Sanitized

STUDY REPORT

[redacted]

Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

DATE	5 October 2018
AUTHOR(S)	J.G. Theuns – van Vliet J.J. van Triel A.J. Kleinnijenhuis
SPONSOR	[redacted]
TRISKELION PROJECT NUMBER	[redacted]
TRISKELION STUDY CODE	[redacted]
SPONSOR STUDY CODE	[redacted]
GUIDELINE	OECD 421
STATUS	Final report
NUMBER OF PAGES	347

Statement of GLP compliance

I, the undersigned, hereby declare that this report constitutes a complete and accurate representation of the study and its results.

All study activities performed by Triskelion B.V. were carried out in compliance with the current OECD Principles of Good Laboratory Practice (GLP)[1]. The OECD principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Community, USA and Japan. Chemical analysis for the verification of the test substances [redacted] and [redacted] identity and properties were not performed under GLP conditions in this study.

Study director

J.G. Theuns – van Vliet

05 October 2018.
Date

[1] The most recent endorsement of compliance of the test facility with these principles is attached to the report as Annex 1

Quality Assurance Statement

I, the undersigned, hereby declare that this report provides an accurate record of the procedures employed and the results obtained in this study; all audits were reported to the respective study director and management on the dates indicated.

Phase	*	Start date of audit	Date of audit report
Authorised study plan	Yes	27 September 2017	27 September 2017
Authorised study plan amendment 1	Yes	27 April 2018	27 April 2018
Animal receipt	No	9 August 2017	9 August 2017
Animal allocation	No	10 November 2017	10 November 2017
Test substance analysis	Yes	30 October 2017	30 October 2017
Dosing	Yes	16 October 2017	16 October 2017
Dosing	Yes	17 October 2017	17 October 2017
Analytical inhalation techniques	Yes	16 October 2017	16 October 2017
Body weight	No	18 October 2017	18 October 2017
Clinical signs	No	20 November 2017	20 November 2017
Food consumption	No	24 October 2017	24 October 2017
Mating	No	9 October 2017	9 October 2017
Sexual maturation	No	24 October 2017	24 October 2017
Necropsy	No	10 November 2017	10 November 2017
Hormone analysis	Yes	3 January 2018	3 January 2018
Terminal blood collection	No	13 October 2017	13 October 2017
Histology	No	29 December 2017	29 December 2017
Pathology	No	30 August 2017	30 August 2017
Vaginal smears	No	11 October 2017	11 October 2017
Litter measurements	No	24 October 2017	24 October 2017
Draft report (annex 7) and study file	Yes	4 July 2018	16 July 2018
Draft report and study file	Yes	4 July 2018	25 July 2018
Draft report (annex 6) and study file	Yes	16 July 2018	2 August 2018
Final report	Yes	5 October 2018	5 October 2018

* Study plan, report and test substance related experimental phases are audited in a study-based manner. Other experimental phases are audited in a process-based manner. This column indicates whether or not the audit was of this particular study.

M.J.A. van Veldhuizen
Quality Assurance auditor

Date : 05 OCTOBER 2018

Contents

Statement of GLP compliance **2**

Quality Assurance Statement **3**

Contents **4**

Abbreviations **6**

Summary **7**

1 General **9**
1.1 Test facility 9
1.2 Responsible Personnel 9
1.3 Time schedule 9

2 Introduction **10**
2.1 Objective 10
2.2 Applicable guidelines 10
2.3 Animal welfare 10

3 Study plan and deviations **11**
3.1 Study plan 11
3.2 Deviations 11

4 Materials and methods **12**
4.1 Characterization of the test substance 12
4.2 Experimental design, groups and exposure levels 13
4.3 Characterization of the test system 14
4.4 Animal allocation 14
4.5 Identification 15
4.6 Animal husbandry 15
4.7 Exposure equipment 16
4.8 Generation of the test atmosphere 16
4.9 Monitoring of the exposure conditions 17
4.10 Observations, analyses and measurements 20

5 Results **26**
5.1 Analysis of the exposure conditions (Table 1) 26
5.2 Mortalities and clinical signs (Table 2, Appendix 1) 27
5.3 Body weights and body weight change (Tables 3 and 4, Appendix 2) 27
5.4 Food consumption (Table 5, Appendix 3) 27
5.5 Oestrous cyclicity (Table 6, Appendix 4) 28
5.6 Hormone analysis (Annex 7) 28
5.7 Parental necropsy observations 28

5.8 Fertility and reproductive performance (Table 11, 12, 13, Appendices 8 and 9) 29
5.9 Litter data and pup data (Tables 13 and 14, Appendix 10) 29

6 Discussion and conclusion 31

7 Documentation and retention of records, samples and specimens 33

8 References 34

Figure 35

Tables 37

Annexes 100

Appendices 174

Abbreviations

AGD	Ano Genital Distance
AWB	Animal Welfare Body
d	day
GD	Gestation Day
GLP	Good Laboratory Practice
LD	Lactation Day
N or n	Number of units (cages or animals)
N + ve	the number of positive observations
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
pc	Post-Coitum
PD	Paring Day
PM	Pre-Mating
PN or PND	Postnatal Day
QA	Quality Assurance
QAU	Quality Assurance Unit
S.d. or SD	Standard Deviation
SPF	specific pathogen free
T4	Thyroid hormone 4 (thyroxine hormone)
Pre-exposure	before exposure (morning)
Post-exposure	after exposure (afternoon)

Pairing date = date of placing male and female together
Mating date = date of copulation, positive sperm finding
Littering date = date of delivery

Pre-mating period	data are relative to the start of exposure
Gestation period	data are relative to the mating date
Lactation period	data are relative to the littering date

Summary

The objectives of this study were to provide data on the possible effects of [redacted] on general toxicity, reproductive performance and pup development. The test substance was administered by inhalation whole body exposure (6 hours/day) at target concentrations of 0 (control), 250, 750 and 1500 ppm during a premating period of 2 weeks (5 days/week, 10 exposure days in total), then daily during mating and post-mating up to sacrifice for the males. Females were exposed to the test atmospheres during a premating period of 2 weeks (5 days/week, 10 exposure days in total), during mating, gestation and lactation. Mated females were not exposed to the test substance between gestation day 19 and lactation day 4 in order to allow the females to litter. Daily exposure was resumed on lactation day 5 up to day 13 of lactation. The total number of exposure days was 31 days for males and 38-42 days for females.

The test atmospheres were stable over the course of the exposure period and the actual exposure concentrations were 250 ± 6 ppm, 748 ± 17 ppm, and 1498 ± 24 ppm [redacted] (mean ± SD) as determined by a total carbon analyzer. The concentration of [redacted] (2,2,3,3,4,4,4-heptafluorobutanenitrile), a 0.23% impurity in the [redacted] test substance was quantitated in exposure atmospheres using a GC/MS method. These results indicated that the quantity of [redacted] in each exposure level atmosphere was consistent with the expected 0.23% as indicated on the certificate of analysis where an overall mean atmospheric concentration of 0.22% [redacted] was determined. Thus, there was no selective enrichment of the impurity in the exposure atmospheres and the exposures were representative for the [redacted] test substance over the course of this study.

There were no test substance-related mortalities in this study. Daily clinical observations did reveal piloerection in the animals exposed to 1498 ppm [redacted] during the first three weeks of exposure and during the re-start of exposure during lactation. Test substance-related reductions in body weight were observed in male and female rats exposed to 1498 ppm and 748 ppm [redacted] which were associated with significant reductions in food consumption when compared to the air-exposed control group (0 ppm). The body weight reductions were considered adverse for females exposed to 1498 ppm as they were consistently > -10% different from the control group values. No effects on body weight and food consumption were observed in 250 ppm exposure group.

At necropsy a concentration dependent increase in mean relative lung weight was observed in males of all exposure levels and in females exposed to 1498 ppm [redacted] but were not considered adverse as no correlative changes in lung histopathology were noted. Histopathology showed a concentration-dependent degeneration of the nasal olfactory epithelium of levels 3, 4, 5, and 6 in male and female rats exposed to 1498 and 748 ppm. In the control group and the low concentration group no degeneration of the olfactory epithelium were observed.

The number of females showing a-cyclic oestrous cycles was increased at 1498 ppm [redacted] and correlates with the significant test substance-related reductions in body weight and food consumption in this group. Functional fertility as measured by the time to pregnancy, gestational length and the number of litters was not affected. Mean number of pups delivered was decreased in dams exposed to 1498 ppm.

There were no effects of the test substance on pup survival or pup development. There were no effects on hormone levels (T4) between the exposed groups and the control groups for adult males nor were there any effects noted in 13-day old male and female pups.

Conclusions:

Based upon adverse reductions in female body weights in the 1498 ppm exposure group as well as on the exposure-related histopathological changes in the nasal olfactory epithelium observed at 1498 ppm and 748 ppm [redacted], the No Observed Adverse Effect Concentration (NOAEC) for **general toxicity** was placed at **250 ppm**.

Although functional fertility was not affected, based on the increased number of females showing acyclic oestrous cycles and the lower mean number of pups per litter in the 1498 ppm [redacted] exposure group, the No Observed Adverse Effect Concentration (NOAEC) for **fertility** was placed at **748 ppm**.

In absence of effects on pup sex and survival, pup observations, AGD and nipple retention
The No Observed Adverse Effect Concentration (NOAEC) for **developmental toxicity** was placed at **1498 ppm** [redacted].

1 General

Sponsor: [redacted]

Monitor: [redacted]
Phone:
E-mail:

1.1 Test facility

Triskelion B.V.	www.triskelion.nl
Postal address:	P.O. Box 844 3700 AV Zeist The Netherlands
Location:	Utrechtseweg 48 3704 HE Zeist The Netherlands
Phone:	+31 88 866 2800

1.2 Responsible Personnel

Study director:	J.G. Theuns – van Vliet, M.Sc. Josianne.theuns@triskelion.nl Phone: +31 88 866 4354
Scientific contributor(s):	J.J. van Triel, M.Sc. (inhalation exposure) A.L. Menke, Ph.D. (study pathologist) A.J. Kleinnijenhuis Ph.D. (chemical analysis) G. van Duijn, Ph.D. (hormone analysis) J.P. Bruijntjes (pathology)

1.3 Time schedule

Arrival of the animals:	20 September 2017
Start of pre-treatment period:	29 September 2017
Start of exposure (premating period):	16 October 2017
Start of mating period:	30 October 2017
Necropsy:	20 November 2017 (males) 5 - 10 December 2017 (females and litters)

2 Introduction

2.1 Objective

The objectives of this study were to provide data on the possible effects of the test substance [redacted] on reproductive performance and development of pups by inhalation exposure during a premating period of 2 weeks, during mating and post-mating period up to at least 28 days in total for male rats and during a premating period of 2 weeks and during mating, gestation and lactation until (or shortly after) postnatal day 13 (PN 13) for female rats.

2.2 Applicable guidelines

This study was conducted in accordance with the OECD Guideline for the Testing of Chemicals 421; Reproduction/developmental toxicity screening test, adopted 29 July 2016.
With respect to the inhalation exposure, the study was conducted – as far as applicable – in accordance with OECD guideline 412 (Subacute Inhalation Toxicity: 28-Day Study, adopted 7 September 2009).

2.3 Animal welfare

The welfare of the animals was maintained in accordance with the general principles governing the use of animals in experiments of the European Communities (Directive 2010/63/EU) and Dutch legislation (The revised Experiments on Animals Act, 2014). This includes licensing of the project by the Central Committee on Animal Experimentation (project license 2016602) and approval of the study by the Triskelion Animal Welfare Body (AWB number TRIS-306).
To reduce the number of animals used for research, any remaining surplus animals were used for training purposes.

3 Study plan and deviations

3.1 Study plan

The study was conducted according to study plan [redacted] entitled ' Inhalation reproduction and developmental toxicity screening test with [redacted] in rats' and 1 amendment. The study plan was approved by the study director on 26 September 2017.

3.2 Deviations

The following deviations from the study plan occurred:

- Surplus animals were uniquely identified by an ear mark.
- Identification container label [redacted].
- Relative humidity was lower than intended for several days due to maintenance of the climate control system.
- Animal 23 (control group) was erroneously not exposed during one day in the study.
- Animal 59 (mid concentration) was sacrificed on lactation day 13 instead of lactation day 14.
- Animal 87 (high concentration) was considered not pregnant and was sacrificed on presumed gestation day 23 instead of 25.
- Food consumption from day 0-7 of gestation was not measured for female 75, as this animal was retrospectively declared mated.
- For 4 males in the 250 ppm group body weight was recorded additionally on day 2 of exposure.
- At arrival female animals were 10 weeks old and males were 9 weeks old.
- Definition of pup runts was calculated as 2 SD less weight than the mean of the control.
- Ancova/Anova & Dunnett was used as statistical test for T4 analysis.

These deviations were considered not to have affected the validity of the study.

4 Materials and methods

4.1 Characterization of the test substance

Name[1]	: [redacted]
Chemical name[1]	: 2,3,3,3-tetrafluoro-2-(trifluoromethyl)propanenitrile
Identification container label[1]	: [redacted]
Molecular formula[1]	: C_4F_7N
CAS Reg No.[1]	: 42532-60-5
Molecular weight[1]	: 195.04 g/mol
Melting point[1]	: -118°C
Boiling point[1]	: -4.7°C
Solubility in water[1]	: 0.272 mg/L at 20°C
Vapor pressure[1]	: 253300 Pa at 20°C
Hygroscopy[1]	: slight
Batch number[1]	: [redacted]
Appearance	: colorless gas
Purity[1]	: >98.95%
Storage conditions[1]	: Ambient temperature (15-25°C)
Quantity	: ~450 kg
Date of receipt	: 10 and 29 August 2017 (9 cylinders per shipment)
Expiration date[1]	: 31-03-2019
Supplier	: Sponsor
Triskelion dispense number	: 1701F4 (received Aug 10th), 170241 (received Aug 29th)

[1] Information provided by the sponsor

Impurity

Name[1]	: [redacted]
Chemical name[1]	: 2, 2, 3, 3, 4, 4, 4-heptafluorobutanenitrile
Identification container label[1]	: [redacted]
Molecular formula[1]	: C_4F_7N
CAS Reg No.[1]	: 375-00-8
Molecular weight[1]	: 195.04
Boiling point[1]	: 2-5 °C
Vapor pressure[1]	: 137895 Pa at 20°C
Hygroscopy[1]	: slight
Batch number[1]	: Synquest item #3137-2-04, lot 28500
Appearance	: colorless gas in lecture bottle
Purity[1]	: 99.3%
Storage conditions[1]	: Ambient temperature (15-25°C)
Quantity	: 23 g
Date of receipt	: 04 August 2017
Approved for use until[1]	: 12 June 2019
Supplier	: Sponsor
Triskelion dispense number	: 170207

[1] Information provided by the sponsor

The sponsor was responsible for the data concerning the characterization, storage conditions, any known hazards, or any specification details of the test substance. A Certificate of Analysis pertaining to the batch used in this study (as provided by the sponsor) is included in Annex 2 to the report.

Remaining test substance will be returned to the sponsor after completion of all studies with this material.

4.2 Experimental design, groups and exposure levels

The study comprised 4 groups of 12 male and 12 female animals each, three test groups exposed to different concentrations of the test substance and one control group exposed to clean air. The animals of the control group were handled in the same manner as those of the other groups, except for exposure to the test substance.

Concentrations were selected in consultation with the sponsor and based on the results of a 28-day study with the test substance in Sprague Dawley rats and a 14-day range finding study (Triskelion study [redacted]) in Wistar Han rats with the same concentrations (500, 1000 and 1500 ppm). In the 14-day range finding study, body weight data showed an exposure-related and concentration-dependent effect on male body weights at all exposure levels with 1000 and 1500 ppm demonstrating an -11.8% and -12.5% reduction from control values, respectively. Females in the ranged finding study demonstrated no effects on body weight. Based on the treatment-related effects in males, the following concentrations were selected for the current OECD 421 study.

The various groups are presented in the table below:

Group	Color code	Target concentration test substance (ppm)	Number of rats	
			♂♂	♀♀
1 Control	White	0	12	12
2 Low-concentration	Blue	250	12	12
3 Mid-concentration	Green	750	12	12
4 High-concentration	Red	1500	12	12

The test substance was administered by inhalation whole body exposure (6 hours/day) at target concentrations of 0 (control), 250, 750 and 1500 ppm during a premating period of 2 weeks (5 days/week, 10 exposure days in total), then daily during mating and post-mating up to sacrifice for the males.

Females were exposed to the test atmospheres during a premating period of 2 weeks (5 days/week, 10 exposure days in total), during mating, gestation and lactation. Mated females were not exposed to the test substance between gestation day 19 and lactation day 4 in order to allow the females to litter. Daily exposure was resumed on lactation day 5 up to day 13 of lactation. The total number of exposure days was 31 days for males and 38-42 days for females.

During fourteen days in the pre-treatment period, vaginal smears were made in every female rat (including surplus females) for monitoring the oestrous cycle.

Subsequently the exposure started. After a two-week premating period, each female was caged with one male from the same group. Animals were caged together until mating occurred.
Mating pairs were clearly identified. Every consecutive morning during the mating period, vaginal smears were made for determination of the presence of sperm. The day on which sperm was detected in the vaginal smear was considered as gestation day (GD) 0. Upon evidence of copulation the females were caged individually for the birth and rearing of their pups.

4.3 Characterization of the test system

The study was conducted with albino rats. The rat was used because this species is considered suitable for this type of study, and is usually required by regulatory agencies. Male and female Wistar Han IGS rats (Crl:WI(Han)) were obtained from a colony maintained under SPF-conditions at Charles River Deutschland, Sulzfeld, Germany. This rat strain was used because it is routinely used at the test facility for this type of studies and has been previously shown to be suitable for developmental and reproductive toxicity studies[2]. In the study, the female rats were about 10 weeks old and the male rats about 9 weeks old at arrival (corresponding to about 12(♀)/11(♂) weeks at the start of pre-treatment period and about 14(♀)/13(♂) weeks at the start of the treatment. The age difference between males and females was deliberate, to avoid mating of siblings. Body weight at allocation was within ±20% of the mean weight for each sex.

4.4 Animal allocation

Upon arrival, the animals were housed in quarantine and checked for overt signs of ill health and anomalies. During the quarantine period, serological investigation of the microbiological status was carried out in a few randomly chosen rats of the lot delivered. Upon satisfactory results the quarantine room was cleared for use as experimental room.
The rats were acclimatized to the laboratory conditions for at least 5 days. After acclimatization, the fourteen-day pre-treatment period was started (in which the rats are not yet treated). During this fourteen day period, daily vaginal smears were made in every female rat (including surplus females) for monitoring the oestrous cycle.
At the end of the pre-treatment period, the animals (males and females separately) were allocated to the various groups by computer randomization proportionately to body weight and taking into account the oestrous cyclicity of the females. Surplus animals were kept in the animal room as sentinel animals (or used in the study if necessary).
Remaining surplus animals were used for training purposes at the end of the in-life phase of the study.

---

[2] Campion, SN, Carvallo, RF, Chapin, RE, Nowland, WS, Beaucham, D, Jaomon, R, Koitz, R, Winton, TR, Cappon, GD, and Hurtt, ME. (2013) Comparative assessment of the timing of sexual maturation in male Wistar Han and Sprague-Dawley rats. *Reproductive Toxicology* **38:** 16-24.

4.5 Identification

The study was identified as Triskelion study number [redacted].
During the pre-treatment period, prior to randomization, all the rats were identified by a temporary tail mark. After allocation to the different treatment groups the individual animals were uniquely identified with a number that is programmed in a transponder which was subcutaneously implanted. During the study each group of rats was coded by a number and a color. Each cage was provided with a card showing the color code, the animal identification numbers, the group number and the study number.
Pups were individually identified within the litter by paw marks (tattoo). Surplus animals were individually identified by an ear mark.

4.6 Animal husbandry

4.6.1 Animal room

The animals were housed under conventional conditions in one animal room. No other test systems were housed in the same room during the study. The room was ventilated with about 10 air changes per hour and was targeted at a temperature of 20-24ºC and a relative humidity of 29.7-65%. Relative humidity was lower than intended for several days due to maintenance of the climate control system. Lighting was artificial with a sequence of 12 hours light and 12 hours dark.

4.6.2 Caging

During exposure, the animals were housed individually in the inhalation unit. After each exposure, the animals returned to their home cages. Animals were housed in Makrolon cages with a bedding of wood shavings (Lignocel, Rettenmaier & Söhne GmbH & Co, Rosenberg, Germany) and strips of paper (Enviro-dri, Shepherd Specialty Papers, Michigan, USA) and a wooden block (ABEDD, Vienna, Austria) as environmental enrichment.
After allocation, the animals were housed four rats to a cage (separated by sex).
For mating, one male and one female were housed together.
Mated females were housed individually in Makrolon cages, which were placed in another cage rack. The location of the mated females in the new cage racks was determined by the date of mating (females found sperm-positive on the same date were considered a 'lot') and by the animal number (within each lot the mated females was housed in the order of animal number).

4.6.3 Food and drinking water

Food and drinking water was provided ad libitum from the arrival of the rats until the end of the study, except during exposure and unless precluded by the performance of certain laboratory investigations.
From their arrival, the rats received a cereal-based (closed formula) rodent diet (VRF1 (FG)) from a commercial supplier (SDS Special Diets Services, Witham, England). Each batch of diet was analysed by the supplier for nutrients and contaminants. The certificate of analysis pertaining to the batch used in this study (3041) is included in the study report in Annex 04.
The food was provided as a powder in stainless steel cans, covered by a perforated stainless steel plate to prevent spillage. The food in the cans were refreshed at least once weekly.
Each cage was supplied with domestic mains tap-water suitable for human consumption (quality guidelines according to Dutch legislation based on EC Council Directive 98/83/EC). The water was given in polypropylene bottles, which were cleaned weekly and filled as needed. Results of

the routine physical, chemical and microbiological examination of drinking water as conducted by the supplier are made available to the test facility. In addition, the supplier periodically (twice per year) analyses water samples taken at the premises for a limited number of physical, chemical and microbiological variables. The results of the samples taken during or close to the conduct of this study are presented in Annex 05 in the report.

4.7 Exposure equipment

The animals were exposed to the test atmosphere in 2.2 m^3 whole body exposure units (based on the design by Hazleton Systems, Inc., Aberdeen, MD, USA). These chambers were constructed of stainless steel, with glass doors on two sides which allowed observation of the animals during exposure. The test atmosphere was introduced at the top and exhausted at the bottom of the chamber (see Figure 1). During exposure, animals were housed individually in Type II Macrolon cages. Each whole body chamber could accommodate 60 cages. Animals were rotated twice weekly with respect to their position in the exposure chamber. The whole body chambers were illuminated externally by normal laboratory fluorescent tube lighting. The ventilation rate was at least 10 air changes per hour. The atmosphere in the chambers was maintained at a temperature of 22 ± 3ºC and a relative humidity between 30 and 70%, as far as possible.

4.8 Generation of the test atmosphere

The inhalation equipment was designed to expose the animals to a continuous supply of fresh test atmosphere. A schematic diagram of the generation and exposure system is presented in Figure 1. To ensure a representative composition of the test atmosphere and to prevent potential enrichment with more volatile impurities, the liquid test substance (the substance is a liquefied gas) was extracted from the cylinder using its liquid valve; the test substance was subsequently evaporated in a closed system and led towards the exposure chambers. The test atmospheres were then generated by mixing a mass flow controlled (Bronkhorst Hi Tec, Ruurlo, The Netherlands) stream of gaseous test substance with a controlled flow of clean air, available as a laboratory provided source of (non-pressurized) filtered air (HEPA filter). The resulting test atmosphere was introduced at the inlets at the top of the exposure chamber; the atmosphere was exhausted at the bottom. The exposure unit for the control animals was supplied with a controlled flow of HEPA-filtered air only.

The flow of test atmosphere was controlled using a constant volume valve and was measured in the exhaust of the exposure chamber using a KIMO air velocity sensor (type CTV110-AOD150; KIMO, Emerainville, France). The flow was continuously measured and recorded on a personal computer (PC) every minute using a CAN transmitter (G. Lufft Mess- und Regeltechnik GmbH, 70719 Felbach, Germany). The animals were placed in the exposure chamber prior to the start of the test atmosphere generation. Test atmosphere generation was stopped six hours after the start of generation. The animals were removed from the exposure chamber after the concentration had dropped below a level of 1% of the target concentration.

Prior to the first exposure of the animals, homogeneous distribution of the test substance in the exposure chambers was confirmed by analysis of samples taken at five different locations in each exposure chamber (deviation of individual values from the mean of all five samples should not exceed 10%; this criterion was passed for all test atmospheres)[3].

---

[3] Confirmation of test atmosphere homogeneity was performed before the start of the preceding range finding study (Triskelion study [redacted]) in which the same exposure setup was used.

