expressed in terms of material as supplied

#### 6.3.2 Administration

Route	Oral gavage.
Treated at	Constant doses in mg/kg/day.
Volume dose	10 mL/kg/day.
Individual dose volume	Calculated from the most recently recorded scheduled body weight.
Controls (Group 1)	Vehicle at the same volume dose as treated groups.
Frequency	Once daily, at approximately the same time each day.
Sequence	Groups dosed in ascending order.
Formulation	<p>A daily record of the usage of formulation will be maintained based on weights before and after dosing. The difference between actual and expected usage will be monitored as a check of correct administration.</p> <p>Formulations are stirred using a magnetic stirrer before and throughout the dosing procedure. Alternative methods may be used; these will be documented in the study records.</p>
Storage of formulation	Refrigerated (2 to 8 °C).
Expected appearance of formulation	Clear colorless solution.

## 7. Serial Observations

### 7.1 General Observations/Measurements

#### 7.1.1 Clinical Observations

Animals and their cages	Visually inspected at least twice daily for evidence of reaction to treatment or ill-health.  Only signs which are indicative of ill-health will be routinely recorded as part of this twice daily health check. Those signs which are not indicative of ill-health will routinely be recorded, as appropriate, as part of the detailed physical examination check or the scheduled pre and post dose checks.
Deviations from normal recorded at the time in respect of	Nature and severity. Date and time of onset. Duration and progress of the observed condition.
Physical examination	Days 1, 6, 12, 18, 24 and 29 after mating.

In addition, detailed observations will be performed daily during the treatment period to establish and confirm a pattern of signs in association with dosing at the following times during the day:

Dose observations	<ul style="list-style-type: none"> <li>• Pre-dose observation</li> <li>• 1 to 2 hours after completion of dosing</li> <li>• As late as possible in the working day.</li> </ul>
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The above schedule will be amended, as necessary, in the light of signs observed.

#### 7.1.2 Mortality

Premature sacrifice	Animals may be killed for reasons of animal welfare or after exhibiting pregnancy loss.
Animals found dead, or killed for reasons of animal welfare	A necropsy is performed as soon as possible.

#### 7.1.3 Body Weight

All adult animals	Days 1, 3, 6-29 after mating.
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#### 7.1.4 Food Consumption

All adult animals	Daily from Day 2 after mating to termination.
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## 8.1 Necropsy

Scheduled kill      Day 29 after mating.

Females that exhibit pregnancy loss      Same day that pregnancy loss is detected.

All animals                      Intravenous injection of sodium pentobarbitone.

Fetuses                      Subcutaneous injection of sodium pentobarbitone.

Sequence of kill	To allow satisfactory inter-group comparison.
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All adult animals will be subject to a complete macroscopic examination. Any abnormal tissue will be sampled as appropriate and retained in appropriate fixative

For females surviving to Day 29 after mating only, the following will be recorded:

Uterus                      Gravid uterine weight (including cervix and ovaries).

The following will be recorded for all animals (including those prematurely sacrificed, where possible):

Each ovary/uterine horn

Number of: Corpora lutea.  
Implantation sites.  
Resorption sites (assessed as early or late).  
Fetuses (live and dead).

Fetuses and placentae dissected from the uterus and weighed individually.

Females exhibiting pregnancy loss	Expelled uterine contents will be identified and examined, as appropriate.
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### 8.1.5 Fetal Examination

All live fetuses      External examination.  
Internal examination of neck and thoracic and abdominal cavities.  
Sex recorded.  
Individual identification within litter.

Approximately 50% of the fetuses in each litter will be decapitated and the heads initially fixed in Bouin's fluid.

Remaining fetuses and torsos will be eviscerated and fixed in Industrial Methylated Spirit.

### 8.1.6 Fetal Processing

Bouin's fixed fetal heads      Subject to free-hand serial sectioning.

Industrial Methylated Spirit fixed torsos and remaining fetuses      Processed and stained with Alizarin Red.

### 8.1.7 Organs Weighed and Fixed

The gravid uterine weight will be recorded, and any abnormal tissues will be retained in appropriate fixative.

The Liver will be weighed and retained in appropriate fixative.

Any target organs identified will be weighed and retained in appropriate fixative, if requested by the Sponsor; any such requirement will be documented in an amendment to study plan.

Organ weights are not routinely recorded for animals killed or dying prematurely; organ weights will be recorded for groups terminated prematurely.

## 8.2 Pathology

### 8.2.1 Detailed Fetal Examination

Fetal heads subject to serial sectioning (Bouin's fixed)      Serial sections examined for abnormalities.

Torsos and fetuses stained with Alizarin Red      Examined for skeletal development and abnormalities.