4.9 Monitoring of the exposure conditions

4.9.1 Actual concentration

The actual concentration of the test substance in the test atmospheres was measured by total carbon analysis (Sick Maihak EuroFID Total Hydrocarbon Analyzer; Sick Instruments Benelux, Hedel, the Netherlands). Test atmosphere samples were taken continuously from the exposure chamber at the animals’ breathing zone and were passed to the total carbon analyzer (TCA) through a sample line. The response of the analyzers were recorded on a PC at least once per minute using a CAN transmitter (G. Lufft Mess- und Regeltechnik GmbH, 70719 Felbach, Germany). The responses of the analyzers were converted to concentrations by means of calibration graphs (the formulas used to convert responses into concentrations are given below). For each exposure day, the mean concentration was calculated from the values determined every minute. The average concentration during exposure was corrected for the duration of the animals’ stay in the exposure chamber and the number of measurements during exposure.

Prior to the first exposure, the output of the flame ionization detector of each TCA was dynamically calibrated using mass flow controlled mixtures of compressed dry air and gaseous test substance. During calibration, test atmospheres were generated as described in paragraph 4.8 and led directly to the TCA (rather than to the inlet of the exposure unit); the excess air was exhausted. At different settings of the mass flow controllers, which were calibrated using a volumetric flow meter (DryCal, Bios International Corporation, Butler, NJ, USA) at the flow settings used for calibrating the TCA, the response of the TCA was recorded (in duplicate). The calibration settings were selected to generate about 80%, 100% and 120% of each target concentration. A zero calibration was included for each TCA, using clean dry air only. Linear relations were found between the response of the analyzers and the concentration of the test substance (see below).

The calibrations were checked weekly during the study. To this end, a test atmosphere was generated at each target concentration as described above using mass flow controllers, the flow of which was measured using a volumetric flow meter. The concentration as calculated from the measured flows, was compared to the concentration as measured by the analyzers. If the measured concentration deviated more than 5% from the calculated concentration, the calibration check was repeated. If the deviation was more than 5% at the re-check, a complete recalibration was carried out. The results of the calibration analyses are presented below.

Group 2 (target concentration 250 ppm)
On 4 October 2017, concentrations of 0, 206, 259 and 314 ppm were analyzed (in duplicate) to calibrate the TCA used for group 2. The response (Y) of the analyzer (in % of full scale) was related to the concentration (X, in ppm) of the test substance as:
$Y (\%) = 8.178*10^{-2} * X (ppm) + 3.318*10^{-1}$, with a coefficient of determination (R^2) of 0.9998.
Since the difference between the measured and calculated concentration was >5% during the calibration check on 15 November 2017, the analyzer was recalibrated on 16 November 2017 at concentrations of 0, 205, 258 and 312 ppm (in duplicate). The response (Y) of the analyzer was related to the concentration (X) of the test substance as:
$Y (\%) = 9.411*10^{-2} * X (ppm) + 5.330*10^{-1}$ ($R^2 = 0.9991$).
This new calibration was used from 15 November 2017 until the end of the study.

Group 3 (target concentration 750 ppm)

On 9 October 2017, concentrations of 0, 608, 768 and 922 ppm were analyzed (in duplicate) to calibrate the TCA used for group 3. The response (Y) of the analyzer was related to the concentration (X) of the test substance as:

$Y (\%) = 8.600*10^{-2} * X (ppm) + 4.321*10^{-1}$ ($R^2 = 0.9998$).

Since the difference between the measured and calculated concentration was >5% during the calibration check on 30 November 2017, the analyzer was recalibrated on 1 December 2017 at concentrations of 0, 615, 778 and 933 ppm (in duplicate). The response (Y) of the analyzer was related to the concentration (X) of the test substance as:

$Y (\%) = 9.357*10^{-2} * X (ppm) + 2.224*10^{-1}$ ($R^2 = 0.9999$).

This new calibration was used from 30 November 2017 until the end of the study.

Group 4 (target concentration 1500 ppm)

On 5 October 2017, concentrations of 0, 1203, 1517 and 1808 ppm were analyzed (in duplicate) to calibrate the TCA used for group 4. The response (Y) of the analyzer was related to the concentration (X) of the test substance as:

Y (%) = $1.094*10^{-2}$ * X (ppm) + $1.850*10^{-1}$ (R^2 = 1.000).

The weekly calibration checks did not necessitate re-calibration.

4.9.2 Time to attain chamber equilibration (T_{95})

The time to reach 95% of the steady state concentration (T_{95}) was calculated as: 3V/F. This follows from the formula $C = C_\infty (1 - e^{-(FT/V)})$, describing the increase in concentration C in a perfectly stirred chamber with volume V [L] and flow F [L/min], where T [min] is the time and C_∞ is the steady state concentration.

4.9.3 Generation efficiency

The amount of test substance used during the study (measured daily), determined as the weight difference of the test substance cylinder before the start and at the end of exposure, was compared to the amount used as calculated from the measured concentration and the flow of test atmosphere during exposure. The generation efficiency was calculated from the calculated daily use and the actual (weighed) daily use of test substance, as follows:

Efficiency = 100 * total calculated use of test substance for all exposure groups combined / weighed use.

4.9.4 Total flow, temperature, relative humidity, oxygen and carbon dioxide concentration

The total flow of test atmosphere during exposure was continuously measured using air velocity sensors (type CTV110-AOD150; KIMO, Emerainville, France) in the chamber exhaust. The measurements of the air velocity sensors were recorded on a PC at least once per minute using CAN transmitters (G. Lufft Mess- und Regeltechnik GmbH, 70719 Felbach, Germany). The responses of the sensors were converted to air flows by means of calibration graphs. Prior to the start of the exposure, the air velocity sensors were calibrated by measuring the response at a range of air flows (approximately 80%, 100% and 120% of the target flow) generated using mass flow controlled streams of clean dry air. The calibrations were checked weekly during the study, by measuring the response at a (mass flow controlled) air flow near the target flow. If the measured flow deviated more than 5% from the calculated flow, the calibration check was repeated. If the deviation was more than 5% at the re-check, a complete re-calibration was carried out.

Temperature and the relative humidity of the test atmospheres were measured continuously during exposure, and recorded on a PC at least once per minute using a CAN transmitter with temperature and relative humidity probes (G. Lufft Mess- und Regeltechnik GmbH, 70719 Felbach, Germany).

The concentrations of oxygen (Oxygen analyzer type PMA-10, M&C Products Analysentechnik GmbH, Ratingen-Lintorf, Germany) and carbon dioxide (GM70 probe with MI70 read-out unit, Vaisala, Helsinki, Finland) in the test atmosphere were measured twice for each group, i.e. during the first week and near the end of the exposure period.

4.9.5 Chemical analysis

A method for the chemical analysis of the concentration [redacted], a known impurity in the [redacted] test substance used in this study, was utilized.
A limited number of study samples was measured during method development. The remaining scheduled study samples were not measured.
A description of the process of method development and the results of a limited number of study samples measured during method development were reported in an Annex 6 to the report.

4.10 Observations, analyses and measurements

4.10.1 General clinical signs

Each animal was observed daily in the morning hours by cage-side observations and, if necessary, handled to detect signs of toxicity. All cages were checked again in the afternoon for dead or moribund animals to minimize loss of animals from the study. The observations include, but are not restricted to, the signs listed in Annex 8. The animals were also observed about halfway through the 6-hour exposure period, in particular to monitor any breathing abnormalities and restlessness. All abnormalities, signs of ill health or reactions to treatment were recorded.

4.10.2 Body weight

The body weight of each animal was recorded at least once during the acclimatization period and at initiation of treatment (day 0). Subsequently, males were weighed weekly. Four males in the 250 ppm group were weighed additionally on day 2 of exposure due to body weight loss. Females were weighed once per week during the premating and mating period. Mated females were weighed on days 1, 7, 14 and 20 during presumed gestation and on day 0, 4, 7 and 13 of lactation. Non-mated females were weighed once per week after the mating period. Body weight changes was calculated over the different weighing days.
In addition, the animals were weighed on their scheduled necropsy date in order to calculate the correct organ to body weight ratios.

4.10.3 Food consumption

The food in the feeders was refreshed once per week. The food consumption was measured per cage over the same periods as the body weight are measured, except during the mating period when food intake was not recorded. The results were expressed in g per animal per day.

4.10.4 Oestrous cycle evaluations

Vaginal smears to evaluate the oestrous cycle length and normality were made daily from the start of the pre-treatment period until confirmation of mating. Smears were made, stained and examined in all females. An additional vaginal smear were made at the day of sacrifice. These smears were only analysed and reported in case of inconclusive results of histopathology of uterus and vagina.

4.10.5 Blood sampling for hormone determinations

During necropsy blood was taken from the aorta under pentobarbital anaesthesia from all adult male and female animals. Blood was collected in tubes with clot activator SST II. Serum was stored in a freezer (at ≤ -18 °C). In addition, blood samples were collected from the surplus pups per litter at culling on lactation day 4 (pooled, PND 4 pups were sacrificed by decapitation for blood collection) and from two pups per litter at sacrifice on or shortly after lactation day 13 (individual blood samples were collected from the heart whilst under CO_2/O_2 anaesthesia). Serum samples were discarded after analysis.

4.10.6 Hormone determinations (T4)

The serum samples from the adult males and two pups per litter (LD13) were analysed for T4 hormone levels.
Analysis were performed with commercially available ELISA kits of Cloud-Clone Corp (kit CEA452Ge). The ELISA was performed according to a validated method based on the manufacturer's protocol and was described in detail, together with the results of the measurements, in Annex 07 to the report.

4.10.7 Blood sampling for possible toxicokinetic evaluations

During necropsy blood was taken from the aorta under pentobarbital anaesthesia from all adult male and female animals. Blood was collected in tubes with clot activator SST II. Serum was stored in a freezer (at ≤ -18 ºC) for possible future bioanalysis and toxicokinetic evaluation. Samples were discarded after finalization of the report.

4.10.8 Sacrifice, blood samples, gross necropsy and histology of adult animals

The animals were sacrificed by exsanguination from the abdominal aorta under pentobarbital anesthesia (intraperitoneal injection of sodium pentobarbital) at necropsy and then subjected to macroscopic examination for pathological changes.

On the day of necropsy of all adult females a vaginal smear was taken to determine the stage of the oestrous cycle. These smears were only analysed and reported in case of inconclusive results of histopathology of uterus and vagina.

- Adult male animals were sacrificed after at least 28 days of treatment.
- Parental female animals were sacrificed on day 14 of lactation. One animal (59), showing complete litter loss, was sacrificed at day 13 of lactation.
- Pups were sacrificed on day 13 of lactation.
- Adult female animals that failed to mate or appeared not pregnant after mating were sacrificed at least 21 days after the last mating date or at least 23 days after the presumed mating date, respectively.

At scheduled necropsy, the organs of the adult animals indicated in the table below were weighed (paired organs together) as soon as possible after dissection to avoid drying.
Samples of the following tissues and organs (see table below) of the adult animals were preserved in a neutral aqueous phosphate-buffered 4% solution of formaldehyde; except for the testes and epididymides which were preserved in Bouin's fixative).

The reproductive organs of all male and female animals were preserved. The number of implantation sites in the uterus was counted.
The other organs/tissues (see table below) were preserved in five adult animals/sex/group (surviving males with the lowest identification numbers in each cage; females with a litter were selected).

In addition to the organs and tissues in the table, all gross lesions were preserved.

Tissue/Organ	Organ weight	Tissue fixation	
Male reproductive organs			
Epididymides	☒	☒	All males
Prostate (dorsolateral and ventral)	☒	☒	All males
Seminal vesicles and coagulation glands	☒	☒	All males
Testes[1]	☒	☒	All males
Levator ani plus bulbocavernosus (LABC) muscle complex, Cowper's glands and glans penis	☒	☒*	All males
Female reproductive organs			
Ovaries	☒	☒	All females
Uterus, including cervix[2]	☒	☒	All females
Vagina	☐	☒	All females
Other organs			
All gross lesions	☐	☒	All males and females
Noses	☐	☒	All males and females
Thyroid gland[3]	☒	☒	All males and females
Lungs with trachea and larynx	☒	☒*	All males and females
Pups on postnatal day 13			
Thyroid gland[3]	☒	☒	2 selected pups per litter, preferably one male and one female pup.

* were preserved after weighing but not further examined.

[1] Organ fixation: The tunica albuginea was gently and shallowly punctured at the both poles of the organ with a needle to permit rapid penetration of the fixative.

[2] The number of implantation sites and resorptions were counted in the uterus. If necessary the implantation sites were made visible following *Salewski, E (1964), Arch. Exp. Path. Pharmacol. 247, 367*.

[3] The weight of the thyroid gland was determined by direct weighing (not after fixation as suggested in the guidelines).

Tissues for microscopic examination were embedded in paraffin wax, sectioned, and stained with haematoxylin and eosin, except for sections of the testes which were stained with PAS haematoxylin.
Histopathological examination (by light microscopy) was performed on the preserved organs and tissues of all animals of the control (group 1) and high-exposure group (group 4). Organs marked with an asterisk (the lungs with trachea and larynx, levator ani plus bulbocavenosus [LABC] muscle complex, Cowper's glands and glans penis) were preserved after weighing but not further examined.
In addition, reproductive organs (ovaries, uterus, testes, epididymides, seminal vesicles and prostate) of males that failed to sire (did not mate or mated females were not pregnant) and

females that were non-mated or non-pregnant, of the low- and mid-exposure groups, were microscopically examined.
Based on effects observed in the nose epithelium in animals in the high exposure group, histopathological examination was extended to the intermediate exposure groups (2 and 3).
Furthermore, organs showing gross lesions of animals of all groups were microscopically examined. Histopathology was subjected to a peer review system.

4.10.9 Parturition

At the end of the gestation period (GD 21), females were examined twice daily for signs of parturition. Any difficulties occurring during parturition were recorded.

4.10.10 Litter evaluation

Litters were evaluated on the day of birth (i.e. day 0 of lactation). To keep nest disturbance to a minimum the litters were examined only once daily for dead pups.

4.10.11 Reproductive performance

The following data was presented for each group:
- number of adult females with normal or abnormal oestrous cycle and cycle duration
- number of females placed with males (and vice versa)
- number of females (not) mated and number of males (not) mated
- number of females (not) pregnant
- number of males that became sire
- number of females killed moribund or found dead
- number of females completing delivery

- number of females with liveborn pups
- number of females with (all) stillborn pups

- total and mean number of pups delivered (liveborn + stillborn)
- total number of liveborn pups
- total number of stillborn pups

- total and mean number of live pups(/litter) at day n
- total number of culled pups
- total number of pups lost (dead, missing, cannibalized) (period)
- number and incidence of litters lost entirely (period)
- total and mean number of live male pups at day n
- total and mean number of implantation sites

The following parameters are calculated per group:

. Pre-coïtal time (period)	= time between the start of mating and successful copulation
. Duration of gestation	= time between gestation day 0 and day of delivery (=gestation days)
. Male mating index	= no. of males mated*100/no. of males placed with females
. Female mating index	= no. of females mated*100/no. of females placed with males
. Male fertility index	= no. of males that became sire*100/no. of males placed with females
. Female fertility index	= no. of females pregnant*100/no. of females placed with males

. Female fecundity index = no. of females pregnant*100/no. of females mated
. Gestation index = no. of females with a viable litter *100/ no. of females pregnant

The following parameters are calculated on a litter basis and reported per group:
. Number of lost implantations = no. of implant sites – no. of liveborn pups
. Post-implantation loss = no. of implant sites – no. of liveborn *100 /no. of implant sites
. Live birth index = no. of liveborn pups *100/no. of newborn pups
. Stillborn index = no. of stillborn pups *100/no. of newborn pups
. Viability index 0 - 4 = no. of live pups on day 4 *100/no. of liveborn pups
. Viability index 4 - 13 = no. of pup live pups on day 13 *100/no. of live pups post cull day 4
. Sex ratio (day n) = no. of live male pups on day n *100/no. of live pups on day n

4.10.12 Observations in pups

4.10.12.1 Pup survival, sex and weight

The total litter size and numbers of each sex as well as the number of stillbirths, live- and dead pups, runts (pups that are 25% less in body weight than the mean body weight of the pups in the control group) and grossly malformed pups was evaluated on days 0, 4, 7 and 13 of lactation. The alive pups were individually weighed on days 0, 4, 7 and 13 of lactation. Mean pup weight was calculated per sex and for both sexes combined per exposure group.

4.10.12.2 Anogenital distance in pups

At day lactation day 4 the anogenital distance (AGD) was measured of each pup before culling of the litter. The AGD was reported corrected for body weight and for the square root of body weight.

4.10.12.3 Blood collection for hormone analysis

Blood collection at culling

On lactation day 4 the litter size was adjusted by eliminating extra pups by random selection to yield, as nearly as possible, four pups per sex per litter.
Whenever the number of male or female pups prevents having four of each sex per litter, partial adjustment was acceptable. Preference was to retain at least four male pups in order to have sufficient male pups for nipple retention determinations on lactation day 13.
Blood samples were collected from all surplus pups per litter, and serum as pooled and stored in a freezer (at ≤ - 18 °C) for possible determination of serum T4 levels. If there was only one pup per litter above the culling target, only one pup was used for possible hormone determinations. If a litter had no surplus pups, no blood was collected for possible hormone determinations. Serum samples were discarded after issuing the final report.

Blood collection at necropsy

Individual blood samples were collected from two pups per litter at sacrifice on or shortly after lactation day 13 (collected from the heart whilst under CO_2/O_2 anaesthesia). Serum was prepared and stored in a freezer (at ≤ -18 °C) for determination of serum T4 levels. Serum samples were discarded after analysis.

4.10.12.4 Hormone determinations (T4) in pups

Hormone determinations were performed using the same ELISA method as in adult animals. Methods and results are described in detail in Annex 07 to the report.

4.10.12.5 Nipple retention in male pups

On postnatal day 13 all surviving male pups were examined for the presence and number of nipples or areolas.

4.10.12.6 Signs and sacrifice, gross necropsy and pathology of pups

Any abnormal behavior of pups was recorded on day 0, 4, 7 and 13 of lactation. Grossly malformed pups were sacrificed and examined. A necropsy was performed on stillborn pups and pups dying during the study and macroscopic abnormalities were recorded. At necropsy of the dams and litter, at or shortly after day 13 of lactation, pups were examined externally for gross abnormalities and will be sacrificed whilst under CO_2/O_2 anaesthesia and necropsied.

5 Results

5.1 Analysis of the exposure conditions (Table 1)

5.1.1 Actual concentrations

The overall average actual concentrations (± standard deviation) of [redacted] in the test atmospheres, as determined by total carbon analysis, were 250 (± 6), 748 (± 17) and 1498 (± 24) ppm for the low-, mid- and high-concentration groups, respectively (Table 1.1). These concentrations were close and within 10% of the respective target concentrations of 250, 750 and 1500 ppm.

The concentration of [redacted] (2,2,3,3,4,4,4-heptafluorobutanenitrile), an impurity of the test substance present in a concentration of 0.23% (based on the Certificate of Analysis), was determined in test atmosphere samples by GC/MS. Although several analytical challenges were encountered and only a limited number of samples could be quantitatively assessed (see Annex 6), the results indicated that the measured concentrations of [redacted] in each test atmosphere were consistent with the expected 0.25% demonstrating an overall mean concentration of 0.22%. Given the method of test atmosphere generation – total evaporation of the liquid test substance, thereby preventing possible enrichment of the test atmosphere with more volatile components – and the fact that the test atmosphere conditions were stable across the entire exposure period, it was concluded that the composition of the test substance in the atmospheres was representative for the original test substance during the course of the study.

5.1.2 Time to attain chamber equilibration

The time to reach 95% of the steady state concentration (T_{95}), based on chamber volume and average total air flow (see paragraphs 4.7 and 5.1.4, respectively) was calculated to be about 16.5 minutes.

5.1.3 Generation efficiency

Test substance consumption and generation efficiency are shown in Table 1.2. The test substance consumption as calculated from the actual concentrations and flows, was close to the consumption as determined from the weight decrease of the test substance cylinder. Thus, the overall generation efficiency was close to 100% (i.e. 97.4%) which is expected for test atmosphere generation from a gaseous test substance.

5.1.4 Total flow, temperature, relative humidity, oxygen and carbon dioxide concentration

The average total flows of test atmosphere (± standard deviation) were 388 (± 11), 396 (± 11), 400 (± 11) and 397 (± 11) L/min for the control, low-, mid- and high-concentration groups, respectively (Table 1.3).

The average temperature (± standard deviation) was 21.4 (± 0.7), 21.2 (± 0.6), 21.0 (± 0.5) and 21.6 (± 0.7) °C for the 0 ppm (control), 250 ppm, 748 ppm, and 1498 ppm concentration groups, respectively (Table 1.4). The average relative humidity during exposure was 41.2 (± 1.9), 36.4 (± 1.2), 42.0 (± 0.9) and 43.8 (± 1.7) % for the 0 ppm (control), 250 ppm, 748 ppm, and 1498 ppm concentration groups, respectively (Table 1.5).

The oxygen concentration during exposure was in the range of 20.7 – 20.8% (v/v) and the carbon dioxide concentration was in the range of 0.068 – 0.087% (v/v), which was well within the limits of >19% oxygen and <1% carbon dioxide as described in the OECD testing guideline (Table 1.6).

5.2 Mortalities and clinical signs (Table 2, Appendix 1)

No animals died during exposure.

Observation of the animals during exposure revealed piloerection in the majority of animals exposed to 1498 ppm, primarily observed during the first 3 weeks of exposure and the first week after restart of exposure during lactation (a pause was included to allow the animals to deliver their litter). Piloerection was also occasionally observed during exposure of animals to 748 ppm, and on a few days also in single animals of the control and 250 ppm group (Table 2.5).

5.3 Body weights and body weight change (Tables 3 and 4, Appendix 2)

In males mean body weight was statistically significantly decreased in the 748 and 1498 ppm groups from the start of exposure onwards up to sacrifice as compared to the control group. When compared to the control group the reduction of male body weights in the 748 and 1498 ppm were -8.2% and -8.6%, respectively.

In females mean body weights were statistically significantly lower in females in the 748 and 1498 ppm groups during the two-week premating period, during mating and gestation and during lactation as compared to the control group. On day 7 of gestation and on days 0 and 4 of lactation, no statistical significance was reached for the 748 ppm group. The maximal difference from control values for females exposed to 748 ppm and 1498 ppm were -8.1% and -12.2%, respectively over the course of the in-life period.

Mean body weight change was statistically significantly lower during several, but not all weighing intervals in males and females in the 748 and 1498 ppm groups as compared to the control group. In addition, mean body weight change was statistically significantly lower during one interval in the females in the 248 ppm group: from day 4-7 during lactation. In absence of statistically significant effects on body weight, this was considered not toxicologically relevant.

The lower mean body weight and body weight changes in the 748 ppm and 1498 ppm groups for both males and females are considered test substance-related but is only considered adverse in females exposed to 1498 ppm as the difference from control was consistently greater than -10% (maximally -12.2%). Males exposed to 1498 ppm and male and females exposed to 748 ppm demonstrated a maximum reduction of -8.6% which were also associated with significant reductions in food consumption (see Section 5.4 below) and are thus considered non-adverse.
No effects on body weight or body weight change were observed in males and females in the 250 ppm group.

5.4 Food consumption (Table 5, Appendix 3)

Mean food consumption was statistically significantly lower in males and females in the 1498 ppm group throughout the study as compared to the control group. In the 748 ppm group, mean

food consumption was statistically significantly lower in males and females during the pre-mating period and in females during the lactation period as compared to the control group. These lower food intakes are considered test substance-related.
No effects on food consumption were observed in males and females in the 250 ppm group.

5.5 Oestrous cyclicity (Table 6, Appendix 4)

An increased number of a-cyclic females was observed in the high concentration group after the start of exposure as compared to the control group. (1, 0, 2 and 5 out of 12 females did not show a regular cycle during exposure in the control group, 250, 748 and 1498 ppm groups, respectively).

5.6 Hormone analysis (Annex 7)

The analysis of T4 and the results are described in Annex 7 to the report.

5.6.1 Hormone analysis in adult males

No statistically significant effects were observed on T4 levels in adult males.

5.6.2 Hormone analysis in male and female PND 13 pups

No statistically significant effects on mean T4 levels were observed in male and female pups at day 13 of lactation.

5.7 Parental necropsy observations

5.7.1 Organ weights of parental animals (Table 7, Appendices 5 and 6)

Mean absolute organ weights were statistically significantly lower for the LABC muscle and Cowpers glands in males in the 748 and 1498 ppm groups as compared to the control group. In absence of effects on the relative organ weights, these effects on absolute organ weights were considered to be related to the slightly lower terminal body weights of the animals in this group and non-adverse.
Mean relative lung weight was statistically significantly increased in males in all groups and in females in the 1498 ppm group as compared to the control group. This was considered test substance-related to the inhalation exposure to [redacted].

5.7.2 Macroscopic examination (Table 9, Appendix 7)

Macroscopic observations at necropsy revealed no treatment-related abnormalities. The findings were considered unremarkable and part of the background pathology of rats of this strain and age.

5.7.3 Microscopic examination (Table 10, Appendix 7)

Microscopic analysis revealed a concentration-dependent degeneration of the olfactory epithelium characterized by disorganization, reduced cellular density and the occasional clustering of cells that might be bipolar olfactory sensory cells.

In the control and the low-exposure groups, no degeneration of the olfactory epithelium could be observed. In rats exposed to 748 ppm, 24/24 animals showed minimal to moderate degeneration of the olfactory epithelium from levels 3 through 6, while 24/24 animals exposed to 1498 ppm showed minimal to marked degeneration of the olfactory epithelium from levels 3 through 6.

The remaining pathological findings were considered unremarkable and part of the background pathology of rats of this strain and age.

5.8 Fertility and reproductive performance (Table 11, 12, 13, Appendices 8 and 9)

In all groups 12 females were placed with males for pairing. In both the 748 and 1498 ppm groups one female was not mated, resulting in 12 mated females in the control and 250 ppm group and 11 mated females in the 748 and 1498 ppm groups, respectively.
All mated females were pregnant and littered, except for one female in the 1498 ppm group. One pregnant female (animal 59) showed complete litter loss on Lactation Day 0 in the 748 ppm group, resulting in 12 litters in the control and 250 ppm groups and 10 litters in the 748 ppm and 1498 ppm groups, respectively.
The male mating and fertility indices were therefore 100% in the control and 250 ppm groups, 91.7% in the 748 ppm group and 91.7% (mating index) and 83.3% (fertility index) in the 1498 ppm group.

The female fecundity index was 100% for the control, 250 ppm and 748 ppm groups and 90.9% for the 1498 ppm group. The female fertility index was 100% for the control and 250 ppm group, 91.7% for the 748 ppm group and 83.3% for the 1498 ppm group.

The mean pre-coital time was comparable in all groups.

5.9 Litter data and pup data (Tables 13 and 14, Appendix 10)

A statistically significantly lower mean and total number of pups were delivered in the 1498 ppm group. No statistically significant lower number of pups were delivered in the 748 ppm group, but in this group a statistically significant increase in mean post-implantation loss was observed (see table 14, litter report). This was considered to be related to the complete litter loss of female 59 around birth.

All pups were live-born and there were no registered stillborn pups. During the first days of lactation three pups in control groups were cannibalized. No pups in the exposed groups died during the first days of lactation. The viability index from day 0-4 was 98% for the control group and 100% for the groups exposed to the test substance.

5.9.1 Pup observations (Table 15, Appendix 11)

No treatment related clinical signs were observed in pups.

5.9.2 Pup sex (Table 14, Appendix 10)

The number of male littermates at birth was comparable in all groups (44.6%, 55.9%, 47.5% and 50% in the control, 250, 748 and 1498 ppm groups, respectively).

5.9.3 Pup body weight (Table 16, Appendix 12)

No statistically significant effects on mean pup weight were observed.

5.9.4 Pup anogenital distance (Table 17, Appendix 13)

No effects on mean anogenital distance was observed in male and female pups.

5.9.5 Nipple retention (Table 18, Appendix 14)

No effect was observed on nipple retention in male pups.

5.9.6 Pup thyroid weight (Table 19, Appendix 15)

Mean pup thyroid weight was comparable in all groups for male and female pups.

5.9.7 Macroscopic observations of stillborn and found dead pups (no Table)

There were no stillborn pups and found dead pups in the study.
Three pups that died between birth and day 4 of lactation in the control group were cannibalized and could not be examined.

5.9.8 Macroscopic observations of pups at sacrifice on postnatal day 13 (Table 20, Appendix 16)

One pup in the 250 ppm group showed discoloration of the liver. No treatment-related effects were observed.

6 Discussion and conclusion

The objectives of this study were to provide data on the possible effects of [redacted] on general toxicity, reproductive performance and pup development. The test substance was administered by inhalation (6 hours/day) at concentrations of 0 (control), 250, 478 and 1498 ppm during a premating period of 2 weeks (5 days/week, 10 exposure days in total), then daily during mating and post-mating up to sacrifice for the males.
Females were exposed to the test atmospheres during a premating period of 2 weeks, during mating, gestation and lactation. Mated females were not exposed to the test substance between gestation day 19 and lactation day 4 in order to allow the females to litter. Daily exposure was resumed on lactation day 5 up to day 13 of lactation. The total number of exposure days was 31 days for males and 38-42 days for females.

The test atmospheres were stable and the actual concentrations were within an acceptable range of the target concentrations.

The concentration of [redacted] (2,2,3,3,4,4,4-heptafluorobutanenitrile), an impurity of the test substance present in a concentration of 0.23% (based on the Certificate of Analysis), was determined in test atmosphere samples by GC/MS. Although several analytical challenges were encountered and only a limited number of samples could be quantitatively assessed (see Annex 6), the results indicated that the measured concentrations of [redacted] in each test atmosphere were consistent with the expected 0.25% demonstrating an overall mean concentration of 0.22%. Given the method of test atmosphere generation – total evaporation of the liquid test substance, thereby preventing possible enrichment of the test atmosphere with more volatile components – and the fact that the test atmosphere conditions were stable across the entire exposure period, it was concluded that the composition of the test substance in the atmospheres was representative for the original test substance during the course of the study.

There was no test substance-related mortality. Daily clinical observations did reveal piloerection in the 1498 ppm group during the first three weeks of exposure and during the re-start of exposure during lactation. Test substance-related reductions in body weight were observed in male and female rats exposed to 1498 ppm and 748 ppm [redacted] which were associated with significant reductions in food consumption when compared to the air-exposed control group (0 ppm). The body weight reductions were considered adverse for females exposed to 1498 ppm as they were consistently > 10% of the control group values. No effects on body weight and food consumption were observed in 250 ppm exposure group.

At necropsy a concentration dependent increase in mean relative lung weight was observed in males at all exposure levels and in females exposed to 1498 ppm [redacted] but were not considered adverse as no correlative changes in lung histopathology were noted.
Histopathology showed a concentration-dependent degeneration of the nasal olfactory epithelium of levels 3, 4, 5, and 6 in male and female rats exposed to 1498 and 748 ppm. In the control group and the low concentration group no degeneration of the olfactory epithelium could be observed.

The number of females showing a-cyclic oestrous cycles was increased at 1498 ppm [redacted]. Functional fertility as measured by the time to pregnancy, gestational length and the number of litters was not affected. Mean number of pups delivered was decreased in dams exposed to 1498 ppm.

There were no effects of the test substance on pup survival or pup development.
There were no effects on hormone levels (T4) between the exposed groups and the control groups for adult males nor were there any effects noted in 13-day old male and female pups.

Conclusions:

Based upon adverse reductions in female body weights in the 1498 ppm exposure group as well as on the exposure-related histopathological changes in the nasal olfactory epithelium observed at 1498 ppm and 748 ppm [redacted], the No Observed Adverse Effect Concentration (NOAEC) for **general toxicity** was placed at **250 ppm**.

Although functional fertility was not affected, based on the increased number of females showing acyclic oestrous cycles and the lower mean number of pups per litter in the 1498 ppm [redacted] exposure group, the No Observed Adverse Effect Concentration (NOAEC) for **fertility** was placed at **748 ppm**.

In absence of effects on pup sex and survival, pup observations, AGD and nipple retention the No Observed Adverse Effect Concentration (NOAEC) for **developmental toxicity** was placed at **1498 ppm** [redacted].

7 Documentation and retention of records, samples and specimens

The following study specific materials will be archived for 5 years:
- Raw data (or true copies if unstable)
- Tissue specimens and paraffin blocks

The following study specific materials will be archived for 15 years
- Original study plan and final report, and any amendments thereof
- Microscopic slides

General raw data will be retained for at least 25 years, after which they may be destroyed without further notice. These may include, but are not necessarily limited to:
- Facility-based documents
- Calibration and quality control data
- General registrations potentially used for more than one study

At the end of the archiving period, tissue specimens and paraffin blocks will be discarded. The sponsor will be asked whether the study plan, final report, amendments, raw data, including microscopic slides, and correspondence should be discarded, retained for an additional period, or transferred to the archives of the sponsor.

Analytical samples will be discarded after finalization of the report.

All materials will be retained in the archives of TNO, Utrechtseweg 48, 3704 HE Zeist, The Netherlands. The archiving period for starts on the cover date of the final report.

8 References

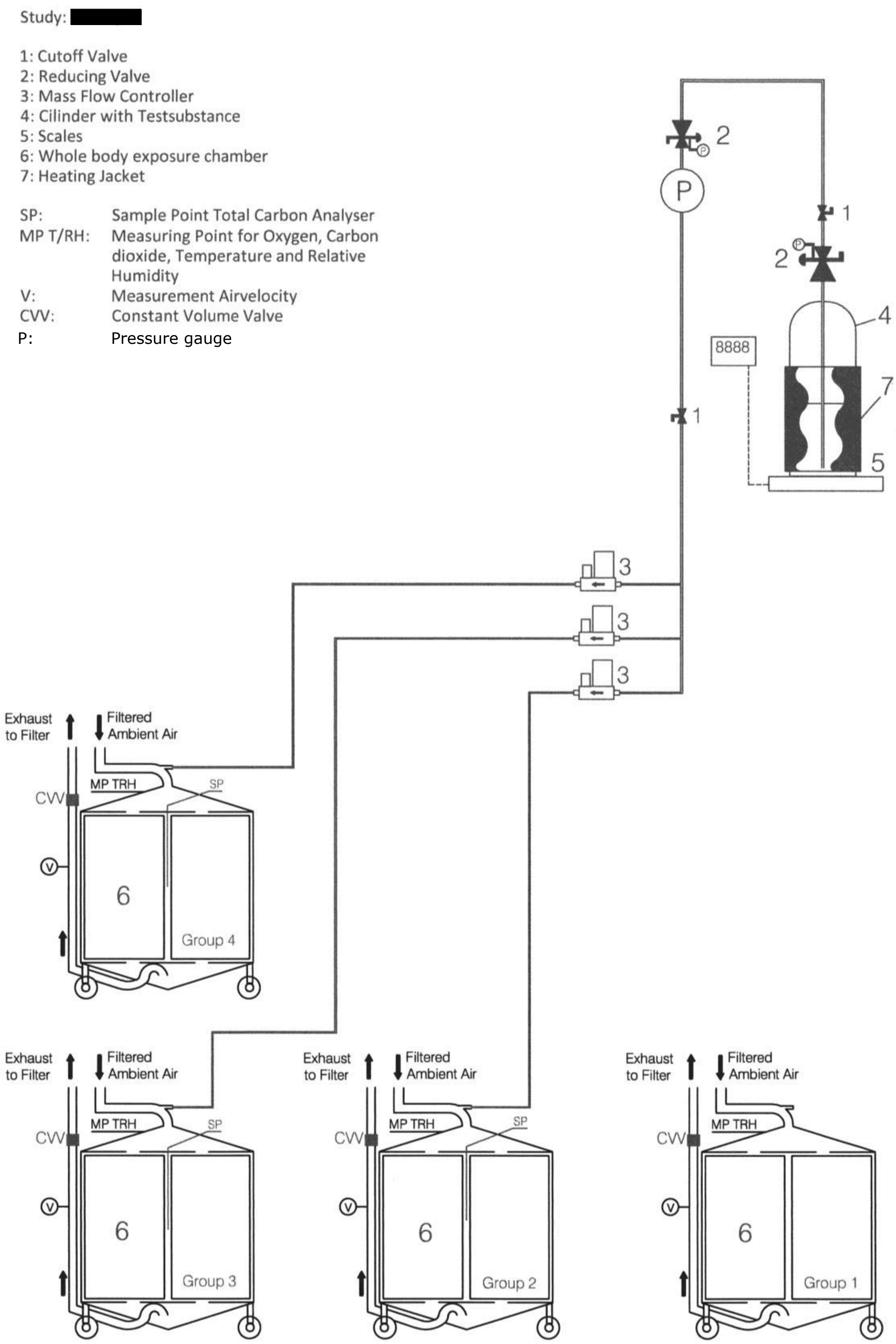
Triskelion B.V. preliminary data of study [redacted] 'A 14-day range finding study with [redacted] in rats' - J.J. van Triel (2017)

Sanitized [redacted]

Figure

Sanitized [redacted]

Figure 1: Schematic diagram of the generation and exposure system



Tables

Table 1.1 – Actual concentration of the test material in the test atmospheres as determined by total carbon analysis

	Group 2 (250 ppm)		Group 3 (750 ppm)		Group 4 (1500 ppm)	
Date (dd-mm-yyyy)	Mean (ppm)	Max (ppm)	Mean (ppm)	Max (ppm)	Mean (ppm)	Max (ppm)
16-10-2017	249	253	763	783	1470	1512
17-10-2017	250	255	760	778	1461	1491
18-10-2017	252	265	731	754	1487	1545
19-10-2017	245	252	731	765	1482	1604
20-10-2017	254	258	770	788	1502	1608
23-10-2017	253	256	761	826	1469	1507
24-10-2017	252	258	742	790	1511	1560
25-10-2017	252	261	740	759	1478	1555
26-10-2017	248	267	740	781	1476	1574
27-10-2017	248	252	731	752	1513	1581
30-10-2017	246	250	761	780	1510	1571
31-10-2017	249	253	761	780	1500	1539
1-11-2017	256	270	755	786	1530	1588
2-11-2017	258	263	768	801	1533	1603
3-11-2017	257	271	742	755	1505	1533
4-11-2017	252	276	770	796	1522	1562
5-11-2017	252	264	732	766	1487	1595
6-11-2017	250	275	759	816	1460	1537
7-11-2017	248	264	765	782	1535	1592
8-11-2017	250	253	759	805	1501	1574
9-11-2017	254	258	740	757	1494	1528
10-11-2017	251	258	746	761	1517	1592
11-11-2017	250	255	730	748	1533	1597
12-11-2017	253	264	735	753	1519	1550
13-11-2017	244	245	764	804	1457	1589
14-11-2017	259	258	764	785	1462	1484
15-11-2017	217	221	736	773	1480	1538
16-11-2017	251	265	734	758	1469	1533
17-11-2017	244	250	774	805	1491	1543
18-11-2017	250	257	757	782	1520	1593
19-11-2017	250	254	760	772	1508	1600

	Group 2 (250 ppm)		Group 3 (750 ppm)		Group 4 (1500 ppm)	
Date (dd-mm-yyyy)	Mean (ppm)	Max (ppm)	Mean (ppm)	Max (ppm)	Mean (ppm)	Max (ppm)
20-11-2017	251	254	757	778	1514	1641
21-11-2017	251	255	744	753	1531	1557
22-11-2017	246	250	753	788	1493	1554
23-11-2017	-	-	737	779	1517	1572
24-11-2017	-	-	743	780	1485	1780
27-11-2017	-	-	759	788	1492	1604
28-11-2017	256	262	759	801	1517	1554
29-11-2017	254	259	762	797	1529	1595
30-11-2017	245	266	700	730	1467	1547
1-12-2017	246	249	685	701	1461	1583
2-12-2017	247	247	736	751	1527	1601
3-12-2017	247	265	733	761	1491	1535
4-12-2017	256	263	739	770	1483	1543
5-12-2017	252	255	744	771	1481	1528
6-12-2017	246	265	747	766	1482	1532
7-12-2017	244	248	766	793	1535	1613
8-12-2017	243	268	753	787	1524	1604
9-12-2017	-	-	747	793	1476	1504
average	250		748		1498	
sd	6		17		24	
n	45		49		49	
min	217		685		1457	
max	259	276	774	826	1535	1780

Notes:

- Concentrations were determined by total carbon analysis once per minute, from the start of test atmosphere generation until removal of the animals from the exposure chamber. The daily average concentration during the 6-hour exposure was corrected for the duration of the animals' stay in the exposure chamber and the number of measurements during exposure.
- No minimum concentrations are given for whole-body exposure, since test atmosphere generation was started after placement of the animals in the exposure chamber (minimum concentrations were therefore, by definition, 0 ppm).
- No animals were exposed in the period: 23-27 November 2017 (group 1), 23-27 November and 9 December 2017 (group 2), and 25-26 November 2017 (groups 3 and 4).
- Very slight deviations from the intended 360-minute exposure duration occurred on 17 and 31 October, and 1, 7 and 13 November 2017 (actual exposure durations were 367, 362, 358, 363 and 361 minutes, respectively).

Table 1.2 – Test material consumption and generation efficiency

Date	TS flow (L/min)[1]			Calculated mass TS used (kg)[2]				Actual mass	Generation
(dd-mm-yyyy)	Group 2	Group 3	Group 4	Group 2	Group 3	Group 4	Total	TS used (kg)[3]	Efficiency (%)[4]
16-10-2017	0.098	0.299	0.592	0.29	0.87	1.73	2.89	3.02	95.6
17-10-2017	0.099	0.297	0.595	0.30	0.89	1.77	2.96	3.08	95.9
18-10-2017	0.096	0.301	0.599	0.28	0.88	1.74	2.89	3.02	95.7
19-10-2017	0.099	0.299	0.595	0.29	0.87	1.72	2.88	3.04	94.7
20-10-2017	0.101	0.306	0.596	0.29	0.88	1.71	2.89	3.02	95.5
23-10-2017	0.100	0.295	0.598	0.29	0.86	1.74	2.89	3.02	95.6
24-10-2017	0.099	0.289	0.603	0.29	0.84	1.76	2.90	2.96	97.8
25-10-2017	0.097	0.292	0.597	0.28	0.85	1.74	2.88	2.98	96.5
26-10-2017	0.098	0.293	0.593	0.29	0.86	1.74	2.88	2.94	98.1
27-10-2017	0.099	0.292	0.612	0.29	0.86	1.79	2.94	3.02	97.4
30-10-2017	0.101	0.303	0.603	0.30	0.89	1.77	2.96	3.08	96.1
31-10-2017	0.102	0.302	0.602	0.30	0.89	1.78	2.98	3.08	96.6
1-11-2017	0.098	0.295	0.626	0.29	0.86	1.82	2.97	2.98	99.5
2-11-2017	0.098	0.295	0.617	0.28	0.86	1.79	2.93	2.94	99.8
3-11-2017	0.099	0.291	0.612	0.29	0.85	1.78	2.92	2.96	98.8
4-11-2017	0.095	0.291	0.598	0.27	0.84	1.73	2.85	3.02	94.2
5-11-2017	0.104	0.309	0.589	0.30	0.89	1.70	2.90	3.08	94.0
6-11-2017	0.102	0.299	0.595	0.30	0.88	1.74	2.91	3.02	96.4
7-11-2017	0.101	0.299	0.605	0.30	0.89	1.79	2.97	3.06	97.1
8-11-2017	0.101	0.286	0.594	0.30	0.84	1.74	2.87	2.92	98.3
9-11-2017	0.099	0.297	0.602	0.29	0.87	1.77	2.93	3.00	97.7
10-11-2017	0.097	0.298	0.627	0.28	0.87	1.82	2.98	2.98	99.8
11-11-2017	0.099	0.305	0.603	0.29	0.89	1.75	2.92	3.00	97.4
12-11-2017	0.098	0.309	0.591	0.28	0.89	1.71	2.88	3.02	95.5
13-11-2017	0.101	0.311	0.596	0.29	0.91	1.74	2.95	3.10	95.2
14-11-2017	0.101	0.304	0.591	0.30	0.89	1.73	2.92	3.02	96.9
15-11-2017	0.088	0.304	0.600	0.26	0.89	1.76	2.92	3.02	96.6
16-11-2017	0.102	0.308	0.595	0.30	0.90	1.74	2.95	3.08	95.7

Date	TS flow (L/min)[1]			Calculated mass TS used (kg)[2]				Actual mass	Generation
(dd-mm-yyyy)	Group 2	Group 3	Group 4	Group 2	Group 3	Group 4	Total	TS used (kg)[3]	Efficiency (%)[4]
17-11-2017	0.101	0.319	0.576	0.30	0.94	1.70	2.93	3.10	94.7
18-11-2017	0.101	0.317	0.579	0.30	0.93	1.69	2.92	3.10	94.1
19-11-2017	0.101	0.318	0.573	0.30	0.93	1.67	2.89	3.04	95.2
20-11-2017	0.101	0.315	0.595	0.30	0.93	1.74	2.97	2.94	100.9
21-11-2017	0.100	0.312	0.588	0.29	0.91	1.71	2.91	2.94	98.9
22-11-2017	0.100	0.297	0.607	0.29	0.86	1.75	2.91	2.90	100.2
23-11-2017	-	0.289	0.615	-	0.83	1.76	2.59	2.58	100.2
24-11-2017	-	0.296	0.608	-	0.86	1.76	2.62	2.72	96.2
27-11-2017	-	0.303	0.615	-	0.89	1.79	2.68	2.58	103.8
28-11-2017	0.103	0.300	0.612	0.30	0.87	1.77	2.94	2.84	103.5
29-11-2017	0.102	0.301	0.609	0.29	0.87	1.76	2.92	2.82	103.7
30-11-2017	0.093	0.274	0.553	0.27	0.79	1.60	2.66	2.84	93.6
1-12-2017	0.094	0.273	0.560	0.28	0.80	1.63	2.71	2.86	94.7
2-12-2017	0.101	0.295	0.580	0.30	0.87	1.71	2.88	3.00	96.1
3-12-2017	0.099	0.294	0.591	0.29	0.87	1.74	2.90	2.88	100.7
4-12-2017	0.098	0.297	0.574	0.29	0.88	1.70	2.87	2.96	96.8
5-12-2017	0.097	0.302	0.572	0.29	0.90	1.69	2.88	2.88	100.0
6-12-2017	0.094	0.303	0.578	0.28	0.90	1.71	2.88	2.88	100.0
7-12-2017	0.093	0.302	0.568	0.27	0.89	1.66	2.82	2.92	96.5
8-12-2017	0.094	0.298	0.582	0.27	0.86	1.69	2.83	2.90	97.5
9-12-2017 [5]	-	0.295	0.541	-	0.86	1.58	2.43	5.98	40.7
						Total	138.38	142.14	97.4

[1] The flow of test substance (TS) was calculated from the average actual concentration (table 1.1) and total flow (table 1.3).
[2] The mass of test substance (TS) used was calculated from flow of test substance (converted to mass using the molecular weight, gas constant, atmospheric pressure and temperature) and the duration of test atmosphere generation.
[3] Actual mass of TS used, as determined by the weight difference of the test material cylinder before the start and at the end of exposure.
[4] Generation efficiency was calculated as: 100 * Total calculated mass TS used / Actual mass TS used.
[5] Results of 9 December 2017 were excluded from the calculation of the overall efficiency; a bypass flow was inadvertently not closed, causing leakage of test material into the exhaust and an aberrant test material consumption.
No animals were exposed in the period: 23-27 November 2017 (group 1), 23-27 November and 9 December 2017 (group 2), and 25-26 November 2017 (groups 3 and 4).

Table 1.3 – Daily mean, minimum and maximum flow (L/min) of test atmosphere

Date	Group 1 (control)			Group 2 (250 ppm)			Group 3 (750 ppm)			Group 4 (1500 ppm)		
(dd-mm-yyyy)	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
16-10-2017	412	399	428	394	373	416	391	380	404	403	377	422
17-10-2017	413	401	423	396	373	431	390	378	402	407	380	432
18-10-2017	410	338	437	380	364	397	412	400	424	403	374	425
19-10-2017	391	375	410	404	373	457	409	360	419	401	377	428
20-10-2017	391	370	410	396	380	416	398	363	409	397	370	422
23-10-2017	394	375	410	395	382	408	387	352	409	407	377	428
24-10-2017	394	375	408	392	380	408	389	367	404	399	377	425
25-10-2017	395	377	408	387	373	399	395	382	409	404	380	425
26-10-2017	396	377	411	393	352	408	396	378	411	402	377	425
27-10-2017	397	381	415	398	330	416	400	382	413	405	384	428
30-10-2017	400	382	420	411	397	429	398	384	411	399	377	422
31-10-2017	395	377	413	411	399	425	396	382	411	401	374	422
1-11-2017	392	375	408	382	364	397	391	380	400	409	384	428
2-11-2017	391	374	408	380	364	397	385	371	396	403	374	428
3-11-2017	392	375	413	386	285	408	393	378	406	407	380	428
4-11-2017	378	362	406	375	272	399	378	365	404	393	370	415
5-11-2017	377	362	389	413	397	427	422	411	437	396	370	418
6-11-2017	383	362	396	406	364	420	394	382	406	408	380	435
7-11-2017	380	362	396	405	377	423	391	380	407	394	367	422
8-11-2017	379	362	399	405	384	420	377	367	387	395	367	428
9-11-2017	379	360	391	390	371	414	402	374	417	403	374	425
10-11-2017	389	367	401	386	369	412	399	354	424	414	387	435
11-11-2017	383	367	398	396	380	410	418	407	431	394	367	418
12-11-2017	381	369	393	387	341	423	421	409	435	389	367	411
13-11-2017	386	372	401	412	395	427	407	350	461	409	363	446
14-11-2017	380	364	393	391	377	408	398	382	413	404	384	425
15-11-2017	383	370	418	407	390	425	413	380	454	405	380	425
16-11-2017	382	369	393	405	388	420	420	406	433	405	380	432

Date	Group 1 (control)			Group 2 (250 ppm)			Group 3 (750 ppm)			Group 4 (1500 ppm)		
(dd-mm-yyyy)	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
17-11-2017	382	369	394	411	397	425	412	398	431	386	360	408
18-11-2017	385	370	398	405	386	423	418	407	430	381	357	408
19-11-2017	380	367	393	404	386	418	418	407	433	380	346	401
20-11-2017	374	355	418	403	386	423	416	402	426	393	363	435
21-11-2017	373	358	387	399	384	416	420	409	430	384	346	408
22-11-2017	393	360	411	408	388	431	395	382	409	407	374	432
23-11-2017	-	-	-	-	-	-	393	380	407	406	380	432
24-11-2017	-	-	-	-	-	-	398	385	411	410	387	432
27-11-2017	-	-	-	-	-	-	399	385	413	412	387	439
28-11-2017	388	375	404	402	384	414	395	380	409	404	374	428
29-11-2017	376	362	393	401	386	418	394	380	406	398	374	418
30-11-2017	374	360	389	378	364	401	392	376	402	377	339	404
1-12-2017	401	386	413	385	371	425	398	385	411	383	346	425
2-12-2017	398	369	410	409	392	423	402	382	417	379	350	404
3-12-2017	392	360	411	402	362	461	402	391	413	396	370	425
4-12-2017	386	357	408	382	364	395	402	385	417	387	360	418
5-12-2017	373	355	386	383	364	399	406	391	420	386	346	428
6-12-2017	373	360	387	381	369	392	405	395	417	390	357	418
7-12-2017	369	348	403	383	339	399	395	380	409	370	329	483
8-12-2017	395	202	437	388	334	425	395	382	406	382	333	411
9-12-2017	402	384	435	-	-	-	394	382	406	366	339	387
average	388			396			400			397		
sd	11			11			11			11		
n	46			45			49			49		
min		202			272			350			329	
max			437			461			461			483

No animals were exposed in the period: 23-27 November 2017 (group 1), 23-27 November and 9 December 2017 (group 2), and 25-26 November 2017 (groups 3 and 4).