### 8.3 Histology and Light Microscopy

#### 8.3.1 Histology

##### Processing to slide

Liver

All females at scheduled termination on GD29

Fetal eye section

Initially four Control fetuses (four litters) will be processed to assess suitability. One of the two main eye sections from the bouin's fixed fetal heads that were subject to free-hand serial sectioning will be selected from the following fetuses/litters:

- Litter no. 3 – Fetus no. 7
- Litter no. 5 – Fetus no. 1
- Litter no. 9 – Fetus no. 3
- Litter no. 16 – Fetus no. 1

All fetuses with eye abnormalities identified either at necropsy or following examination of bouin's fixed serial sections from groups that received Sodium Trifluoroacetate.

Group	Litter no	Fetus no
2	26	1
	40	6
3	49	3
	57	5
	63	3
	64	1
		5
		11
	66	1
4	70	3
	73	1
		3
	76	2
	82	3
	87	1
	88	7
	91	1
		3
	92	7
	95	5
		7
Total available		20 24

##### Staining

Routine staining

4-5 µm sections stained with haematoxylin and eosin.

Special staining

None scheduled.

### 8.3.2 Light Microscopy

Category	Animals	Tissues
Terminal sacrifice	All adult females at scheduled termination on GD29	Liver
	Four Control fetuses	Fetal eye section
	<u>All fetuses from treated groups with macroscopic eye abnormalities</u>	<u>Fetal eye section</u>

Peer review      Carried out by a reviewing pathologist to internationally accepted standards.

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## 9. Data Evaluation

### 9.1 Data Processing

Where appropriate, group mean values, each with standard deviation (SD), will be calculated from individual data; restricted to females/litters with live young at Day 29 after mating.

#### Treatment of data

Adjusted maternal body weight      Calculated from body weight on Day 29 after mating minus gravid uterine weight.

Litter data

Pre-implantation loss      
$$\frac{(\text{Number corpora lutea} - \text{Number implantations})}{\text{Number corpora lutea}} \times 100$$

Where the total number of implantations exceeds corpora lutea pre-implantation loss is taken as 0%.

Post implantation loss      
$$\frac{(\text{Number implantations} - \text{Number live fetuses})}{\text{Number implantations}} \times 100$$

Findings from external, visceral and skeletal examination of fetuses will be presented as an appendix of individual observations and tabulated as group incidences of fetuses and litters affected. Totals affected are routinely recorded for major and minor abnormalities.

Observations categorized as:

Major abnormalities: normally rare, definitely detrimental to normal subsequent development, possibly lethal, e.g. partially open eyelids, absent kidney/ureter for rabbits.

Minor abnormalities: minor differences from normal that are detected relatively frequently considered to have little detrimental effect and may be a transient stage in development, e.g. bipartite centrum, dilated ureter.

Variants: alternative structures or stages of development occurring regularly in the control population, e.g. number of ribs and thoracolumbar vertebra, incomplete ossification of 5th and 6th sternbrae,

Findings from the initial necropsy examinations are followed up in the subsequent visceral and/or skeletal examinations and are included in the listing.

Historical Control data will be routinely supplied for selected observations where this information is considered to assist interpretation of study data, and will normally include both fetal and litter incidences.

## 9.2 Statistical Analysis

### Data-types

The following data types will be analyzed at each timepoint separately, where required, in support of interpretation:-

body weight, using absolute weights and gains over appropriate study periods.  
gravid uterine weight and adjusted body weight.  
food consumption, over appropriate study periods.  
organ weights, either absolute or adjusted for terminal body weight where appropriate.  
litter size and survival indices.  
fetal, placental and litter weight.

### Methods

For categorical data, the proportion of animals will be analyzed for each treated group (as appropriate) versus the control group.

For continuous data, Bartlett's test will first be applied to test the homogeneity of variance between the groups. Using tests dependent on the outcome of Bartlett's test, treated groups will then be compared with the control group, incorporating adjustment for multiple comparisons where necessary.

Under the advice of the Associate Director, Global Statistics, or other qualified statistician, alternative or additional methods may be carried out if deemed appropriate following data review. Details will be included in the study report.

## 10. Major Computerized Systems

The computer systems used may include (but not be limited to) those listed below:

Liberate:	In-house system used for reporting in-life, necropsy and statistics
Pristima:	Pharmacy test item management, in-life and necropsy data collection
Quasar:	In-house statistical analysis
Sample Registry System:	Dose Formulation Analysis data, Sample tracking
SAS:	Statistical evaluation
StarTox:	In-house statistical analysis
Waters Empower:	Dose Formulation Analysis

Computer systems used by [REDACTED] will be documented in the [REDACTED] report.