Table 1.4 – Daily mean, minimum and maximum temperature (°C) in the test atmospheres

Date	Group 1 (control)			Group 2 (250 ppm)			Group 3 (750 ppm)			Group 4 (1500 ppm)		
(dd-mm-yyyy)	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
16-10-2017	22.1	21.2	22.5	22.0	21.2	22.6	21.6	20.7	21.9	22.4	21.0	22.7
17-10-2017	22.2	21.4	22.5	22.0	21.2	22.3	21.6	20.8	21.9	22.4	21.1	22.9
18-10-2017	22.1	21.6	22.6	22.0	21.5	22.7	21.7	21.1	21.9	22.5	21.5	22.9
19-10-2017	22.1	21.2	22.5	22.0	21.0	22.4	21.6	20.6	21.9	22.4	21.0	22.9
20-10-2017	22.1	21.2	22.4	22.0	21.0	22.3	21.6	20.6	21.9	22.4	20.9	22.9
23-10-2017	22.0	20.9	22.5	21.8	20.7	22.4	21.5	20.5	21.9	22.2	20.7	22.8
24-10-2017	22.0	21.2	22.3	21.8	21.0	22.2	21.5	20.6	21.9	22.3	20.8	22.8
25-10-2017	22.1	21.4	22.5	21.9	21.3	22.3	21.6	20.8	21.9	22.4	21.0	22.8
26-10-2017	22.0	21.1	22.5	21.9	21.0	22.3	21.5	20.6	22.0	22.3	20.8	22.9
27-10-2017	21.9	20.8	22.6	21.8	20.7	22.4	21.5	20.5	21.9	22.3	20.8	22.8
30-10-2017	22.1	21.4	23.6	21.9	21.3	23.2	21.5	21.0	21.9	22.3	21.3	22.9
31-10-2017	21.8	21.1	22.0	21.6	21.0	21.9	21.4	20.5	21.7	22.2	20.9	22.6
1-11-2017	21.8	21.1	22.0	21.6	20.9	21.9	21.4	20.6	21.6	22.2	20.9	22.6
2-11-2017	21.8	21.0	22.6	21.7	20.7	22.4	21.4	20.5	21.7	22.1	20.7	22.7
3-11-2017	21.6	21.0	21.9	21.4	20.7	21.7	21.2	20.5	21.5	22.0	20.7	22.4
4-11-2017	21.7	20.8	22.0	21.5	20.6	21.8	21.3	20.4	21.7	22.1	20.6	22.6
5-11-2017	21.9	20.8	23.7	21.6	20.6	23.5	21.3	20.4	21.8	22.1	20.6	22.8
6-11-2017	22.7	21.9	25.5	22.4	21.8	24.8	21.9	21.7	22.2	22.9	22.3	23.4
7-11-2017	21.7	20.3	24.8	21.5	20.3	24.1	21.2	20.3	21.9	21.9	20.4	22.8
8-11-2017	21.3	20.3	21.6	21.2	20.3	21.5	21.1	20.3	21.4	21.8	20.4	22.2
9-11-2017	21.4	20.4	22.1	21.3	20.3	21.9	21.1	20.1	21.5	21.7	20.3	22.5
10-11-2017	21.9	20.9	22.9	21.7	20.7	22.6	21.3	20.5	21.7	22.2	20.7	22.7
11-11-2017	21.3	20.2	21.8	21.1	20.0	21.5	21.0	19.7	21.3	21.6	20.1	22.2
12-11-2017	21.1	20.2	21.8	21.0	19.9	22.0	20.9	19.9	21.3	21.5	20.1	22.0
13-11-2017	21.4	20.3	22.8	21.2	20.1	22.3	20.9	20.1	21.4	21.6	20.1	22.4
14-11-2017	21.2	20.4	21.8	21.0	20.3	21.5	21.0	20.2	21.3	21.6	20.4	22.1
15-11-2017	21.6	20.5	22.0	21.4	20.3	21.7	21.1	20.0	21.5	21.9	20.4	22.4
16-11-2017	21.7	20.9	22.1	21.5	20.5	21.9	21.3	20.4	21.7	22.1	20.6	22.6

Date	Group 1 (control)			Group 2 (250 ppm)			Group 3 (750 ppm)			Group 4 (1500 ppm)		
(dd-mm-yyyy)	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
17-11-2017	21.4	20.5	21.9	21.2	20.3	21.6	21.1	20.4	21.4	21.8	20.4	22.3
18-11-2017	21.1	19.9	21.7	21.0	19.8	21.5	20.9	19.6	21.3	21.5	19.9	22.1
19-11-2017	21.1	20.2	21.7	20.9	20.0	21.4	20.9	19.8	21.3	21.5	20.0	22.0
20-11-2017	20.6	19.6	20.8	20.5	19.5	20.7	20.4	19.5	20.7	20.8	19.7	21.2
21-11-2017	21.2	20.5	21.5	21.0	20.3	21.4	20.8	20.1	21.1	21.4	20.4	21.8
22-11-2017	21.3	20.6	21.7	21.2	20.4	21.5	20.9	20.2	21.2	21.5	20.5	21.9
23-11-2017	-	-	-	-	-	-	20.9	20.3	21.3	21.5	20.6	21.9
24-11-2017	-	-	-	-	-	-	20.8	20.1	21.1	21.4	20.5	21.7
27-11-2017	-	-	-	-	-	-	20.8	19.0	21.6	21.3	19.1	22.3
28-11-2017	20.5	19.7	20.7	20.2	19.5	20.4	20.3	19.5	20.5	20.6	19.6	20.9
29-11-2017	20.3	19.7	20.6	20.3	19.6	20.5	20.2	19.5	20.5	20.6	19.6	20.9
30-11-2017	20.4	19.6	20.7	20.4	19.6	20.7	20.4	19.5	20.6	20.7	19.6	21.1
1-12-2017	20.4	19.7	20.7	20.3	19.6	20.6	20.3	19.5	20.5	20.7	19.6	21.0
2-12-2017	20.3	19.6	20.5	20.2	19.5	20.4	20.3	19.3	20.5	20.6	19.5	21.0
3-12-2017	20.2	19.7	20.4	20.1	19.6	20.3	20.1	19.5	20.3	20.5	19.6	20.8
4-12-2017	20.4	19.3	21.1	20.2	19.2	20.9	20.2	19.1	20.6	20.6	19.2	21.3
5-12-2017	20.9	19.9	21.5	20.7	19.7	21.2	20.5	19.6	20.9	21.0	19.7	21.6
6-12-2017	21.4	20.5	21.7	21.1	20.3	21.4	20.8	20.0	21.1	21.4	20.4	21.9
7-12-2017	20.7	20.1	20.9	20.5	19.9	20.7	20.5	19.8	20.7	21.0	20.0	21.3
8-12-2017	20.3	19.7	20.5	20.1	19.5	20.3	20.2	19.5	20.5	20.5	19.6	20.8
9-12-2017	20.0	19.3	20.3	-	-	-	19.9	19.1	20.2	20.2	19.3	20.6
average	21.4			21.2			21.0			21.6		
sd	0.7			0.6			0.5			0.7		
n	46			45			49			49		
min		19.3			19.2			19.0			19.1	
max			25.5			24.8			22.2			23.4

On 6 November 2017, temperature in the exposure chamber of group 1 was briefly above 25°C (max 25.5°C) due to direct sunlight.
No animals were exposed in the period: 23-27 November 2017 (group 1), 23-27 November and 9 December 2017 (group 2), and 25-26 November 2017 (groups 3 and 4).

Table 1.5 – Daily mean, minimum and maximum relative humidity (%) in the test atmospheres

Date	Group 1 (control)			Group 2 (250 ppm)			Group 3 (750 ppm)			Group 4 (1500 ppm)		
(dd-mm-yyyy)	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
16-10-2017	43.0	40.0	48.0	36.6	34.5	40.5	42.9	41.5	45.0	46.8	44.5	52.0
17-10-2017	41.9	39.0	47.0	35.9	34.5	39.0	41.7	41.0	44.0	45.2	43.0	51.0
18-10-2017	42.5	38.5	48.0	36.1	33.5	40.0	41.5	40.5	43.0	45.1	42.5	49.5
19-10-2017	41.2	38.0	48.5	35.8	34.5	41.0	41.3	40.0	44.5	44.3	42.5	51.0
20-10-2017	41.0	38.0	47.0	35.7	33.5	43.0	41.3	39.5	45.0	44.1	42.0	50.5
23-10-2017	41.8	36.5	54.0	35.8	33.5	46.0	42.3	40.5	48.0	45.5	43.0	53.5
24-10-2017	41.6	39.0	47.0	36.1	34.5	41.0	42.2	41.0	45.5	44.8	42.0	52.0
25-10-2017	41.8	39.0	49.5	35.5	33.5	44.0	41.9	41.0	45.5	44.8	43.0	51.5
26-10-2017	41.5	38.0	53.5	35.9	33.5	45.5	41.7	40.5	47.0	45.2	43.0	52.0
27-10-2017	42.7	40.0	49.0	36.9	35.0	46.0	42.2	40.5	46.5	45.1	43.0	51.5
30-10-2017	41.4	35.0	49.5	36.1	32.0	44.0	42.5	40.5	45.5	45.1	42.0	51.0
31-10-2017	42.0	39.0	51.0	36.0	34.5	43.0	42.2	41.0	46.5	45.0	43.0	53.0
1-11-2017	41.3	38.5	51.0	35.8	34.5	44.0	41.7	41.0	45.5	44.9	43.0	52.0
2-11-2017	41.3	36.5	51.0	36.4	33.5	45.5	41.8	40.5	46.5	44.8	41.5	53.0
3-11-2017	42.4	40.0	52.0	36.0	34.5	44.0	42.1	41.5	46.5	46.1	43.0	52.5
4-11-2017	38.7	36.0	46.0	35.6	34.5	40.0	42.1	41.0	45.5	41.8	40.5	46.5
5-11-2017	39.8	33.5	45.0	35.6	31.5	40.5	41.7	40.5	45.0	43.4	42.0	46.5
6-11-2017	36.7	28.5	41.0	34.3	28.0	39.0	41.2	39.5	42.0	42.0	39.5	45.0
7-11-2017	41.3	31.0	49.5	36.8	29.5	42.0	42.9	41.0	45.5	44.1	37.5	49.0
8-11-2017	40.5	39.0	44.0	36.8	35.0	40.0	42.6	41.5	44.5	41.6	40.0	44.0
9-11-2017	39.7	36.0	45.0	36.3	34.5	40.0	42.4	41.0	45.0	42.4	40.0	46.0
10-11-2017	38.8	36.0	47.0	35.8	33.5	43.0	41.9	41.0	46.0	42.9	40.5	51.0
11-11-2017	42.4	39.0	48.5	37.9	36.0	43.0	42.8	41.5	48.0	44.4	42.0	53.0
12-11-2017	43.6	40.0	49.5	38.7	34.5	44.5	43.4	42.0	46.5	45.5	43.5	53.5
13-11-2017	41.9	36.0	51.0	37.9	34.5	45.0	43.1	41.5	48.0	45.3	42.0	54.5
14-11-2017	43.7	40.0	49.0	37.8	35.5	41.0	42.8	41.5	45.5	44.9	43.0	50.0
15-11-2017	42.6	39.0	51.0	37.4	35.0	44.0	42.4	41.5	47.0	44.3	42.0	53.0
16-11-2017	41.3	38.0	48.5	36.2	34.5	44.0	42.0	41.0	46.0	44.0	42.0	52.0

Date	Group 1 (control)			Group 2 (250 ppm)			Group 3 (750 ppm)			Group 4 (1500 ppm)		
(dd-mm-yyyy)	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max
17-11-2017	43.6	40.0	49.5	38.0	36.0	43.0	42.9	41.5	46.0	45.2	42.5	52.0
18-11-2017	43.2	39.0	50.5	38.1	35.5	45.5	43.3	42.0	49.0	45.4	43.0	53.5
19-11-2017	43.7	40.0	51.0	38.2	36.0	44.0	43.8	42.5	48.0	46.1	43.5	54.0
20-11-2017	43.2	41.0	49.0	37.9	36.0	45.0	43.4	42.0	47.5	45.0	43.0	52.0
21-11-2017	39.6	36.5	46.0	35.6	33.5	40.0	42.0	40.5	45.5	42.9	41.5	50.5
22-11-2017	38.1	36.0	45.0	34.7	33.5	42.0	41.2	40.0	46.5	41.3	40.0	48.5
23-11-2017	-	-	-	-	-	-	39.8	35.5	54.0	39.1	35.0	49.5
24-11-2017	-	-	-	-	-	-	41.2	40.5	44.5	41.9	40.5	46.5
27-11-2017	-	-	-	-	-	-	41.7	39.5	47.0	41.9	39.0	50.5
28-11-2017	42.5	40.0	48.0	36.0	34.5	40.0	42.6	41.5	46.0	43.5	42.0	49.5
29-11-2017	42.7	40.0	48.0	37.5	35.0	42.5	43.1	42.0	46.0	43.9	43.0	50.0
30-11-2017	43.3	41.0	48.5	38.8	36.0	45.0	43.3	42.5	47.0	44.9	43.0	51.5
1-12-2017	44.6	41.0	50.5	38.8	35.0	44.0	43.7	41.5	46.5	46.2	43.0	53.0
2-12-2017	40.2	38.0	46.5	35.3	33.5	40.0	40.8	40.0	43.5	42.9	41.0	49.5
3-12-2017	41.1	38.0	45.5	36.0	34.5	39.0	41.3	40.5	42.5	43.5	41.0	46.5
4-12-2017	41.1	37.5	52.0	36.2	34.5	49.5	41.6	40.0	57.0	44.0	40.5	53.5
5-12-2017	39.0	36.0	48.0	35.0	32.5	42.5	40.6	39.5	43.5	42.7	39.5	51.5
6-12-2017	37.5	35.0	45.0	34.1	32.0	42.0	40.0	39.0	44.0	40.1	38.5	48.5
7-12-2017	39.6	36.0	51.0	35.7	33.5	48.5	41.1	39.0	56.5	42.4	39.5	54.0
8-12-2017	38.0	33.0	46.0	34.2	30.0	44.0	40.6	37.0	52.0	41.1	37.0	49.5
9-12-2017	37.9	35.0	44.5	-	-	-	40.5	40.0	43.0	40.2	39.0	48.5
average	41.2			36.4			42.0			43.8		
sd	1.9			1.2			0.9			1.7		
n	46			45			49			49		
min		28.5			28.0			35.5			35.0	
max			54.0			49.5			57.0			54.5

Relative humidity in the exposure chambers of group 1 (on 6 November 2017) and 2 (on 6 and 7 November 2017) was briefly below 30% (min 28.5 and 28.0%, resp.) due to direct sunlight.

No animals were exposed in the period: 23-27 November 2017 (group 1), 23-27 November and 9 December 2017 (group 2), and 25-26 November 2017 (groups 3 and 4).

Table 1.6 – Oxygen and carbon dioxide concentration in the test atmosphere

	Group 1 (control)		Group 2 (250 ppm)		Group 3 (750 ppm)		Group 4 (1500 ppm)	
Date (dd-mm-yyyy)	O_2 (% v/v)	CO_2 (% v/v)	O_2 (% v/v)	CO_2 (% v/v)	O_2 (% v/v)	CO_2 (% v/v)	O_2 (% v/v)	CO_2 (% v/v)
18-10-2017	20.7	0.086	20.7	0.087	20.7	0.078	20.7	0.085
2-12-2017	20.7	0.083	20.8	0.073	20.8	0.068	20.7	0.071

30/Jan/2018 13:50:03

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.1.1: Clinical observations males during the study pre-exposure

Observation Type: All Types	Male			
From Day -3 (Start Date) to 35 (Start Date)	0 ppm	250 ppm	750 ppm	1500 ppm
DEAD Killed scheduled	12	12	12	12
SKIN Sparsely haired area(s)	2	0	0	0
SKIN Piloerection	0	0	0	7
EARS Encrustration(s)	1	0	0	0

Values = Number of Animals Affected

30/Jan/2018 09:24:22

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.1.2: Clinical observations males during the study post-exposure

Observation Type: All Types	Male			
From Day 0 (Start Date) to 34 (Start Date)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	2	0	0	0
SKIN Piloerection	0	0	2	10
EARS Encrustration(s)	1	0	0	0

Values = Number of Animals Affected

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.2.1: Clinical observations females premating pre-exposure

Observation Type: All Types	Female			
From Day -3 (Start Date) to 14 (Start Date)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	1	0	0	0

Values = Number of Animals Affected

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.2.2: Clinical observations females premating post-exposure

Observation Type: All Types	Female			
From Day 0 (Start Date) to 14 (Start Date)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	1	0	0	0
SKIN Piloerection	0	0	3	4

Values = Number of Animals Affected

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.3.1: Clinical observations females gestation pre-exposure

Observation Type: All Types	Female			
From Day 0 (Mating (A)) to 21 (Mating)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	1	0	0	0
SKIN Piloerection	0	0	2	5
SKIN Encrustation(s)	1	0	0	0
EARS Encrustration(s)	0	2	0	0

Values = Number of Animals Affected

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.3.2: Clinical observations females gestation post-exposure

Observation Type: All Types	Female			
From Day 0 (Mating (A)) to 19 (Mating)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	1	0	0	0
SKIN Piloerection	0	0	2	7
SKIN Encrustation(s)	1	0	0	0
EARS Encrustration(s)	0	2	0	0

Values = Number of Animals Affected

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.4.1: Clinical observations females lactation pre-exposure

Observation Type: All Types	Female			
From Day 0 (Littering (A)) to 14 (Littering)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	1	0	0	0
SKIN Piloerection	4	1	2	3
SKIN Encrustation(s)	1	0	0	0
EARS Encrustration(s)	0	1	0	0

[redacted]

Values = Number of Animals Affected

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 2.4.2: Clinical observations females lactation post-exposure

Observation Type: All Types	Female			
From Day 5 (Littering (A)) to 13 (Littering)	0 ppm	250 ppm	750 ppm	1500 ppm
SKIN Sparsely haired area(s)	1	0	0	0
SKIN Piloerection	7	3	5	7
SKIN Encrustation(s)	1	0	0	0
EARS Encrustration(s)	0	1	0	0

Values = Number of Animals Affected

Table 2.5: Clinical observations during exposure

Group	Observation	From date (dd-mm-yyyy) to date (dd-mm-yyyy)
0 ppm	No abnormalities Piloerection	16-10-2017 to 21-11-2017, 29-11-2017 to 9-12-2017 22-11-2017 (animal no. 9), 28-11-2017 (nos. 1 and 17)
250 ppm	No abnormalities Piloerection	16-10-2017 to 21-11-2017, 30-11-2017 to 9-12-2017 22-11-2017 (animal no. 29), 28-11-2017 (no. 33), 29-11-2017 (no. 27)
750 ppm	No abnormalities Piloerection (several animals) Piloerection (all animals)	18 to 24-10-2017, 26-10-2017 to 21-11-2017, 23 to 24-11-2017, 27-11-2017, 30-11-2017 to 3-12-2017, 5 to 9-12-2017 16-10-2017, 22-11-2017, 28-11-2017, 29-11-2017, 4-12-2017 17 and 25-10-2017
1500 ppm	No abnormalities Piloerection (several animals) Piloerection (all animals)	1-11-2017, 4-11-2017, 10 to 21-11-2017, 23 to 24-11-2017, 3-12-2017, 5 to 9-12-2017 30-10-2017, 22-11-2017, 28 to 29-11-2017, 1-12-2017, 4-12-2017 16 to 29-10-2017, 31-10-2017, 2 to 3-11-2017, 5 to 9-11-2017, 27-11-2017, 30-11-2017, 2-12-2017

[redacted]

The above observations were noted during group-wise observation about halfway through the 6-hour exposure period.

First exposure: 16 October 2017; last exposure: 9 December 2017.
No animals were exposed in the period: 23-27 November 2017 (group 1), 23-27 November and 9 December 2017 (group 2), and 25-26 November 2017 (groups 3 and 4), because animals in these groups were littering.

30/Jan/2018 16:29:09

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 3.1: Body weight males during the study

Day(s) Relative to Start Date

Sex: Male		Bodywt day -x (g) [G]	Bodywt day 0 (g) [G]	Bodywt (g) [C]	Bodywt (g) [C]	Bodywt (g) [C]	Bodywt (g) [C]	Bodywt (g) [C]
		-3	0	7	14	21	28	34
0 ppm	Mean	334.85	341.77	351.22	362.92	366.55	378.28	387.13
	SD	20.14	21.16	24.19	28.83	30.07	33.61	36.46
	N	12	12	12	12	12	12	12
250 ppm	Mean	333.83	333.35	344.93	353.18	353.81	363.63	372.19
	SD	21.63	30.16	29.78	32.62	34.03	39.10	41.25
	N	12	12	12	12	12	12	12
750 ppm	Mean	333.29	339.60	338.14**	340.96**	339.63**	347.13**	355.55**
	SD	22.13	23.62	25.85	27.93	31.90	34.14	35.12
	N	12	12	12	12	12	12	12
1500 ppm	Mean	333.47	340.37	336.85**	339.60**	339.88**	345.76**	353.96**
	SD	19.72	19.71	19.50	22.22	24.56	24.54	24.36
	N	12	12	12	12	12	12	12

[G] - Ancova/Anova & Dunnett
[C] - Ancova/Anova & Dunnett {Covariate: Bodywt day 0}: ** = $p < 0.01$

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 3.2: Body weight females premating

Day(s) Relative to Start Date

Sex: Female		Bodywt day -x (g) [G]	Bodywt day 0 (g) [G]	Bodywt (g) [C]	Bodywt (g) [C]
		-3	0	7	14
0 ppm	Mean	215.73	220.80	224.11	227.88
	SD	8.59	9.75	9.65	12.80
	N	12	12	12	12
250 ppm	Mean	216.05	224.03	224.73	226.09
	SD	9.91	11.56	9.29	10.06
	N	12	12	12	12
750 ppm	Mean	215.46	220.48	217.48 *	220.50 *
	SD	8.66	6.88	7.65	7.23
	N	12	12	12	12
1500 ppm	Mean	215.10	220.58	216.48 **	215.90 **
	SD	9.29	7.71	7.90	8.43
	N	12	12	12	12

[G] - Ancova/Anova & Dunnett
[C] - Ancova/Anova & Dunnett {Covariate: Bodywt day 0}: * = $p < 0.05$; ** = $p < 0.01$

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 3.3: Body weight females gestation

Day(s) Relative to Mating (Litter: A)

Sex: Female		Bodyweights			
		Bodywt (g) [G]	Bodywt (g) [G]	Bodywt (g) [G]	Bodywt (g) [G]
		1	7	14	20
0 ppm	Mean	233.33	247.34	271.13	327.73
	SD	10.81	11.92	13.80	17.37
	N	12	12	12	12
250 ppm	Mean	233.33	249.31	270.60	329.93
	SD	10.94	13.22	13.59	17.84
	N	12	12	12	12
750 ppm	Mean	222.40*	236.93	255.98*	301.47**
	SD	8.38	9.76	13.53	23.93
	N	11	11	11	11
1500 ppm	Mean	216.26**	227.43**	246.03**	287.80**
	SD	8.19	10.34	8.68	14.03
	N	9	10	10	10

[G] - Ancova/Anova & Dunnett: * = $p < 0.05$; ** = $p < 0.01$
Litter: A = First litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 3.4: Body weight females lactation

Day(s) Relative to Littering (Litter: A)

Sex: Female		Bodyweights			
		Bodywt (g) [G]	Bodywt (g) [G]	Bodywt (g) [G]	Bodywt (g) [G1]
		0	4	7	13
0 ppm	Mean	249.84	269.34	280.63	292.46
	SD	10.75	15.29	13.73	11.94
	N	12	12	12	12
250 ppm	Mean	251.82	272.58	278.29	289.82
	SD	16.23	13.75	15.36	13.98
	N	12	12	12	12
750 ppm	Mean	239.32	257.68	262.19**	271.35**
	SD	11.09	13.92	15.42	18.95
	N	11	11	11	11
1500 ppm	Mean	224.85**	243.96**	248.93**	261.36**
	SD	11.01	10.26	9.62	10.40
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett: ** = p < 0.01
[G1] - Kruskal-Wallis & Dunnett on Ranks: ** = p < 0.01
Litter: A = First litter

[redacted]

31/Jan/2018 08:47:49

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 4.1: Body weight changes males during the study

Day(s) Relative to Start Date

Sex: Male		Wgt change last -x to 0 (g) [G]	Body wt change (g) [G1]	Body wt change (g) [G1]	Body wt change (g) [G1]	Body wt change (g) [G]	Body wt change (g) [G1]
		-3 - 0	0 - 7	7 - 14	14 - 21	21 - 28	28 - 34
0 ppm	Mean	6.92	9.45	11.70	3.63	11.73	8.85
	SD	1.94	4.73	5.38	3.52	4.72	3.32
	N	12	12	12	12	12	12
250 ppm	Mean	-0.48	11.58	8.24	0.63	9.83	8.56
	SD	13.09	6.68	4.27	4.56	8.07	2.71
	N	12	12	12	12	12	12
750 ppm	Mean	6.31	-1.46**	2.82**	-1.33	7.51	8.42
	SD	2.89	3.38	3.47	4.91	4.73	2.31
	N	12	12	12	12	12	12
1500 ppm	Mean	6.90	-3.52**	2.75**	0.28	5.88*	8.20
	SD	3.57	4.41	4.75	5.28	2.66	2.49
	N	12	12	12	12	12	12

[G] - Kruskal-Wallis & Dunnett on Ranks: * = p < 0.05
[G1] - Ancova/Anova & Dunnett: ** = p < 0.01

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 4.2: Body weight changes females premating

Day(s) Relative to Start Date

Sex: Female		Wgt change last -x to 0 (g) [G]	Body wt change (g) [G]	Body wt change (g) [G]
		-3 - 0	0 - 7	7 - 14
0 ppm	Mean	5.07	3.31	3.78
	SD	4.96	4.57	5.43
	N	12	12	12
250 ppm	Mean	7.98	0.70	1.37
	SD	4.91	4.73	2.12
	N	12	12	12
750 ppm	Mean	5.02	-2.99 *	3.02
	SD	5.74	5.14	3.66
	N	12	12	12
1500 ppm	Mean	5.48	-4.10 **	-0.58
	SD	4.59	7.20	4.57
	N	12	12	12

[G] - Ancova/Anova & Dunnett: * = p < 0.05; ** = p < 0.01

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 4.3: Body weight changes females gestation

Day(s) Relative to Mating (Litter: A)

Sex: Female		Body wt change (g) [G]	Body wt change (g) [G]	Body wt change (g) [G]
		1 - 7	7 - 14	14 - 20
0 ppm	Mean	14.01	23.79	56.59
	SD	3.25	4.42	6.58
	N	12	12	12
250 ppm	Mean	15.98	21.29	59.33
	SD	5.07	3.25	7.53
	N	12	12	12
750 ppm	Mean	14.53	19.05*	45.49*
	SD	3.67	4.27	12.60
	N	11	11	11
1500 ppm	Mean	10.77	18.60*	41.77**
	SD	6.01	3.97	9.31
	N	9	10	10

[G] - Ancova/Anova & Dunnett: * = $p < 0.05$; ** = $p < 0.01$
Litter: A = First litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 4.4: Body weight changes females lactation

Day(s) Relative to Littering (Litter: A)

Sex: Female		Body wt change (g) [G]	Body wt change (g) [G]	Body wt change (g) [G]
		0 - 4	4 - 7	7 - 13
0 ppm	Mean	19.50	11.29	11.83
	SD	9.74	2.83	5.23
	N	12	12	12
250 ppm	Mean	20.76	5.72 *	11.53
	SD	8.74	5.77	4.63
	N	12	12	12
750 ppm	Mean	18.36	4.51 *	9.16
	SD	10.33	4.92	4.68
	N	11	11	11
1500 ppm	Mean	19.11	4.97 *	12.43
	SD	7.78	7.23	3.93
	N	10	10	10

[G] - Ancova/Anova & Dunnett: * = $p < 0.05$
Litter: A = First litter

Sanitized

31/Jan/2018 14:29:44

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 5.1: Food consumption males during the study

Daily Food Cons Per Animal (Gram)

Sex: Male		Day(s) Relative to Animal Start Date 0 - 7	7 - 14	21 - 28	28 - 34
0 ppm	Mean	21.1	21.0	20.8	20.4
	SD	1.5	1.2	0.9	1.5
	N	3	3	3	3
250 ppm	Mean	20.9	19.6	20.0	19.9
	SD	2.1	2.3	1.5	2.0
	N	3	3	3	3
750 ppm	Mean	17.1*	17.2*	18.3	18.9
	SD	0.4	0.7	0.8	0.6
	N	3	3	3	3
1500 ppm	Mean	17.2*	16.8*	18.4	18.8
	SD	1.3	1.4	1.2	1.0
	N	3	3	3	3

Dunnett: * = $p < 0.05$
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 5.2: Food consumption females premating

Daily Food Cons Per Animal (Gram)

Sex: Female		Day(s) Relative to Animal Start Date 0 - 7	7 - 14
0 ppm	Mean	15.6	14.5
	SD	0.2	0.1
	N	3	3
250 ppm	Mean	15.0	14.2
	SD	0.7	0.9
	N	3	3
750 ppm	Mean	13.0**	13.2
	SD	0.6	0.2
	N	3	3
1500 ppm	Mean	12.7**	11.9**
	SD	0.3	1.1
	N	3	3

Dunnett: ** = $p < 0.01$
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 5.3: Food consumption females gestation

Daily Food Cons Per Animal

Sex: Female		Day(s) Relative to Mating (Litter: A) 0 - 7	7 - 14	14 - 20
0 ppm	Mean	16.90	17.90	20.11
	SD	1.30	1.56	1.24
	N	12	12	12
250 ppm	Mean	17.47	18.71	20.68
	SD	1.42	1.42	1.52
	N	12	12	12
750 ppm	Mean	15.86	17.29	19.40
	SD	1.33	1.88	1.86
	N	11	11	11
1500 ppm	Mean	14.78**	15.28**	17.48**
	SD	1.80	1.55	1.53
	N	9	10	10

Dunnett: ** = $p < 0.01$
Litter: A = First litter
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 5.4: Food consumption females lactation

Daily Food Cons Per Animal

Sex: Female		Day(s) Relative to Littering (Litter: A) 0 - 4	4 - 7	7 - 13
0 ppm	Mean	30.25	38.26	44.32
	SD	2.38	2.43	2.94
	N	12	12	12
250 ppm	Mean	31.15	37.44	43.77
	SD	3.18	1.69	2.06
	N	12	12	12
750 ppm	Mean	28.40	32.51*	40.07**
	SD	6.34	8.61	3.70
	N	11	11	10
1500 ppm	Mean	26.24	30.96**	36.63**
	SD	3.73	4.13	3.97
	N	10	10	10

Dunnett: * = $p < 0.05$; ** = $p < 0.01$
Litter: A = First litter
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 6: Estrus cyclicity

			pre-treatment				Pre-mating				
			Control	Low dose	Mid dose	High dose	Control		Low dose	Mid dose	High dose
Number of females evaluated		n	12	12	12	12	12		12	12	12
Number of acyclic females		n	0	0	0	0	1	f	0	2	5
		%	0.0	0.0	0.0	0.0	8.3		0.0	16.7	41.7
Length of the longest cycle											
	4	n	12	12	12	12	11		12	9	6
	5	n	0	0	0	0	0		0	1	1
	>5	n	0	0	0	0	0		0	0	0
Mean length of the		mean	4.0	4.0	4.0	4.0	4.0	kw	4.0	4.1	4.1
longest cycle (days)		sd	0	0	0	0	0.0		0.0	0.3	0.4
		n	12	12	12	12	11		12	10	7
Number of animals with prolonged		n	0	0	0	0	0	f	0	0	0
estrus period		%	0.0	0.0	0.0	0.0	0.0		0.0	0.0	0.0
Number of complete cycles		mean	2.3	2.2	2.2	2.2	3.0	kw	3.0	2.8	2.7
per animal in 14 (pretreatment)		sd	0.5	0.4	0.4	0.4	0.0		0.0	0.4	0.5
or 15 (premating) days		n	12	12	12	12	11		12	10	7

Statistics: Fisher exact test (f), Kruskal/Wallis non-parametric Anova (kw)

31/Jan/2018 14:57:59

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 7: Absolute organ weights

Day(s): 35 Relative to Start Date

Sex: Male		Terminal body wgt (g) [G]	Lungs (g) [G1]	Thyroid (g) [G2]	Testes (g) [G1]	Epididy mides (g) [G1]	Prostate (g) [G]	Seminal vesicles (g) [G]	LABC Muscle (g) [G]	Cowpers Glands (g) [G2]	Glans Penis (g) [G2]
0 ppm	Mean	365.79	1.434	0.0168	3.487	1.188	0.898	1.344	1.1098	0.1197	0.1463
	SD	33.15	0.119	0.0038	0.171	0.070	0.125	0.246	0.1003	0.0201	0.0412
	N	12	12	12	12	12	12	12	12	12	12
250 ppm	Mean	351.60	1.488	0.0163	3.384	1.180	0.840	1.343	1.0637	0.1038	0.1341
	SD	39.73	0.141	0.0037	0.309	0.095	0.136	0.257	0.1171	0.0292	0.0473
	N	12	12	12	12	12	12	12	12	12	12
750 ppm	Mean	335.73	1.408	0.0172	3.408	1.129	0.801	1.121	0.9338**	0.0922*	0.1307
	SD	33.85	0.132	0.0042	0.361	0.126	0.168	0.339	0.1303	0.0212	0.0345
	N	12	12	12	12	12	12	12	12	12	12
1500 ppm	Mean	332.44	1.440	0.0153	3.391	1.123	0.813	1.147	0.9331**	0.0940*	0.1298
	SD	23.62	0.086	0.0077	0.189	0.080	0.163	0.252	0.0971	0.0123	0.0332
	N	12	12	12	12	12	12	12	12	12	12

[G] - Ancova/Anova & Dunnett: ** = $p < 0.01$
[G1] - Ancova/Anova & Dunnett(Log)
[G2] - Kruskal-Wallis & Dunnett on Ranks: * = $p < 0.05$

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 7: Absolute organ weights

Day(s): 14 Relative to Littering (Litter: A)

Sex: Female		Terminal body wgt (g) [G]	Lungs (g) [G]	Thyroid (g) [G]	Ovaries (g) [G]	Uterus (g) [G1]
0 ppm	Mean	256.43	1.262	0.0161	0.0933	0.5328
	SD	11.39	0.061	0.0051	0.0066	0.1230
	N	12	12	12	12	12
250 ppm	Mean	254.58	1.241	0.0185	0.1015	0.5204
	SD	14.13	0.074	0.0049	0.0109	0.0954
	N	12	12	12	12	12
750 ppm	Mean	244.17	1.215	0.0148	0.0863	0.5259
	SD	17.15	0.058	0.0027	0.0117	0.1757
	N	11	11	11	11	11
1500 ppm	Mean	230.53**	1.204	0.0154	0.0814	0.4189
	SD	7.28	0.067	0.0046	0.0158	0.1122
	N	10	10	10	10	10

[G] - Ancova/Anova & Dunnett: ** = p < 0.01
[G1] - Ancova/Anova & Dunnett(Log)
Litter: A = First litter

[redacted]

Sanitized

31/Jan/2018 14:58:32

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 8: Relative organ weights

Day(s): 35 Relative to Start Date

Sex: Male		Terminal body wgt (g) [G]	Lungs rel.wgt (g/kg body wgt) [G]	Thyroid rel.wgt (g/kg body wgt) [G1]	Testes rel.wgt (g/kg body wgt) [G]	Epididy rel.wgt (g/kg body wgt) [G2]	Prostate rel.wgt (g/kg body wgt) [G]	Sem ves rel.wgt (g/kg body wgt) [G1]	LABC Muscle rel.wgt (g/kg body wgt) [G2]	Cowpers Gl. rel.wgt (g/kg body wgt) [G2]	Glans Penis rel.wgt (g/kg body wgt) [G1]
0 ppm	Mean	365.79	3.928	0.0454	9.602	3.273	2.476	3.712	3.0604	0.3303	0.3989
	SD	33.15	0.204	0.0070	0.968	0.389	0.429	0.817	0.4271	0.0697	0.1041
	N	12	12	12	12	12	12	12	12	12	12
250 ppm	Mean	351.60	4.244 **	0.0465	9.726	3.390	2.400	3.812	3.0427	0.2967	0.3837
	SD	39.73	0.236	0.0092	1.304	0.446	0.373	0.549	0.3548	0.0890	0.1319
	N	12	12	12	12	12	12	12	12	12	12
750 ppm	Mean	335.73	4.208 *	0.0513	10.185	3.380	2.409	3.323	2.7817	0.2755	0.3891
	SD	33.85	0.318	0.0122	0.856	0.361	0.564	0.925	0.2540	0.0655	0.0926
	N	12	12	12	12	12	12	12	12	12	12
1500 ppm	Mean	332.44	4.339 **	0.0454	10.249	3.395	2.459	3.462	2.8198	0.2836	0.3966
	SD	23.62	0.187	0.0218	0.955	0.352	0.541	0.816	0.3589	0.0391	0.1262
	N	12	12	12	12	12	12	12	12	12	12

[G] - Ancova/Anova & Dunnett: * = p < 0.05; ** = p < 0.01
[G1] - Kruskal-Wallis & Dunnett on Ranks
[G2] - Ancova/Anova & Dunnett(Log)

31/Jan/2018 14:57:53

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 8: Relative organ weights

Day(s): 14 Relative to Littering (Litter: A)

Sex: Female		Terminal body wgt (g) [G]	Lungs rel.wgt (g/kg body wgt) [G]	Thyroid rel.wgt (g/kg body wgt) [G]	Ovaries rel.wgt (g/kg body wgt) [G]	Uterus rel.wgt (g/kg body wgt) [G1]
0 ppm	Mean	256.43	4.925	0.0624	0.3643	2.068
	SD	11.39	0.246	0.0184	0.0310	0.413
	N	12	12	12	12	12
250 ppm	Mean	254.58	4.877	0.0727	0.3991	2.047
	SD	14.13	0.209	0.0191	0.0407	0.373
	N	12	12	12	12	12
750 ppm	Mean	244.17	4.992	0.0611	0.3557	2.191
	SD	17.15	0.360	0.0127	0.0631	0.898
	N	11	11	11	11	11
1500 ppm	Mean	230.53**	5.222*	0.0669	0.3530	1.815
	SD	7.28	0.224	0.0200	0.0669	0.463
	N	10	10	10	10	10

[G] - Ancova/Anova & Dunnett: * = $p < 0.05$; ** = $p < 0.01$
[G1] - Ancova/Anova & Dunnett(Log)
Litter: A = First litter

13/Sep/2018 15:51:49

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 9: Macroscopic observations adults

Removal Reason(s): ALL	Male				Female			
	0 ppm	250 ppm	750 ppm	1500 ppm	0 ppm	250 ppm	750 ppm	1500 ppm
Number of Animals:	12	12	12	12	12	12	12	12
all organs/tissues								
no visible lesions	9	6	5	4	6	7	3	7
adipose tissue								
abdominal adipose tissue; nodules; yellow	-	-	-	-	1	-	-	-
cavity, abdominal								
nodule; dark, 1 cm	-	-	-	-	-	1	-	-
lungs								
discoloration; red, partly	0	0	0	0	-	0	1	-
spot(s); dark / red	2	2	4	5	-	1	3	-
spots; white	0	1	0	1	-	0	0	-
lymph node, cervical/mandibular								
discoloration; red	-	-	1	1	-	0	-	-
enlarged; red	-	-	0	0	-	1	-	-
lymph node, mesenteric								
discoloration; red	-	1	-	-	-	-	-	-
enlarged	-	1	-	-	-	-	-	-
ovaries								
cyst; unilateral	-	-	-	-	-	-	1	-
seminal vesicles								
small	-	-	1	-	-	-	-	-
skin/subcutis								
sparsely haired	-	-	-	-	1	-	-	-
encrustations	-	-	-	-	1	-	-	-
stomach								
deposition; white	-	-	-	0	0	0	2	1
glandular stomach; ulcer	-	-	-	1	2	1	3	2
thymus								
discoloration; red	1	1	0	0	0	0	0	0
spots; red	2	2	3	2	3	3	3	3
uterus								
swollen	-	-	-	-	-	-	1	-

13/Sep/2018 15:58:07

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 10: Microscopic observations adults

Removal Reason(s): ALL	Male				Female			
	0 ppm	250 ppm	750 ppm	1500 ppm	0 ppm	250 ppm	750 ppm	1500 ppm
Number of Animals:	12	12	12	12	12	12	12	12
adipose tissue								
Examined	-	-	-	-	1	0	0	0
necrosis; fatty, focal	-	-	-	-	1	-	-	-
.... mild	-	-	-	-	1	-	-	-
cavity, abdominal								
Examined	-	-	-	-	0	1	0	0
fat necrosis	-	-	-	-	-	1	-	-
coagulating glands								
Examined	12	0	1	12	-	-	-	-
No Visible Lesions	12	-	1	12	-	-	-	-
epididymides								
Examined	12	0	1	12	-	-	-	-
No Visible Lesions	11	-	1	12	-	-	-	-
inflammation; mononuclear, focal	1	-	0	0	-	-	-	-
.... minimal	1	-	0	0	-	-	-	-
liver								
Examined	-	-	-	-	0	1	0	0
inflammation; mononuclear, focal	-	-	-	-	-	1	-	-
.... marked	-	-	-	-	-	1	-	-
lungs								
Examined	2	3	4	6	0	1	4	0
gross finding not confirmed	1	1	3	4	-	0	2	-
haemorrhage(s); alveolar	0	2	0	2	-	1	2	-
.... minimal	0	0	0	1	-	0	1	-
.... mild	0	2	0	1	-	1	1	-
bone spicule	0	2	2	2	-	0	1	-
alveolitis	1	1	1	1	-	0	0	-
.... minimal	0	1	0	0	-	0	0	-
.... mild	1	0	1	1	-	0	0	-
crystal; haemoglobin	1	0	0	0	-	0	0	-
.... mild	1	0	0	0	-	0	0	-
inflammation; mononuclear	0	1	1	1	-	0	0	-
.... mild	0	1	1	1	-	0	0	-
peri-vascular; inflammation; granulocytic	0	0	1	0	-	0	1	-
.... minimal	0	0	1	0	-	0	1	-
accumulation of alveolar macrophages	0	1	2	1	-	0	0	-
.... minimal	0	1	0	1	-	0	0	-

Fisher's Exact:

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 10: Microscopic observations adults

Removal Reason(s): ALL	Male				Female			
	0 ppm	250 ppm	750 ppm	1500 ppm	0 ppm	250 ppm	750 ppm	1500 ppm
Number of Animals:	12	12	12	12	12	12	12	12
lungs (Continued...)								
.... mild	0	0	1	0	-	0	0	-
.... moderate	0	0	1	0	-	0	0	-
lymph node, cervical/mandibular								
Examined	0	0	1	1	0	1	0	0
sinusoidal blood	-	-	1	1	-	1	-	-
.... mild	-	-	1	1	-	1	-	-
lymph node, mesenteric								
Examined	0	1	0	0	-	-	-	-
haemorrhage(s)	-	1	-	-	-	-	-	-
.... moderate	-	1	-	-	-	-	-	-
sinusoidal blood	-	1	-	-	-	-	-	-
nasal associated lymphoid tissue								
Examined	-	-	-	-	1	0	0	0
germinal centre development	-	-	-	-	1	-	-	-
.... mild	-	-	-	-	1	-	-	-
nose, level 1								
Examined	12	0	0	12	12	0	0	12
No Visible Lesions	12	-	-	12	10	-	-	11
inflammation; granulocytic	0	-	-	0	0	-	-	1
.... minimal	0	-	-	0	0	-	-	1
inflammation; mixed	0	-	-	0	2	-	-	0
.... minimal	0	-	-	0	2	-	-	0
nose, level 2								
Examined	12	0	0	12	12	0	0	12
No Visible Lesions	12	-	-	10	10	-	-	12
inflammation; mononuclear	0	-	-	1	2	-	-	0
.... minimal	0	-	-	1	1	-	-	0
.... mild	0	-	-	0	1	-	-	0
transitional epithelium; degeneration	0	-	-	1	0	-	-	0
.... minimal	0	-	-	1	0	-	-	0
nose, level 3								
Examined	12	12	12	12	12	12	12	12
No Visible Lesions	12	12	9	4	10	12	8	0
olfactory epithelium; degeneration	0	0	1	8**	0	0	4	12***
.... minimal	0	0	1	1	0	0	4	2
.... mild	0	0	0	5	0	0	0	7
.... moderate	0	0	0	2	0	0	0	3

Fisher's Exact: * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 10: Microscopic observations adults

Removal Reason(s): ALL	Male				Female			
	0 ppm	250 ppm	750 ppm	1500 ppm	0 ppm	250 ppm	750 ppm	1500 ppm
Number of Animals:	12	12	12	12	12	12	12	12
nose, level 3 (Continued...)								
olfactory epithelium; haemorrhage(s)	0	0	2	0	0	0	0	0
.... minimal	0	0	2	0	0	0	0	0
respiratory epithelium; haemorrhage(s)	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
respiratory epithelium; inflammation; mixed	0	0	1	0	0	0	0	0
.... minimal	0	0	1	0	0	0	0	0
inflammation; mononuclear	0	0	0	0	2	0	0	0
.... minimal	0	0	0	0	1	0	0	0
.... mild	0	0	0	0	1	0	0	0
nose, level 4								
Examined	12	12	12	12	12	12	12	12
No Visible Lesions	12	11	2	0	10	10	2	0
olfactory epithelium; degeneration	0	0	9***	12***	0	0	9***	12***
.... minimal	0	0	7	0	0	0	7	0
.... mild	0	0	2	3	0	0	2	6
.... moderate	0	0	0	5	0	0	0	5
.... marked	0	0	0	4	0	0	0	1
olfactory epithelium; haemorrhage(s)	0	0	2	1	0	1	1	0
.... minimal	0	0	2	0	0	1	1	0
.... mild	0	0	0	1	0	0	0	0
respiratory epithelium; degeneration	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
inflammation; mononuclear	0	1	0	2	2	1	1	1
.... minimal	0	0	0	0	0	0	1	1
.... mild	0	1	0	2	1	1	0	0
.... moderate	0	0	0	0	1	0	0	0
rhinitis	0	0	0	0	1	0	0	0
.... mild	0	0	0	0	1	0	0	0
nose, level 5								
Examined	12	12	12	12	12	12	12	12
No Visible Lesions	12	11	1	0	10	12	0	0
olfactory epithelium; degeneration	0	0	11***	12***	0	0	12***	12***
.... minimal	0	0	1	0	0	0	0	0
.... mild	0	0	10	0	0	0	11	4
.... moderate	0	0	0	6	0	0	1	7

Fisher's Exact: * = p < 0.05; ** = p < 0.01; *** = p < 0.001

13/Sep/2018 15:58:07

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 10: Microscopic observations adults

Removal Reason(s): ALL	Male				Female			
	0 ppm	250 ppm	750 ppm	1500 ppm	0 ppm	250 ppm	750 ppm	1500 ppm
Number of Animals:	12	12	12	12	12	12	12	12
nose, level 5 (Continued...)								
.... marked	0	0	0	6	0	0	0	1
olfactory epithelium; haemorrhage(s)	0	1	2	0	0	0	0	0
.... minimal	0	1	2	0	0	0	0	0
inflammation; mononuclear	0	0	1	1	2	0	0	0
.... minimal	0	0	1	1	1	0	0	0
.... mild	0	0	0	0	1	0	0	0
nose, level 6								
Examined	12	12	12	12	12	12	12	12
No Visible Lesions	12	11	0	0	12	11	0	0
olfactory epithelium; degeneration	0	0	12***	12***	0	0	12***	12***
.... minimal	0	0	1	0	0	0	0	0
.... mild	0	0	6	0	0	0	4	2
.... moderate	0	0	5	4	0	0	8	4
.... marked	0	0	0	8	0	0	0	6
olfactory epithelium; haemorrhage(s)	0	1	3	1	0	1	3	0
.... minimal	0	1	2	1	0	1	3	0
.... mild	0	0	1	0	0	0	0	0
respiratory epithelium; degeneration	0	0	0	1	0	0	0	0
.... minimal	0	0	0	1	0	0	0	0
ovaries								
Examined	-	-	-	-	12	0	1	12
No Visible Lesions	-	-	-	-	12	-	0	12
cyst(s)	-	-	-	-	0	-	1	0
prostate gland								
Examined	12	0	1	12	-	-	-	-
No Visible Lesions	10	-	1	6	-	-	-	-
inflammation; mononuclear	2	-	0	6	-	-	-	-
.... minimal	2	-	0	3	-	-	-	-
.... mild	0	-	0	3	-	-	-	-
seminal vesicles								
Examined	12	0	2	12	-	-	-	-
No Visible Lesions	12	-	1	12	-	-	-	-
decreased content	0	-	1	0	-	-	-	-
skin/subcutis								
Examined	-	-	-	-	2	0	0	0
gross finding not confirmed	-	-	-	-	1	-	-	-