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## 11. Quality Assurance

The [REDACTED] GLP Quality Assurance Unit (QAU) will perform authorised Study Plan verifications, inspections of procedures, data and draft report audits for activities performed at the Test Facility according to their established standard operating procedures.

QA findings will be reported to the Study Director and Test Facility Management promptly on completion of each action, except for process based inspections which will be reported to appropriate Test Facility Management with the Study Director being informed of any related findings.

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## 12. Study Plan Amendment and Deviation

Any intended change to the study plan will result in an amendment to study plan approved by the Study Director and the Sponsor. Modifications will be described in the summary of changes, and within the body of the Study Plan Amendment any deleted statements are struck through and new statements are underlined and in bold. Amendments will be distributed to all recipients of the study plan.

Deviations (unplanned changes) from the study plan and study plan amendment will be documented and acknowledged by the Study Director.

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### 13. Reporting

Study progress	Periodic verbal and written updates on study progress will be provided by the Study Director. Routine synopsis reports will be sent as considered appropriate during, and at termination of, the in-life phase.
Draft Report	<p>A GLP compliant report will be prepared. An audited draft report, in [REDACTED] report format will be provided to the Sponsor for their review. The Draft report will be provided electronically in PDF (non-hyperlinked) format. In addition, an MS Word copy of the text will also be provided electronically at Sponsor request.</p> <p>After receipt and review of the Sponsor's comments, appropriate changes will be made and revisions provided to the Sponsor.</p>
Final Report	<p>Once authorized by the Sponsor, the audited, signed final report will be issued.</p> <p>The Final report will be provided electronically in eCTD compliant fully hyperlinked PDF format. A Word file with the text of the report can be provided at Sponsor request. No paper version will be supplied to the Sponsor unless specifically requested and at additional cost. Paper reports, if requested, will be supplied on A4 size paper.</p> <p>Any additions or corrections to a signed, authorized final report will be documented as a formal addendum/amendment to the final report.</p> <p>In the absence of ongoing communications and after notification in writing to the Sponsor, [REDACTED] reserves the right to finalize, sign and issue the Final report from this study six months after the issue of the draft. Any subsequent requests for modifications, corrections or additions to the Final Report will be the subject of a formal report amendment (or new study, as appropriate) and will be subject to additional cost.</p>

## 14. Archiving

Records and documentation relating to this study (including electronic records) will be maintained in the archives of [REDACTED] for a period of one year from the issue of the final report. This will include raw data and specimens that support the reconstruction of the study. 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.

In the 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 a copy of the study plan, final report and any amendments indefinitely.

Document disclosed in reply to an application for access to documents under Regulation (EC) No 1049/2001

## 15. References

Study Number [LC59WX](#)

Sodium Trifluoroacetate: Validation of an Analytical Method and Formulation Accuracy and Stability in Purified Water

Study Number [YQ44HR](#)

Preliminary Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration

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## 16. Contact Details/Shipping Addresses

In temporary absence of the Study Director, routine duties and technical questions will be attended to by the alternative [REDACTED] study contact.

### Co – Sponsors

Bayer AG  
Crop Science Division  
Alfred-Nobel-Straße 50  
40789 Monheim  
Germany

Rhodia Operations  
25, rue de Clichy  
Paris 75009  
France

### Study Monitors

Mobile: [REDACTED]  
Email: [REDACTED]

Tel: [REDACTED]  
Mobile: [REDACTED]  
Email: [REDACTED]

### Test facility (Primary Location)

[REDACTED]

Building number for live phase: 5

### Alternate location

[REDACTED]

### Location of specific tasks

[REDACTED]: Formulation analysis - Dose Formulation  
Analysis department

**Study Director** [REDACTED]  
**From 16 June 2020 until**  
**06 August 2020**

Tel: [REDACTED]

Mobile: [REDACTED]

Email: [REDACTED]

**Study Director**  
**From 07 August 2020**

Tel: [REDACTED]

Email: [REDACTED]

**[REDACTED] Toxicologist**

Tel: [REDACTED]

Email: [REDACTED]

**Lead QA Unit Head**

Tel: + [REDACTED]

Email: [REDACTED]

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## 17. Signatures

### Sodium Trifluoroacetate: Study for Effects on Embryo-Fetal Development in the New Zealand White Rabbit by Oral Gavage Administration

This final study plan amendment has been reviewed and approved by:

[Redacted Signature]  
Study Director  
[Redacted]

16 June 2021  
Date

[Redacted Signature]  
Study Monitor  
Bayer AG  
[Redacted]

16 June 2021  
Date

[Redacted Signature]  
Study Monitor  
Solvay Industrial Function - HSE  
[Redacted]

16 June 2021  
Date

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