Fisher's Exact: * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$;

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 10: Microscopic observations adults

Removal Reason(s): ALL	Male				Female			
	0 ppm	250 ppm	750 ppm	1500 ppm	0 ppm	250 ppm	750 ppm	1500 ppm
Number of Animals:	12	12	12	12	12	12	12	12
skin/subcutis (Continued...)								
dermatitis; focal	-	-	-	-	1	-	-	-
.... moderate	-	-	-	-	1	-	-	-
stomach								
Examined	0	0	0	1	1	1	4	3
gross finding not confirmed	-	-	-	1	1	1	3	1
degeneration; epithelial, focal	-	-	-	0	0	0	1	2
.... mild	-	-	-	0	0	0	1	2
testes								
Examined	12	0	1	12	-	-	-	-
No Visible Lesions	11	-	1	12	-	-	-	-
seminiferous tubular atrophy	1	-	0	0	-	-	-	-
.... minimal	1	-	0	0	-	-	-	-
thymus								
Examined	3	3	3	2	3	3	4	3
No Visible Lesions	0	0	0	0	0	0	1	0
microhaemorrhage(s)	3	3	3	2	3	3	3	2
gross finding not confirmed	0	0	0	0	0	0	0	1
thyroid gland								
Examined	12	0	0	12	12	0	0	12
No Visible Lesions	12	-	-	11	12	-	-	12
inflammation; mononuclear	0	-	-	1	0	-	-	0
.... mild	0	-	-	1	0	-	-	0
ureters								
Examined	-	-	-	-	1	0	0	0
No Visible Lesions	-	-	-	-	1	-	-	-
uterus								
Examined	-	-	-	-	12	0	1	12
No Visible Lesions	-	-	-	-	12	-	0	11
lumen; dilatation	-	-	-	-	0	-	1	1
.... mild	-	-	-	-	0	-	1	1
vagina								
Examined	-	-	-	-	12	0	0	12
No Visible Lesions	-	-	-	-	12	-	-	12

Fisher's Exact:

15/May/2018 14:09:39

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 11: Mating report

Sex: Both Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Females Placed with Males	N+ve	12	12	12	12
Females Mated	N+ve	12	12	11	11
Females Not Mated	N+ve	0	0	1	1
Female Mating Index	%	100.0	100.0	91.7	91.7
Males Placed with Females	N+ve	12	12	12	12
Males Mated	N+ve	12	12	11	11
Males Not Mated	N+ve	0	0	1	1
Males that became sire	N+ve	12	12	11	10
Male Mating Index	%	100.0	100.0	91.7	91.7
Male Fertility Index	%	100.0	100.0	91.7	83.3

Litter: A = First litter
Female mating index: no. of females mated * 100/no. of females placed with males
Male mating index: no. of males mated * 100/no. of males placed with females
Male fertility index: no. of males that became sire *100/no. of males placed with females

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 11: Mating report

Sex: Both Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Pre-coital time (days) [k]	Mean	3.2	3.2	3.0	3.5
	SD	0.8	0.7	1.1	1.5
	N	12	12	11	11
Day 1-4 [f]	N+ve	12	12	11	10
	%	100.0	100.0	100.0	90.9
Day 5-7 [f]	N+ve	0	0	0	1
	%	0.0	0.0	0.0	9.1
Day 8-14 [f]	N+ve	0	0	0	0
	%	0.0	0.0	0.0	0.0
Day 1-14 [f]	N+ve	12	12	11	11
	%	100.0	100.0	100.0	100.0

[k] - Kruskal-Wallis & Wilcoxon
[f] - Chi-Squared & Fisher's Exact
Litter: A = First litter
Female mating index: no. of females mated * 100/no. of females placed with males
Male mating index: no. of males mated * 100/no. of males placed with females
Male fertility index: no. of males that became sire *100/no. of males placed with females

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 12: Pregnancy report

Sex: Female Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Females Pregnant [f]	N+ve	12	12	11	10
Females Not Pregnant	N+ve	0	0	1	2
Pregnant, Found Dead	N+ve	0	0	0	0
Pregnant, Killed Moribund	N+ve	0	0	0	0
Females Completing Delivery	N+ve	12	12	11	10
Females with Liveborn [f]	N+ve	12	12	10[1]	10
Female Fecundity Index	%	100.0	100.0	100.0	90.9
Female Fertility Index	%	100.0	100.0	91.7	83.3
Gestation Index	%	100.0	100.0	90.9	100.0
Gestation Days [k]	Mean	22.3	22.1	22.5	22.2
	SD	0.5	0.3	0.7	0.4
	N	12	12	11	10
Females with Stillborn Pups [f]	N+ve	0	0	0	0
	%	0.0	0.0	0.0	0.0
Females with all Stillborn Pup [f]	N+ve	0	0	0	0
	%	0.0	0.0	0.0	0.0

[f] - Chi-Squared & Fisher's Exact
[k] - Kruskal-Wallis & Wilcoxon
[1] Female 59 was observed littering, but the litter was lost (cannibalized) before the number of pups was registered.
In the tables animal 59 was pregnant and completed delivery, but no live born or stillborn pups were registered.
Litter: A = First litter
Female fecundity index: no. of females pregnant * 100 /no. of females mated
Female fertility index: no. of females pregnant *100/no. of females placed with males
Gestation index: no. of females with a viable litter *100/no. of females pregnant

[redacted]

15/May/2018 14:09:43

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 13: Delivery report

Sex: Female Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Pups Delivered (Total) [k]	Mean	11.6	12.1	9.1	9.6 *
	SD	1.3	1.6	3.4	2.5
	Sum	139	145	100	96
Liveborn [f]	Sum	139	145	100	96
Live Birth Index (%)		100.0	100.0	100.0	100.0
Stillborn day 0 [f]	Sum	0	0	0	0
Stillborn Index (%)		0.0	0.0	0.0	0.0

[k] - Kruskal-Wallis & Wilcoxon: * = $p < 0.05$
[f] - Chi-Squared & Fisher's Exact
Litter: A = First litter
Live birth index: no. of liveborn pups *100/no. of total pups delivered
Stillborn index: no. of stillborn pups *100/no. of total pups delivered

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 14: Litter report

Sex: Female Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Live Pups/Litter day 0 [k]	Mean	11.6	12.1	9.0	9.6 *
	SD	1.3	1.6	3.7	2.5
	N	12	12	11	10
	Sum	139	145	99	96
Live Pups/Litter day 4 Pre [k]	Mean	11.3	12.1	9.0	9.6
	SD	1.4	1.6	3.7	2.5
	N	12	12	11	10
	Sum	136	145	99	96
Culled pups	Sum	40	49	22	20
Live Pups/Litter day 4 Post [k]	Mean	8.0	8.0	7.0	7.6
	SD	0.0	0.0	2.4	1.3
	N	12	12	11	10
	Sum	96	96	77	76
Live Pups/Litter day 7 [k]	Mean	8.0	8.0	7.0	7.6
	SD	0.0	0.0	2.4	1.3
	N	12	12	11	10
	Sum	96	96	77	76

[k] - Kruskal-Wallis & Wilcoxon: * = $p < 0.05$
Litter: A = First litter
Viability index 0-4: no. of live pups on day 4 *100/no. of liveborn pups
Viability index 4-13: no. of live pups on day 13 * 100/no. of live pups post cull
Sex ratio day n: no. of live male pups on day n *100/ no. of live pups on day n
Post-implantation loss: no. of implant sites - no. of liveborn *100/no. of implant sites

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 14: Litter report

Sex: Female Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Live Pups/Litter day 13 [k]	Mean	8.0	8.0	7.0	7.6
	SD	0.0	0.0	2.4	1.3
	N	12	12	11	10
	Sum	96	96	77	76
Dead, Missing, Cannibalized d0-d4		3	0	1[1]	0
Dead, Missing, Cannibalized d5-d7		0	0	0	0
Dead, Missing, Cannibalized d8-d13		0	0	0	0
No. of litters lost entirely d0-d4 [f]	N+ve	0	0	1	0
	%	0.0	0.0	9.1	0.0
No. of litters lost entirely d5-d7 [f]	N+ve	0	0	0	0
	%	0.0	0.0	0.0	0.0
No. of litters lost entirely d8-d13 [f]	N+ve	0	0	0	0
	%	0.0	0.0	0.0	0.0
No. of litters lost entirely d0-d13 [f]	N+ve	0	0	1	0
	%	0.0	0.0	9.1	0.0
Viability Index 0-4 (%)		98	100	99	100
Viability Index 4-13 (%)		100	100	100	100

[k] - Kruskal-Wallis & Wilcoxon
[f] - Chi-Squared & Fisher's Exact
[1] Female 59 was observed littering, but the litter was lost (cannibalized) before the number of pups was registered. One missing pup was entered, representing the entire litter.
Litter: A = First litter
Viability index 0-4: no. of live pups on day 4 *100/no. of liveborn pups
Viability index 4-13: no. of live pups on day 13 * 100/no. of live pups post cull
Sex ratio day n: no. of live male pups on day n *100/ no. of live pups on day n
Post-implantation loss: no. of implant sites - no. of liveborn *100/no. of implant sites

15/May/2018 14:46:15

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 14: Litter report

Sex: Female Day(s) Relative to Littering (Litter: A)		0 ppm	250 ppm	750 ppm	1500 ppm
Live Males on Day 0	Mean	5.2	6.8	4.3	4.8
	SD	1.3	2.4	2.5	2.3
	N	12	12	11	10
	Sum	62	81	47	48
Sex Ratio Day 0 - Males (%)		44.6	55.9	47.5	50.0
Live Males on Day 13	Mean	3.9	4.2	3.6	3.8
	SD	0.3	0.4	1.1	1.4
	N	12	12	10	10
	Sum	47	50	36	38
Sex Ratio Day 13 - Males		49.0	52.1	46.8	50.0
Implantation Sites Total	Mean	12.2	13.1	10.4	10.0
	SD	1.1	1.8	3.3	2.7
	N	12	12	11	10
	Sum	146	157	114	100
No. of lost implantations	Sum	7	12	14	4
Post-Implantation Loss % [k]	Mean	4.4	7.3	15.7 *	3.5
	SD	10.8	7.6	14.1	4.6

[k] - Kruskal-Wallis & Wilcoxon: * = p < 0.05
Litter: A = First litter
Viability index 0-4: no. of live pups on day 4 *100/no. of liveborn pups
Viability index 4-13: no. of live pups on day 13 * 100/no. of live pups post cull
Sex ratio day n: no. of live male pups on day n *100/ no. of live pups on day n
Post-implantation loss: no. of implant sites - no. of liveborn *100/no. of implant sites

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 15: Pup clinical observations

Observation types: All types		0 ppm	250 ppm	750 ppm	1500 ppm
Number of Litters Examined:		12	12	10	10
Number of Pups Examined:		139	145	99	96
Skin					
Haematoma	Pups N	1	0	0	0
	Litters N	1	0	0	0
Sparsely haired area(s)	Pups N	8	8	0	0
	Litters N	1	1	0	0
Wound(s)	Pups N	0	2	0	0
	Litters N	0	2	0	0

Table 16.1: Pup body weight per litter

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Male Pup BW/L d0 (g) [G]	Mean Male Pup BW /L (g) [G1]	Mean Male Pup BW /L (g) [G1]	Mean Male Pup BW /L (g) [G1]
		0	4	7	13
0 ppm	Mean	6.33	11.44	17.40	28.60
	SD	0.48	1.22	1.47	2.52
	N	12	12	12	12
250 ppm	Mean	6.21	10.88	16.85	28.01
	SD	0.43	0.75	1.03	1.50
	N	12	12	12	12
750 ppm	Mean	6.59	11.97	17.32	28.18
	SD	0.75	1.57	1.64	2.78
	N	10	10	10	10
1500 ppm	Mean	6.01	10.82	15.84	25.90
	SD	0.57	1.53	1.75	3.14
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett
[G1] - Ancova/Anova & Dunnett {Covariate: Male pup Bodyweight day zero}
Litter: A = First litter
/L = per Litter

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 16.1: Pup body weight per litter

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Female Pup BW/L d0 (g) [G]	Mean Female Pup BW /L (g) [G1]	Mean Female Pup BW /L (g) [G1]	Mean Female Pup BW /L (g) [G1]
		0	4	7	13
0 ppm	Mean	5.94	10.84	16.55	27.52
	SD	0.46	1.19	1.47	2.53
	N	12	12	12	12
250 ppm	Mean	5.83	10.47	16.18	27.18
	SD	0.41	0.75	0.94	1.64
	N	12	12	12	12
750 ppm	Mean	6.31	11.66	17.01	27.84
	SD	0.67	1.44	1.68	3.09
	N	10	10	10	10
1500 ppm	Mean	5.78	10.59	15.63	25.53
	SD	0.68	1.58	2.02	3.29
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett
[G1] - Ancova/Anova & Dunnett {Covariate: Female pup Bodyweight day zero}
Litter: A = First litter
/L = per Litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 16.1: Pup body weight per litter

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Total Pup BW/L d0 (g) [G]	Mean Total Pup BW /L (g) [G1]	Mean Total Pup BW /L (g) [G1]	Mean Total Pup BW /L (g) [G1]
		0	4	7	13
0 ppm	Mean	6.12	11.11	16.97	28.06
	SD	0.47	1.21	1.46	2.51
	N	12	12	12	12
250 ppm	Mean	6.04	10.69	16.52	27.60
	SD	0.40	0.69	0.91	1.51
	N	12	12	12	12
750 ppm	Mean	6.42	11.78	17.14	27.95
	SD	0.68	1.47	1.65	2.99
	N	10	10	10	10
1500 ppm	Mean	5.90	10.71	15.73	25.71
	SD	0.62	1.56	1.88	3.19
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett
[G1] - Ancova/Anova & Dunnett {Covariate: Pup bodyweight on day zero}
Litter: A = First litter
/L = per Litter

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 16.2: Pup body weight changes

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Male Pup BW Gain [G]	Mean Male Pup BW Gain [G]	Mean Male Pup BW Gain [G]	Mean Male Pup BW Gain [G]
		0 - 4	4 - 7	7 - 13	0 - 13
0 ppm	Mean	5.095	5.897	11.208	22.226
	SD	0.849	0.610	1.317	2.237
	N	12	12	12	12
250 ppm	Mean	4.671	5.968	11.165	21.807
	SD	0.491	0.425	0.948	1.319
	N	12	12	12	12
750 ppm	Mean	5.377	5.332	10.855	21.581
	SD	0.948	0.657	1.307	2.387
	N	10	10	10	10
1500 ppm	Mean	4.810	5.082**	10.061	19.916
	SD	1.034	0.453	1.509	2.779
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett: ** = p < 0.01
Litter: A = First litter
/L = per Litter

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 16.2: Pup body weight changes

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Female Pup BW Gain [G]	Mean Female Pup BW Gain [G]	Mean Female Pup BW Gain [G]	Mean Female Pup BW Gain [G]
		0 - 4	4 - 7	7 - 13	0 - 13
0 ppm	Mean	4.895	5.654	10.966	21.565
	SD	0.832	0.639	1.296	2.270
	N	12	12	12	12
250 ppm	Mean	4.637	5.726	10.994	21.342
	SD	0.489	0.409	1.073	1.666
	N	12	12	12	12
750 ppm	Mean	5.353	5.287	10.836	21.523
	SD	0.853	0.766	1.602	2.761
	N	10	10	10	10
1500 ppm	Mean	4.803	5.030	9.904	19.744
	SD	0.952	0.650	1.356	2.725
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett
Litter: A = First litter
/L = per Litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 16.2: Pup body weight changes

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Pup Pup BW Gain [G]	Mean Pup Pup BW Gain [G]	Mean Pup Pup BW Gain [G]	Mean Pup Pup BW Gain [G]
		0 - 4	4 - 7	7 - 13	0 - 13
0 ppm	Mean	4.980	5.771	11.093	21.896
	SD	0.839	0.621	1.285	2.239
	N	12	12	12	12
250 ppm	Mean	4.650	5.849	11.077	21.575
	SD	0.469	0.391	1.002	1.462
	N	12	12	12	12
750 ppm	Mean	5.360	5.308	10.813	21.517
	SD	0.887	0.727	1.515	2.640
	N	10	10	10	10
1500 ppm	Mean	4.807	5.059*	9.975	19.823
	SD	1.001	0.529	1.400	2.738
	N	10	10	10	10

[G] - Ancova/Anova & Dunnett: * = $p < 0.05$
Litter: A = First litter
/L = per Litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 17: Pup anogenital distance

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Male Pup BW /L (g) [G]	Mean Male Pup AGD /L (mm) [G1]	AGDcorrected for BW - M (mm/g3) [G1]	Mean Female Pup BW /L (g) [G2]	Mean Female Pup AGD /L (mm) [G1]	AGDcorrected for BW - F (mm/g3) [G1]
		4	4	4	4	4	4
0 ppm	Mean	11.44	6.153	2.734	10.84	3.581	1.620
	SD	1.22	0.706	0.288	1.19	0.494	0.216
	N	12	12	12	12	12	12
250 ppm	Mean	10.88	6.125	2.768	10.47	3.734	1.710
	SD	0.75	0.316	0.155	0.75	0.359	0.169
	N	12	12	12	12	12	12
750 ppm	Mean	11.97	6.193	2.714	11.66	3.666	1.620
	SD	1.57	0.551	0.206	1.44	0.405	0.173
	N	10	10	10	10	10	10
1500 ppm	Mean	10.82	6.006	2.719	10.59	3.557	1.623
	SD	1.53	0.710	0.271	1.58	0.421	0.178
	N	10	10	10	10	10	10

[G] - Ancova/Anova & Dunnett
[G1] - Kruskal-Wallis & Dunnett on Ranks
[G2] - Ancova/Anova & Dunnett(Log)
Litter: A = First litter
/L = per Litter

Sanitized

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 18: Pup nipple retention

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Male Pup NR /L [k]
		13
0 ppm	Mean	0.1
	SD	0.2
	N	12
250 ppm	Mean	0.0
	SD	0.1
	N	12
750 ppm	Mean	0.0
	SD	0.0
	N	10
1500 ppm	Mean	0.0
	SD	0.1
	N	10

[k] - Kruskal-Wallis & Wilcoxon
Litter: A = First litter
/L = per Litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 19: Pup organ weights

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Pup TermBW /L (g) [G]	Mean Pup (M) TermBW /L (g) [G]	Mean Pup (F) TermBW /L (g) [G]	Mean Pup Thyroid wgt (g) [G1]	Mean Pup (M) Thyroid wgt (g) [G]	Mean Pup (F) Thyroid wgt (g) [G1]
		13	13	13	13	13	13
0 ppm	Mean	28.233	28.850	27.617	0.0040	0.0039	0.0041
	SD	2.400	2.294	2.614	0.0007	0.0011	0.0009
	N	12	12	12	12	12	12
250 ppm	Mean	27.754	28.217	27.292	0.0035	0.0033	0.0037
	SD	1.902	1.678	2.399	0.0009	0.0012	0.0010
	N	12	12	12	12	12	12
750 ppm	Mean	28.155	28.400	27.910	0.0041	0.0042	0.0040
	SD	3.075	2.934	3.335	0.0013	0.0014	0.0016
	N	10	10	10	10	10	10
1500 ppm	Mean	25.570	25.620*	25.520	0.0039	0.0039	0.0038
	SD	2.969	2.960	3.082	0.0008	0.0008	0.0014
	N	10	10	10	10	10	10

[G] - Ancova/Anova & Dunnett: * = p < 0.05
[G1] - Ancova/Anova & Dunnett(Log)
Litter: A = First litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 19: Pup organ weights

Day(s) Relative to Littering (Litter: A)

Sex: Female		Mean Pup Thyroid relw (g/kg body wgt) [G]	Mean Pup (M) Thyroid relw (g/kg body wgt) [G1]	Mean Pup (F) Thyroid relw (g/kg body wgt) [G]
		13	13	13
0 ppm	Mean	0.1424	0.1352	0.1496
	SD	0.0259	0.0380	0.0337
	N	12	12	12
250 ppm	Mean	0.1262	0.1173	0.1351
	SD	0.0317	0.0392	0.0376
	N	12	12	12
750 ppm	Mean	0.1464	0.1496	0.1431
	SD	0.0483	0.0522	0.0614
	N	10	10	10
1500 ppm	Mean	0.1518	0.1539	0.1496
	SD	0.0312	0.0325	0.0524
	N	10	10	10

[G] - Ancova/Anova & Dunnett(Log)
[G1] - Ancova/Anova & Dunnett
Litter: A = First litter

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Table 20: Pup macroscopic observations, necropsy

Exam Type: Pup Necropsy		0 ppm	250 ppm	750 ppm	1500 ppm
Number of Litters Examined:		12	12	10	10
Number of Pups Examined:		24	24	20	20
General					
Skin, Total	Pups N(%)	2(8.3)	0(0.0)	0(0.0)	0(0.0)
	Litters N(%)	1(8.3)	0(0.0)	0(0.0)	0(0.0)
Liver					
Liver, Discolored	Pups N(%)	0(0.0)	1(4.2)	0(0.0)	0(0.0)
	Litters N(%)	0(0.0)	1(8.3)	0(0.0)	0(0.0)

Annexes

ENDORSEMENT OF COMPLIANCE

WITH THE OECD PRINCIPLES OF GOOD LABORATORY PRACTICE

Pursuant to the Netherlands GLP Compliance Monitoring Programme and according to Directive 2004/9/EC the conformity with the OECD Principles of GLP was assessed on 17-20 October 2017, 7 December 2017 and 31 January 2018 at

Triskelion BV
Utrechtseweg 48, 3704 HE Zeist
PO Box 844, 3700 AV Zeist

It is herewith confirmed that the afore-mentioned test facility is currently operating in compliance with the OECD Principles of Good Laboratory Practice in the following areas of expertise: Toxicity, mutagenicity, analytical and clinical chemistry, safety pharmacology, kinetics, metabolism and in-vitro studies.

.

Utrecht, 12 February 2018

NEDERLAND
STAATSTOEZICHT OP DE VOLKSGEZONDHEID

Dr R.M.A. Jaspers
Coordinating/specialist senior inspector

Health and Youth Care Inspectorate, Ministry of Health, Welfare and Sport
Stadsplateau 1, 3521 AZ Utrecht
P.O. Box 2518, 6401 DA Heerlen, The Netherlands

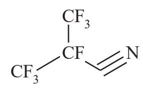
Sanitized [redacted]

[redacted]

[redacted] Analytical Laboratory

An ISO9001/2015 Certified Laboratory

Certificate of Analysis

Nominal Product: 

Product Code: [redacted]

Product Name: 2,3,3,3-tetrafluoro-2-(trifluoromethyl)propanenitrile

Physical State: Clear and colorless liquid at approximately -17 °C

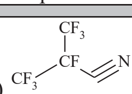
Issue Date: May 1, 2017

The sample of [redacted] was subjected to low temperature $^{1}H/^{19}F$-NMR spectral analyses to determine the purity of the nominal product and to characterize as many impurity components as possible. The qualitative and quantitative compositional results that were derived from the combined $^{1}H/^{19}F$-NMR spectral analyses are summarized below.

TABLE-1

[redacted] Sample: [redacted]

Compositional Results by Low Temperature $^{1}H/^{19}F$-NMR Cross Integration Spectral Analysis

Components [1]	$^{1}H/^{19}F$-NMR **Relative Wt.%** Concentrations
1) 	98.95%
2) CF_3-CFH-CF_3	0.78%
3) $CF_3CF_2CF_2$-CN	0.25%
4) Acetone	0.0079%
5) CH_3-CF_2-CN	0.0025%
6) Water	0.0021%
7) C_nH_{2n+2} saturated aliphatic hydrocarbons	0.0005%

1) Trace amounts of a couple other unassigned impurity components are also detected in the NMR spectra.

Analytical Chemist:
[redacted]

[redacted] Analytical Laboratory [redacted]

Sanitized

[redacted]

[redacted]

[redacted] Analytical Laboratory

An ISO9001/2015 Certified Laboratory

Certificate of Analysis

Nominal Product: 

Product Code: [redacted] ([redacted]), Synquest item # 3137-2-04, lot 28500

Product Name: 2,2,3,3,4,4,4-heptafluorobutanenitrile

Physical State: Clear and colorless liquid at approximately -17 °C

Issue Date: June 12, 2017

The sample of [redacted] ([redacted]) was subjected to GCMS, GC-FID, and low temperature $^{1}H/^{19}F$-NMR analyses to determine the purity of the nominal product and to characterize as many impurity components as possible. The qualitative and quantitative compositional results that were derived from the combined GCMS, GC-FID, and $^{1}H/^{19}F$-NMR spectral analyses are summarized below.

TABLE-1

Sample: [redacted] ([redacted]), Synquest item # 3137-2-04, lot 28500

Compositional Results by GCMS, GC-FID, and Low Temperature $^{1}H/^{19}F$-NMR Analyses

Components	$^{1}H/^{19}F$-NMR **Relative Wt.%** Concentrations & GC-FID **Relative Area%** Concentrations
1) $CF_3CF_2CF_2$-CN (mw =195)	**Purity = 99.3 relative wt.%** from combined GC-FID and NMR
2) H-CF_2CF_2-CN (mw=127)	0.26% (NMR)
At least 19 unassigned components detected by GCMS, GC-FID and NMR	0.15% (GC-FID)
3) $CF_3CF_2CF_2$-(O)-NH_2 (mw=213)	0.067% (NMR)
4) CF_3-O-CF_2CF_2-CN (mw =211)	0.067% (NMR)
5) $(CF_3)_2$-CF-CN (mw =195)	0.060% (NMR)
6) CF_3-CFH-CN (mw =127)	0.036% (NMR)
7) Probable Acetone (mw =58)	0.021% (NMR)
8) Probable H-$CF_2CF_2CF_2$-CN (mw = 177)	0.012% (NMR)
9) CF_3CF_2-O-CF_2-CN (mw =211)	0.0086% (NMR)
10) C_nH_{2n+2} saturated aliphatic hydrocarbons	$\leq$ 0.0049% (NMR)
11) Possible $CH_3CF_2CF_2$-CN (mw = 141)	0.0036% (NMR)
12) CH_3-CF_2-CN (mw =91)	0.0028% (NMR)
13) CF_3-O-CF(CF_3)-CN (mw =211)	0.0028% (NMR)

Analytical Chemists:

[redacted] (NMR)
(GCMS & GC-FID) [redacted] Analytical Laboratory [redacted]

Annex 3: Cross reference list

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Animal number	Group	Cage	Sex	Animal number	Group	Cage	Sex
2	Control	2	M	1	Control	1	F
4	Control	2	M	3	Control	1	F
6	Control	2	M	5	Control	1	F
8	Control	2	M	7	Control	1	F
10	Control	4	M	9	Control	3	F
12	Control	4	M	11	Control	3	F
14	Control	4	M	13	Control	3	F
16	Control	4	M	15	Control	3	F
18	Control	6	M	17	Control	5	F
20	Control	6	M	19	Control	5	F
22	Control	6	M	21	Control	5	F
24	Control	6	M	23	Control	5	F
26	Low-dose	8	M	25	Low-dose	7	F
28	Low-dose	8	M	27	Low-dose	7	F
30	Low-dose	8	M	29	Low-dose	7	F
32	Low-dose	8	M	31	Low-dose	7	F
34	Low-dose	10	M	33	Low-dose	9	F
36	Low-dose	10	M	35	Low-dose	9	F
38	Low-dose	10	M	37	Low-dose	9	F
40	Low-dose	10	M	39	Low-dose	9	F
42	Low-dose	12	M	41	Low-dose	11	F
44	Low-dose	12	M	43	Low-dose	11	F
46	Low-dose	12	M	45	Low-dose	11	F
48	Low-dose	12	M	47	Low-dose	11	F
50	Mid-dose	14	M	49	Mid-dose	13	F
52	Mid-dose	14	M	51	Mid-dose	13	F
54	Mid-dose	14	M	53	Mid-dose	13	F
56	Mid-dose	14	M	55	Mid-dose	13	F
58	Mid-dose	16	M	57	Mid-dose	15	F
60	Mid-dose	16	M	59	Mid-dose	15	F
62	Mid-dose	16	M	61	Mid-dose	15	F
64	Mid-dose	16	M	63	Mid-dose	15	F
66	Mid-dose	18	M	65	Mid-dose	17	F
68	Mid-dose	18	M	67	Mid-dose	17	F
70	Mid-dose	18	M	69	Mid-dose	17	F
72	Mid-dose	18	M	71	Mid-dose	17	F
74	High-dose	20	M	73	High-dose	19	F
76	High-dose	20	M	75	High-dose	19	F
78	High-dose	20	M	77	High-dose	19	F
80	High-dose	20	M	79	High-dose	19	F
82	High-dose	22	M	81	High-dose	21	F
84	High-dose	22	M	83	High-dose	21	F
86	High-dose	22	M	85	High-dose	21	F
88	High-dose	22	M	87	High-dose	21	F
90	High-dose	24	M	89	High-dose	23	F
92	High-dose	24	M	91	High-dose	23	F
94	High-dose	24	M	93	High-dose	23	F
96	High-dose	24	M	95	High-dose	23	F

Sanitized [redacted]

Special Diets Services

Special Diets Services
P.O. Box 705, Witham
Essex, CM8 3AD, England
Tel: +44 (0) 1376 511260
Fax: +44 (0) 1376 511247

Tuesday, 05 September 2017

OOG

Dear Sir/Madam,

I am writing to inform you that analysis results for a batch of diet has varied more than we were expecting. The information is as follows:-

PRODUCT:	**VRF1 (P) & (FG)**
BATCH NUMBER:	**3041**

FOUND LEVEL			GUIDELINE LEVEL	
Parameter	Unit	Result	Lower	Upper
Potassium	**mg/kg**	**9792**	**5700**	**9700**
Moisture	**%**	**8.6**	**9.0**	**11.5**
Sodium	**mg/kg**	**2008**	**2500**	**3500**

Although the moisture is below the minimum level for this diet, the hardness result of the pellet is within guidelines. The Sodium figure is outside our guidelines, but our minimum tolerance has a safety margin built in. The sodium levels will more than adequately meet the nutrient requirements of the animals. The National Research Council (1995) estimates the nutrient requirements to be 500mg/kg Sodium. Although the Potassium is very slightly higher than expected, our upper tolerance has a safety margin built in and this level should not be detrimental to the animal's health or performance. When using fixed formulations, natural variation within raw materials will occasionally cause nutrients to move outside of their expected values to some extent; we will endeavour to continue to investigate and monitor these parameters.

On the basis of the information above, the above diet has been passed for use by the undersigned.

Yours faithfully,

SPECIAL DIETS SERVICES

R S Fifield

Ralph Fifield
Product Manager

Penny Buttling
Senior Nutritionist

Sanitized [redacted]

Certificate of Analysis

SDS Special Diets Services

Product:	**VRF1 (P)** **VRF1 (P) FG**
Premix Batch Numbers:	**18815**

Batch Number:	**3041**
Date of Manufacture:	**26.06.2017**
Expiry Date	**25.03.2018**

	Unit	Result	Tolerance Limits		Analysis Error (actual) or (%)	Limit of Quantification
PHYSICAL QUALITY			Min	Max		
Diameter	mm	11.1	10.5	12.5	-	-
Resistance to Abrasion (Durability)	%	97.4	-	>97.0	-	-
Hardness (Kahl)	kg	19				
Specific Mass	g/l	627.71	-	-	-	-
Average Pellet Weight	g	2.2	-	-	-	-
Average Length	mm	18.4	15.0	24.0	-	-
NUTRIENTS						
Moisture	%	8.6	9.0	11.5	2.0	0.1 g/100g
Crude Fat (A)	%	4.7	3.8	6.2	16.4	0.1 g/100g
Crude Protein	%	18.2	17.4	20.4	1.9	0.1 g/100g
Crude Fibre	%	3.6	2.8	5.2	14.0	0.1 g/100g
Ash	%	5.9	4.5	7.0	2.7	0.1 g/100g
NFE (by difference)	%	59.0	48.0	60.0	n/a	n/a
Starch	%	36.9	-	-	2.8	2 g/100g
Total Sugars (Luff Schoorl)	%	3.8	-	-	9.6	0.1 g/100g
Calcium	mg/kg	9740	8000	12000	6.5	5 mg/kg
Phosphorus	mg/kg	6460	4000	8300	7.5	2 mg/kg
Sodium	mg/kg	2008	2500	3500	8	10 mg/kg
Potassium	mg/kg	9792	5700	9700	6.9	50 mg/kg
Copper	mg/kg	16	13	25	18	0.6 mg/kg
Manganese	mg/kg	124	85	185	2.1	0.6 mg/kg
Vitamin A	iu/kg	22200	20000	55000	15	700 iu/kg
Vitamin E	mg/kg	100	80	150	10	1 mg/kg

Sanitized [redacted]

CONTAMINANTS

Nitrogen Derivative Quality	Unit	Result	Tolerance Limits		Analysis Error (actual) or (%)	Limit of Detection
			Min	Max		
Nitrate	mg/kg	69.5	sum of NO_3 and NO_2 <500		13.8	5.0 mg/kg
Nitrite	mg/kg	Non Detected	sum of NO_3 and NO_3 <500		25.0	5.0 mg/kg
N-nitrosodimethylamine (NDMA)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg
N-nitrosodiethylamine (NDEA)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg
N-nitrosodipropylamine (NDPA)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg
N-nitrosodibutylamine (NDBA)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg
N-nitrospyrrolidine (Npyr)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg
N-nitrosdiperidine (Npip)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg
N-nitrosomorpholine (Nmor)	µg/kg	<0.25	-	<10.0	-	0.5 µg/kg

Heavy Metal Quality

Arsenic	mg/kg	0.13	-	1.00	7.7	0.002 mg/kg
Cadmium	mg/kg	0.14		0.25	17.8	0.001 mg/kg
Lead	mg/kg	0.13	-	1.50	17.4	0.005 mg/kg
Mercury	mg/kg	Non Detected	-	0.10	20.0	0.001 mg/kg

Mycotoxin Quality

B1 Aflatoxin	µg/kg	<0.2	-	-	-	0.2 µg/kg
B2 Aflatoxin	µg/kg	<0.2	-	-	-	0.2 µg/kg
G1 Aflatoxin	µg/kg	<0.2	-	-	-	0.2 µg/kg
G2 Aflatoxin	µg/kg	<0.2	-	-	-	0.2 µg/kg
Total Aflatoxins (by HPLC)	µg/kg	<0.8	-	5.0	25.0	0.8 µg/kg each of B1, B2, G1, G2

Microbiological Quality

Entero Bacteriaceae	cfu/g	<5	-	5.0	-	5 cfu/g
Escherichia Coli	cfu/g	Non Detected	-	None Detected	-	5.0 cfu/g
Fungal Units	cfu/g	Non Detected	-	1000	-	10.0 cfu/g
Salmonellae Species	cfu/g	Non Detected	-	None Detected	-	Absent in 25g
Total Viable Organisms	cfu/g	Non Detected	-	100000	-	10.0 cfu/g

Miscellaneous Quality

Antibiotic Activity M. luteus S. aureus B. subtilis		Non Detected	-	None	-	-
Selenium	µg/kg	234	-	600	13.8	20.0 µg/kg

Sanitized [redacted]

Pesticides Organos-Chlorine	Unit	Result	Tolerance Limits Min	Max	Analysis Error (actual) or (%)	Limit of Detection
Aldrin	µg/kg	Not Detected	-	<10.0	-	1.0 µg/kg
Dieldrin	µg/kg	Not Detected	-	<20.0	-	1.0 µg/kg
o.p ' DDD	µg/kg	Not Detected	-	sum<50.0	-	1.0 µg/kg
p.p ' DDD	µg/kg	Not Detected	-	sum<50.0	-	1.0 µg/kg
o.p ' DDE	µg/kg	Not Detected	-	sum<50.0	-	1.0 µg/kg
p.p ' DDE	µg/kg	Not Detected	-	sum<50.0	-	1.0 µg/kg
o.p ' DDT	µg/kg	Not Detected	-	sum<50.0	-	1.0 µg/kg
p.p ' DDT	µg/kg	Not Detected	-	sum<50.0	-	1.0 µg/kg
Endosulfan	µg/kg	Not Detected	-	<100	-	1.0 µg/kg
Endrin	µg/kg	Not Detected	-	<10.0	-	1.0 µg/kg
α HCH	µg/kg	Not Detected	-	<20.0	-	1.0 µg/kg
β HCH	µg/kg	Not Detected	-	<10.0	-	2.0 µg/kg
γ HCH	µg/kg	Not Detected	-	<100	-	2.0 µg/kg
HCB	µg/kg	Not Detected	-	<10.0	-	1.0 µg/kg
Heptachlor	µg/kg	Not Detected	-	sum<10.0	-	1.0 µg/kg
Heptachlor Epoxide	µg/kg	Not Detected	-	sum<10.0	-	1.0 µg/kg
Lindane	µg/kg	Not Detected	-	<100	-	1.0 µg/kg
PCB	µg/kg	Not Detected	-	<50.0	-	10 µg/kg

Pesticides Organos-Phosphorous

Acephate	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Azinphos methyl	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Chlorfenvinphos	µg/kg	Not Detected	-	<5000	-	50.0 µg/kg
Chlorpyriphos ethyl	µg/kg	Not Detected	-	<5000	-	50.0 µg/kg
Chlorpyriphos methyl	µg/kg	Not Detected	-	<5000	-	50.0 µg/kg
Diazinon	µg/kg	Not Detected	-	<5000	-	50.0 µg/kg
Dichlorvos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Dimethoate	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Ethoprophos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Fenitrothion	µg/kg	Not Detected	-	<5000	-	50.0 µg/kg
Fenthion	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Fonofos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Heptenophos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Malathion	µg/kg	Not Detected	-	<5000	-	20.0 µg/kg
Methamidophos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Methidathion	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Mevinphos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Monocrotophos	µg/kg	Not Detected	-	<5000	-	10.0 µg/kg
Parathion ethyl	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Parathion methyl	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Phosalone	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Phosmet	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Phosphamidon	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Profenofos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Pyridaphenthion	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Pyrimiphos ethyl	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Pyrimiphos methyl	µg/kg	Not Detected	-	<5000	-	10.0 µg/kg
Tetrachlorvinphos	µg/kg	Not Detected	-	<5000	-	100 µg/kg
Triazophos	µg/kg	Not Detected	-	<5000	-	100 µg/kg

Sanitized [redacted]

Notes:

The results are in line with expected values.

SDS AUTHORISATION	
Signed	R S Fifield
Dated	04/09/2017
Name	Ralph Fifield
Position	Product Manager

P Buttling.
04/09/2017
Penny Buttling
Senior Nutritionist

Results of periodical analyses in drinking water collected on the premises of the test facility.

Drinking water was sampled and analysed by the local waterworks (Vitens). The samples were collected on 24-05-2017 (08:15 hr) in room number 05.1.11 at Triskelion B.V., Utrechtseweg 48, Zeist.
The results presented in the table below were reported by Vitens on 02-08-2017

Parameter	Unit	Result
Temperature in situ	°C	22.0
Odour (semi-quantitative)[1,2]		0
Taste (semi-quantitative)[1,2]		0
pH		8.14
Electrical conductivity (20°C)	mS/m	25.9
Turbidity	FTE	<0.1
Oxygen	mg/l O_2	10.4
Nitrite	mg/l NO_2	<0.01
Nitrate	mg/l NO_3	6.86
Ammonia	mg/l NH_4	<0.03
Cadmium	µg/l	<0.10
Lead	µg/l	<0.5
Copper	µg/l	78.0
Iron	mg/l	0.010
Manganese	mg/l	<0.005
Total Organic Carbon (Non Purgeable Organic Carbon)	mg/l C	<0.5
Coli bacteria (37°C)	CFU/100 ml	<1
Escherichia coli (37°C)	CFU/100 ml	<1
Aeromonas bacteria (30°C)	CFU/100 ml	<10
Plate count (22°C)	CFU/ml	2

[1] Remark: The expiration date for the determination of odour and taste was exceeded. This may have increased the inaccuracy of the measurement.
[2] This observation was evaluated by Vitens as 'No abnormal change'.

Conclusion:
The above parameters meet the requirements of the Dutch Drinking Water Act.

Results of periodical analyses in drinking water collected on the premises of the test facility.

Drinking water was sampled and analysed by the local waterworks (Vitens). The samples were collected on 16-11-2017 (09:02 hr) in room number 05.1.11 at Triskelion B.V., Utrechtseweg 48, Zeist.
The results presented in the table below were reported by Vitens on 04-12-2017

Parameter	Unit	Result
Temperature in situ	°C	23.3
Odour (semi-quantitative)[1,2]		0
Taste (semi-quantitative)[1,2]		0
pH		8.10
Electrical conductivity (20°C)	mS/m	25.7
Turbidity	FTE	0.13
Oxygen	mg/l O_2	10.5
Nitrite	mg/l NO_2	<0.01
Nitrate	mg/l NO_3	6.86
Ammonia	mg/l NH_4	<0.03
Cadmium	µg/l	<0.10
Lead	µg/l	<0.5
Copper	µg/l	95.7
Iron	mg/l	0.020
Manganese	mg/l	<0.005
Total Organic Carbon (Non Purgeable Organic Carbon)	mg/l C	<0.5
Coli bacteria (37°C)	#/100 ml	<1
Escherichia coli (37°C)	#/100 ml	<1
Aeromonas bacteria (30°C)	#/100 ml	<1
Plate count (22°C)	#/ml	5

[1] Remark: The expiration date for the determination of odour and taste was exceeded. This may have increased the inaccuracy of the measurement.
[2] This observation was evaluated by Vitens as 'No abnormal change'.

Conclusion:
The above parameters meet the requirements of the Dutch Drinking Water Act.

Annex 6 Analysis of [redacted] in test atmosphere

Quantitative analysis of [redacted] in test atmosphere for an inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Author	Dr. A.J. Kleinnijenhuis
Sponsor	[redacted]
Triskelion project number	[redacted]
Triskelion study code	[redacted]
Date	27 August 2018
Status	audited draft
Number of pages of this annex	11

1 Introduction

This annex describes the analytical part of study [redacted] with regard to detection of [redacted] in test atmosphere. During the analytical part of the study several issues arose. Because of these issues only one of the performed analytical runs gave suitable results. In this annex the general outcomes of the analytical study are described and the results of the suitable run in more detail.

2 Experimental

2.1 Test substance

The test substance was [redacted] (2,3,3,3-tetrafluoro-2-(trifluoromethyl) propanenitrile, molecular formula C_4F_7N, monoisotopic mass 194.992 Da, boiling point -4.7 °C, solubility in water 0.272 mg/L, vapor pressure 253300 Pa at 20 °C, colorless gas, purity 98.95%, storage at ambient temperature). The test substance contained the impurity [redacted] at 0.25%. The sponsor provided the impurity [redacted] in a separate cylinder (2,2,3,3,4,4,4-heptafluorobutanenitrile, molecular formula C_4F_7N, monoisotopic mass 194.992 Da, boiling point 2-5 °C, vapor pressure 137895 Pa at 20 °C, colorless gas, purity > 99.3%, storage at ambient temperature, dispense number 170207, Synquest item #3137-2-04, lot 28500) was used to prepare calibration solutions.

2.2 Method development

2.2.1 Summary

The method to quantify [redacted] in test atmosphere consisted of 3 parts: 1) sampling from test atmosphere, 2) extraction and 3) instrumental analysis.

A headspace Gas Chromatography – Mass Spectrometry (GC-MS) method was implemented with regard to the instrumental analysis (part 3). Because no complete chromatographic separation could be obtained during method development, a distinguishing electron impact fragment at m/z 119 was used to discriminate between the main component of the test substance ([redacted]) and the impurity [redacted]. The fragment at m/z 119 was very intense for [redacted] and relatively low in intensity for [redacted], which made this fragment suitable for detecting the impurity and at the same time monitoring the main component of the test substance.

The first approach to sample the impurity from test atmosphere (part 1) was to use a high-boiling solvent (dimethylacetamide, DMA) as impinger liquid. In this setup, a mass flow controlled amount of test atmosphere was drawn through a impinger bottle filled with the impinger liquid. The sampling efficiency using this approach was found to be too low and therefore it was decided to switch to sampling using a sorbent. Using the sorbents XAD-2 and Porapak N the impurity could be sampled from test atmosphere with much higher efficiency. The extraction (part 2) was performed in the headspace vial during the incubation prior to headspace analysis. Porapak N sampling gave a slightly higher signal for [redacted] than XAD-2 sampling and therefore Porapak N was used in further experiments.

However, it was observed that there was considerable breakthrough to the back section of the Porapak N tubes and even to the 2nd head and back sections when 2 sorbent tubes were connected in series during test atmosphere sampling. Subsequently Porapak Q sorbent tubes were implemented during test atmosphere sampling and it was found that this sorbent exhibited the best performance of all tested sorbents. An analytical run was performed on 02 November 2017 (run 7), which was actually the only run during the study which gave suitable results.

Unfortunately, after run 7, a major issue occurred. Quite abruptly the signal for [redacted] was lost almost completely in prepared standards, although the procedure to prepare stock solutions, dilutions and calibration samples had not been changed. The signal obtained for Porapak Q samples, which were used to sample test atmosphere, appeared to be normal but could not be compared to a reference signal anymore, in order to quantify [redacted]. It was concluded that the loss of signal was thus not related to the GC-MS analysis itself, but still confirmative tests were performed with different batches of solvent and using a different detection technique (GC-)FID. The cylinder with [redacted] was stored according to the specs and the weight indicated that ample material should still be present in the cylinder to conduct the remaining analyses. Although the loss of signal in reference samples could not be explained, it was concluded that there must have been a change in the contents of the impurity cylinder. Ultimately, in consultation with the sponsor, it was decided to discontinue the analytical experiments in this study.

2.2.2 Response shift

Because response shift was observed during the analytical runs, control standards were implemented in the runs and these were injected at regular intervals. Initially it was thought that the response shift was related to the analytical performance of the system. However, in a later stage of the study it appeared that, in general, the signal decreased with increasing residence time of dissolved [redacted] in the headspace vial of the sample. Therefore it was decided to extract [redacted] from sorbent during the headspace pre-incubation and to calculate the results using the calibration curve instead of correcting for the decreasing signal in the control standards.

2.3 Analysis of the impurity in test atmosphere (run 7)

2.3.1 Experimental set up

Test atmosphere was sampled using Porapak Q tubes (SKC). The sorbent material was transferred to a headspace vial, together with 5 ml DMA. The samples were incubated at 80 °C for 30 minutes and analyzed using GC-MS. Ions at m/z 119 were detected using selected ion monitoring (SIM).

2.3.2 *Preparation of stock solutions and calibration samples.*

- Bring a 50 ml volumetric flask to volume with DMA.
- Place on an analytical balance and tare the balance.
- Open the gas cylinder and place the outlet tube in waste DMA.
- Adjust the gas flow to obtain regular bubbles.
- Transfer the tube to below the surface of the DMA in the volumetric flask.
- Lead the gaseous [redacted] through the DMA for approximately 1 minute.
- Remove the tube, subsequently close the gas cylinder and the volumetric flask.
- Weigh back the volumetric flask.
- The concentration will be approximately 50 mg / 50 ml.
- Prepare a second stock using the same procedure.

- Dilute the stock solutions 10-fold using DMA in a 5 ml volumetric flask. The diluted stock solutions will have an approximate concentration of 100 µg/ml.

- Prepare calibration solutions in an alternating fashion from the diluted stock solutions, according to the table below:

Name	Stock	Volume 100 µg/ml diluted stock (µl)	Approximate added amount (µg)	Volume DMA (µl)
Kal0	-	0	0	5000
Kal1	A	1	0.1	5000
Kal2	B	2	0.2	5000
Kal3	A	3	0.3	5000
Kal4	B	5	0.5	5000
Kal5	A	10	1	5000
Kal6	B	20	2	5000

- Close the vials using a crimp cap (with a quarter turn in between).
- Analyze the calibration samples using GC-MS.

2.3.3 *Test atmosphere sampling*

Representative test atmosphere samples were obtained from the animals' breathing zone at the center of the exposure chamber by passing mass flow controlled (Bronkhorst Hi Tec, Ruurlo, the Netherlands) amounts of test atmosphere through Porapak Q adsorption tubes using a sample flow of 24 mLn/min (in which mLn stands for normal-milliliter, the volume of a gas at standardized conditions of 273.15 K and 1013.25 hPa). Samples with a volume of 120.0, 120.0, 40.8 and 19.2 mLn were taken for groups 1, 2, 3, and 4, respectively. Thus, the expected total amount of test material captured on the adsorption tubes was comparable across the different exposure groups (~250 µg [redacted] / ~0.625 µg [redacted] per sample).

2.3.4 *Sample preparation*

- Each study sample consists of a head and a back (breakthrough) section.
- Sections are added separately to headspace vials, together with 5 ml DMA.
- Close the vials using a crimp cap (with a quarter turn in between).
- Analyze the samples using GC-MS.

[redacted]

The following study samples were analyzed:

Group	Sample codes Run 7	Target amount of test substance (µg)
1	1-9 A tm C	0
2	2-9 A t/m C	250
3	3-11 A t/m C	250
4	4-9 A t/m C	250

2.3.5 Preparation of matrix effect samples

Matrix effect samples were prepared in triplicate by addition of a blank head section to a headspace vial, together with 5 ml DMA and 10 µl of a diluted stock solution (1 µg).

- Close the vials using a crimp cap (with a quarter turn in between).
- Analyze the calibration samples using GC-MS.

2.3.6 GC-MS conditions

The following GC-MS conditions were applied:

GC	Hewlett Packard 5973 Mass selective detector
Column	PoraBond Q (25 m x 0.32 mm x 5 µm)
Injection volume	1 ml (head space), incubation 30 min at 80 °C.
Injection temperature	250 °C
Oven	40 °C (3 min) - 5 °C/min - 100 °C – 15 °C/min – 250 °C (1 min)
Run time	26 min
Injection	splitless
Carrier gas	helium
Flow	1.7 ml/min (constant flow)
Detection	MS m/z 119 (SIM)

3 Results and discussion

During run 7 two stock solutions of [redacted] were prepared in DMA. Stock 1 contained 37.82 mg / 50 ml (concentration 0.7564 mg/ml) and stock 2 contained 45.80 mg / 50 ml (concentration 0.9160 mg/ml). Diluted stock 1 was prepared by bringing 650 µl of stock 1 to 5 ml volume using DMA (concentration 98.33 µg/ml) and diluted stock 2 was prepared by bringing 550 µl of stock 2 to 5 ml volume using DMA (concentration 100.8 µg/ml). The calibration solutions were prepared according to Table 1.

Table 1: preparation of calibration solutions.

Name	Stock	Volume 100 µg/ml diluted stock (µl)	Added amount [redacted] (µg)	Volume DMA (µl)
Kal0	-	0	0	5000
Kal1	1	1	0.09833	5000
Kal2	2	2	0.2015	5000
Kal3	1	3	0.2950	5000
Kal4	2	5	0.5038	5000
Kal5	1	10	0.9833	5000
Kal6	2	20	2.015	5000

The peak areas obtained for the calibration solutions and the calibration curve equation are reported in Table 2.

Table 2: peak areas obtained for calibration solutions and calibration curve equation.

Sample name	Added amount [redacted] (µg)	[redacted] peak area (arbitrary units) [1]	[redacted] peak area (arbitrary units)
Blank DMA	0	0	0
Kal0	0	0	0
Kal1	0.09833	0	499570
Kal2	0.2015	0	1015788
Kal3	0.2950	0	1407506
Kal4	0.5038	0	2291485
Kal5	0.9833	0	3981150
Kal6	2.015	0	8781195
Intercept			66369
Slope			4274200
Correlation coefficient			0.999

[1]As expected, the main component of the test substance was not detected in calibration solutions.

The calibration graph is presented in Figure 1 of this annex and chromatograms of the lowest-concentration calibration sample are shown in Figure 2. The calibration graph had a correlation coefficient of > 0.996 and was therefore considered to be linear.

The peak areas obtained for the subsequently injected study samples are reported in Table 3. The group 1 samples were generated by sampling test atmosphere from the control group and were therefore expected to contain no [redacted]. The group 2, 3 and 4 samples were generated by sampling target amounts of 250 µg test substance from the test atmospheres.

Sample A was obtained by sampling test atmosphere using a single Porapak Q tube, which contained a head section (HS) and a back section (BS). Samples B (front) and C were obtained by sampling test atmosphere using two Porapak Q tubes, which both contained a head and back section, connected in series. Therefore sample C functioned as a breakthrough sorbent tube for sample B.

Chromatograms of a blank group 1 sample and a group 2 sample are shown in Figures 3/4 and 5/6, respectively. The chromatograms of the blank sample did not show a significant peak at the position of [redacted].

Using the determined amounts of [redacted] found on the (front) head sections, it was calculated that the mean determined concentration (in mass percentage (m%)) of [redacted] in the test atmospheres was 0.22 m% with an RSD of 17%, when it would be assumed that the recovery was 100%. The mean recovery for the matrix effect samples was 90.0% with an RSD of 6.4%. It was observed that the amount of [redacted] found on the back sections of the (front) sampling tubes was always lower than 10% with a decreasing trend going from group 2 to 4, which means that a shorter sampling time resulted in a more efficient sampling. The amount of [redacted] found on the samples C was negligible.

4 Conclusion

During the method development phase several issues prevented the regular analysis of the test atmospheres generated in study [redacted]. The analytical run performed on 02 November 2017 (run 7) was the only run which gave suitable results during the study. The mean determined concentration of [redacted] in the test atmospheres was 0.22 m% with an RSD of 17% during this run. Based on the results of run 7, it was concluded that the sampling of [redacted] from test atmosphere was sufficiently efficient, even when a single Porapak Q tubes were used under the applied sampling conditions. Although the repeatability of the method was suboptimal and the results were obtained in a single run, it was concluded that the test atmosphere did contain [redacted] and that the concentration was close to the expected concentration.

Table 3: study sample results.

Sample name	[redacted] peak area (arbitrary units) [1]	[redacted] peak area (arbitrary units)	Calculated amount [redacted] (µg)	Calculated conc. [redacted] (ppm)	Measured conc. (TWA) [redacted] (ppm)	Conc. [redacted] (m%)
Blank DMA	0	0	< 0.1			
Kal5 + blank HS 1	0	4110200	0.946			
Kal5 + blank HS 2	0	3802592	0.874			
Kal5 + blank HS 3	0	3630941	0.834			
Kal4	0	1872187	0.422			
Blank DMA	0	0	< 0.1			
1-9 A HS	2205	912	< 0.1	< 0.1	-	-
1-9 A BS	320	0	< 0.1			
1-9 B HS	1960	397	< 0.1	< 0.1	-	-
1-9 B BS	585	0	< 0.1			
1-9 C HS	319	0	< 0.1			
1-9 C BS	0	0	< 0.1			
Kal4	0	1222806	0.271			
Blank DMA	0	0	< 0.1			
2-9 A HS	10899706	2990321	0.684	0.66	258	0.25
2-9 A BS	1718163	242422	< 0.1			
2-9 B HS	10289466	2159747	0.490	0.47	258	0.18
2-9 B BS	1732496	154600	< 0.1			
2-9 C HS	167188	12328	< 0.1			
2-9 C BS	3434	0	< 0.1			
Kal4	0	460235	< 0.1			
Blank DMA	0	0	< 0.1			
Blank DMA	0	0	< 0.1			
Kal4	0	674142	0.142			
Blank DMA	0	0	< 0.1			
3-11 A HS	12789207	2754815	0.629	1.78	768	0.23
3-11 A BS	484520	36875	< 0.1			
3-11 B HS	14301641	3194298	0.732	2.07	768	0.27
3-11 B BS	541394	46050	< 0.1			
3-11 C HS	1598	0	< 0.1			
3-11 C BS	0	0	< 0.1			
Blank DMA	0	0	< 0.1			
4-9 A HS	11949057	2014915	0.456	2.74	1533	0.18
4-9 A BS	134884	7144	< 0.1			
4-9 B HS	13805652	2303382	0.523	3.14	1533	0.20
4-9 B BS	178585	10344	< 0.1			
4-9 C HS	0	0	< 0.1			
4-9 C BS	0	0	< 0.1			
Kal4	0	347168	< 0.1			
Blank DMA	0	0	< 0.1			

[1]Peak areas for the main component were also detected at m/z 119, see section 2.2.1. The peak area results for the main component are qualitative and cannot be used for quantitative purposes.

Figures

Figure 1: calibration curve of [redacted] in run 7.

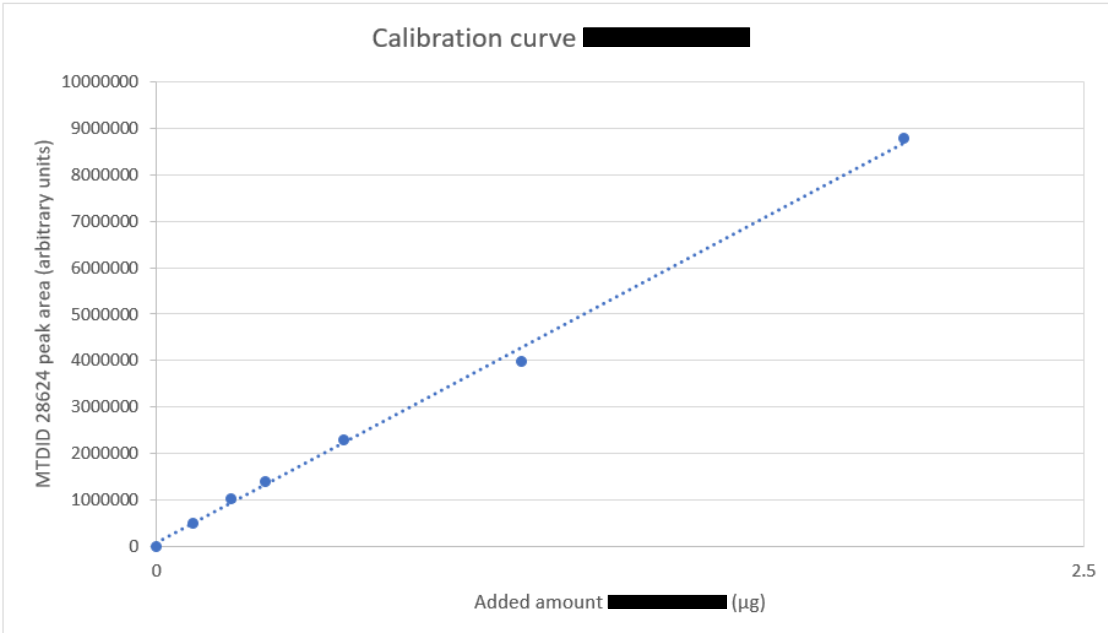


Figure 2: GC-MS chromatograms of Kal1, containing 0.09833 µg [redacted]. Top: full chromatogram, bottom left: [redacted] signal at m/z 119 and bottom right: [redacted] signal at m/z 119.

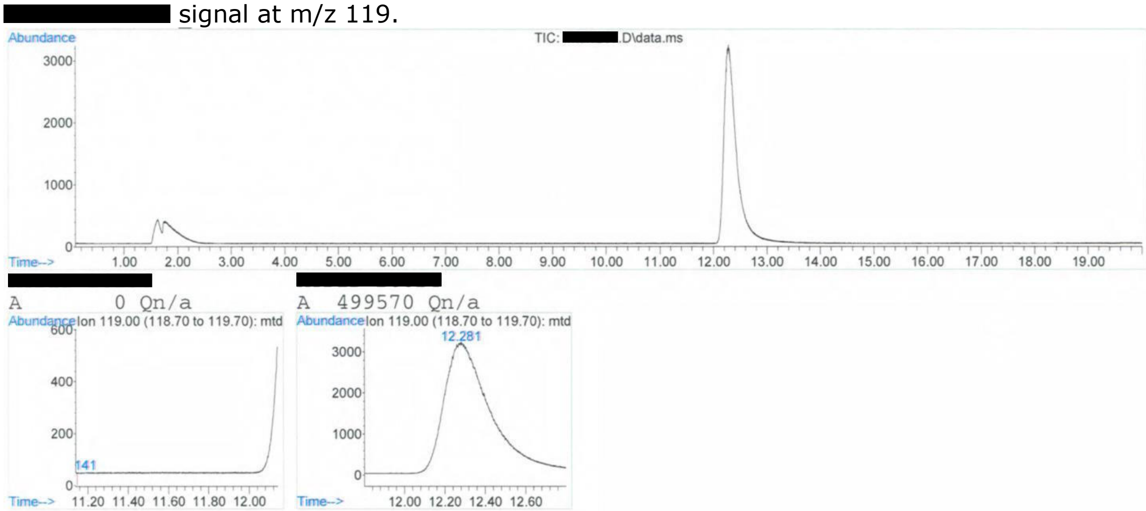


Figure 3: GC-MS chromatograms of 1-9 A HS. Top: full chromatogram, bottom left: [redacted] signal at m/z 119 and bottom right: [redacted] signal at m/z 119.

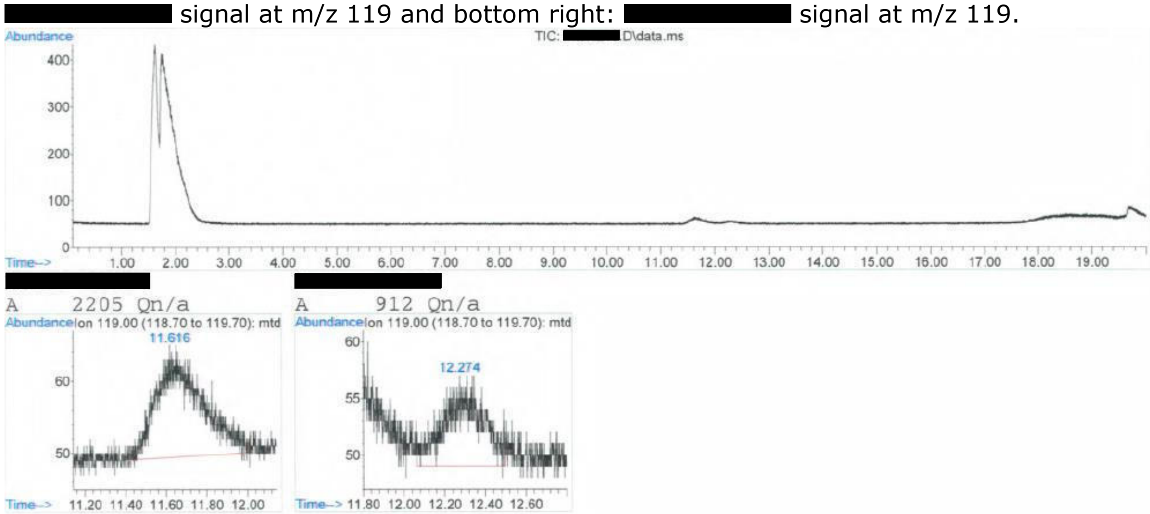


Figure 4: GC-MS chromatograms of 1-9 A BS. Top: full chromatogram, bottom left: [redacted] signal at m/z 119 and bottom right: [redacted] signal at m/z 119.

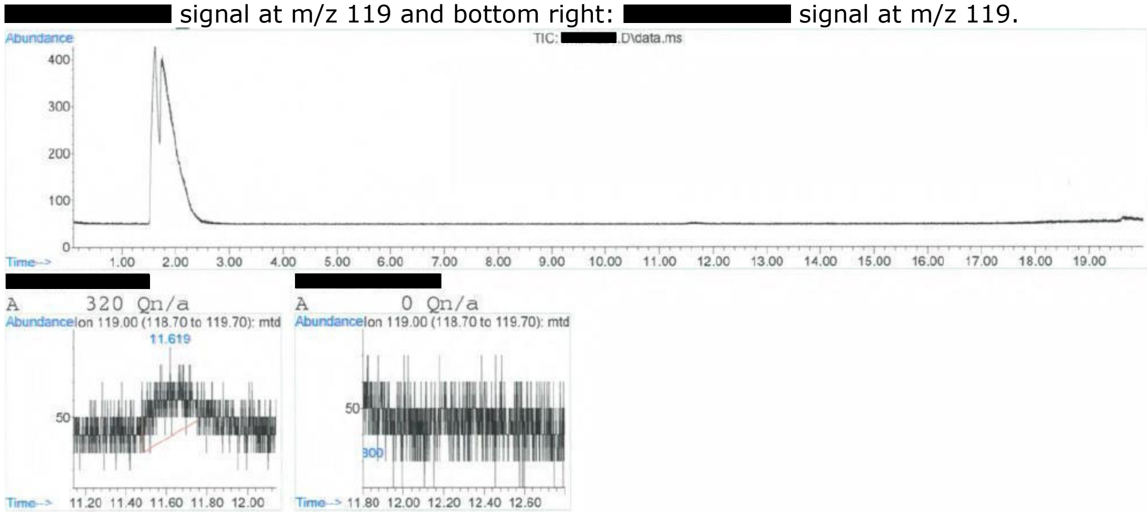


Figure 5: GC-MS chromatograms of 2-9 A HS. Top: full chromatogram, bottom left: [redacted] signal at m/z 119 (retention time 11.4 minutes) and bottom right: [redacted] signal at m/z 119 (retention time 12.2 minutes).

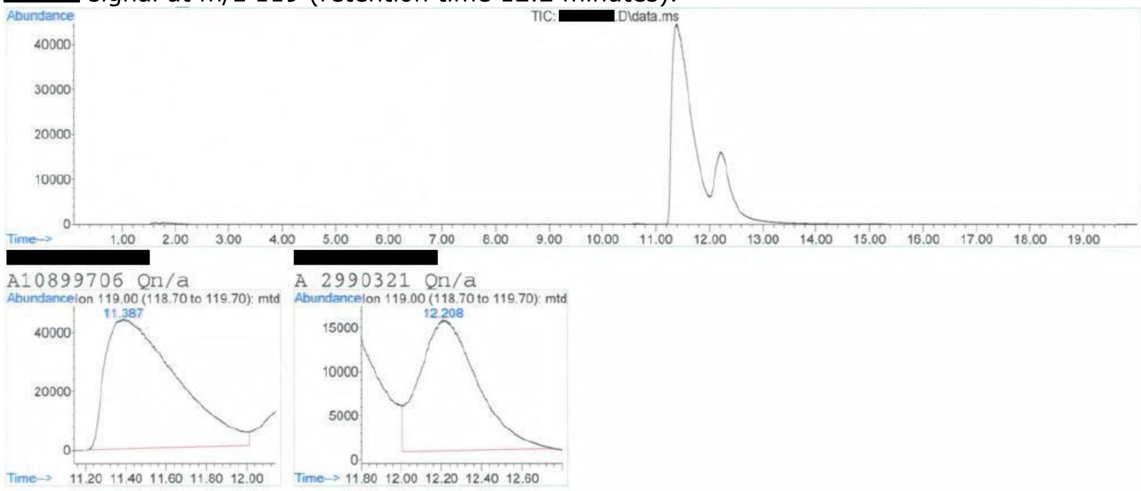
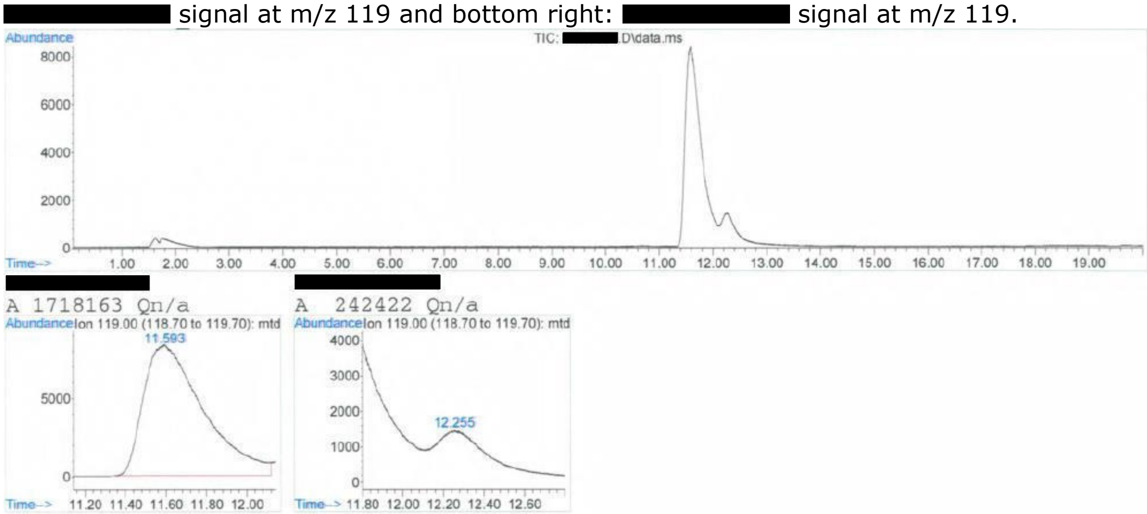


Figure 6: GC-MS chromatograms of 2-9 A BS. Top: full chromatogram, bottom left: [redacted] signal at m/z 119 and bottom right: [redacted] signal at m/z 119.



Sanitized

[redacted]

STUDY REPORT

[redacted] ANNEX 7

Quantification of Thyroxine (T4) in serum

DATE	28 September 2018
AUTHOR(S)	G. van Duijn, PhD
SPONSOR	[redacted]
TRISKELION PROJECT NUMBER	[redacted]
TRISKELION STUDY CODE	[redacted]
SPONSOR STUDY CODE	--
GUIDELINE	
STATUS	Final
NUMBER OF PAGES	

Abbreviations

CV	Coefficient of Variation
ELISA	Enzyme-Linked ImmunoSorbent Assay
HRP	Horse Radish Peroxidase
mg	milligram
ml	milliliter
ng	nanogram
OD	Optical Density
PBS	Phosphate buffered saline
pg	picogram
QC	Quality Control
QC high	Quality Control high
QC med	Quality Control medium
QC low	Quality Control low
QC XX low	Quality Control Extra low
SD	Standard deviation
µl	microliter

1 Introduction

1.1 Objective and background

The objective of this study was to perform ELISA assays for the quantification of Thyroxine (T4) in rat serum. The Enzyme – linked Immunosorbent Assay kits used were derived from Cloud-Clone Corp. (CEA452Ge). T4 was analysed in rat sera obtained from the control group (0 ppm), the low-dose group (250 ppm), the mid-dose group (750 ppm), and the high-dose group (1500 ppm). For each concentration, serum concentrations were measured for adult F0 males and for 13 days- old pups (F1 males and F1 females).

1.2 Study outline

This study was performed using a validated T4 ELISA method. The validation of this ELISA assay was described in the Validation report V20776 [Chapter 5:1]. This study was performed according to the Triskelion Working Plan: “ELISA assay for the quantification of Thyroxine Hormone (T4) in rat serum” ([redacted]).

[redacted]

2 Materials and Methods

2.1 *ELISA*

This assay employs the competitive inhibition enzyme immunoassay technique. A monoclonal antibody specific to T4 has been pre-coated onto a microplate. A competitive inhibition reaction was launched between biotin labelled T4 and unlabelled T4 (from standards or samples) with the pre-coated antibody specific to T4. After incubation the unbound biotin labelled T4 and unbound unlabelled T4 were washed off. Next, avidin conjugated to Horseradish Peroxidase (HRP) was added to each microplate well and incubated. The amount of bound HRP conjugate is inversely proportional to the concentration of T4 in the sample. After addition of the substrate solution, the intensity of colour development is inversely proportional to the concentration of T4 in the sample. The ELISA checklists for the ELISA format and the ELISA assay procedure are given in the Triskelion working plans for T4 ([redacted]).

2.2 *Disposable equipment, reagents and buffers*

Pre-coated 96-well strip plates (inclusive sealers), standard (inclusive standard diluent), detection reagents A and B (inclusive assay diluents A and B), TMB substrate, stop solution and wash buffer were parts of the ELISA kits for T4 as delivered by Cloud-Clone Corp.
T4 kits: CEA452Ge; GROS no. 159439, 159440, 159441 and 159442

PBS tablets were purchased from GIBCO (Cat no. 18912014). PBS buffer was made by dissolving 1 tablet in 500 ml milli-Q water (7.5 > pH > 7.0).

2.3 *Equipment and software*

Spectra Max M5, 450 nm	Molecular Devices, The Netherlands
Soft Max Pro GXP software	Molecular Devices, The Netherlands
Excel spreadsheet	Microsoft

2.4 *Study samples*

The study samples (136 rat serum samples) were received on January 3th 2018.
All samples were in frozen condition and stored at < -18°C .

2.5 *Calibration samples*

The reconstitution of the calibration samples was prepared using the standards as delivered with the ELISA kits for T4 (Cloud-Clone Corp; CEA452Ge). Preparation of the 8 standard samples was performed according to the scheme given in working plan [redacted]. In each individual run, a calibration line comprised of 8 duplicate standards was included.
The actual concentrations of these 8 T4 standard samples were 300, 100, 50, 25, 12.5, 6.25, 3.12 and 1.56 ng/ml, respectively.

Requirements for the results of each experimental run: for at least for 6 out of 8 non-zero standard samples, the mean concentration should not deviate more than 20% from the nominal concentration, except for the lowest and the highest standard sample where 25% deviation is allowed. All standard samples were analyzed in duplicate in each run. For each duplicate of a standard, repeatability (precision), expressed as coefficient of variation (% CV), should be within 30 %.

2.6 *Quality control samples*

The following quality control (QC) samples were prepared:

- QC High (T4): undiluted sample pool
- QC Medium (T4): sample pool diluted 1:1 with PBS
- QC Low (T4): sample pool diluted 1:3 with PBS
- QC XX-Low(T4): sample pool diluted 1:7 with PBS

For each run, a sample pool was prepared as described in the checklist QC preparation given in working plans [redacted] for T4. This sample pool was composed of 24 serum samples selected out of the adult male samples.
These samples were stored at <-18 °C. Alternatively, in case the samples were used for analyses on the same day, these were stored on ice.

Requirements for the results of each experimental run:
The repeatability (precision), expressed as coefficient of variation (CV), should be within 30% for all QC samples.
For the 4 QC samples, the precision (%CV) between the samples in the dilution series (parallelism), should be within 40% (all back-calculated concentrations after dilution correction).
In the situation that the QC High or QC XX Low was out of range, these criteria should be valid for the other 3 QC samples (Medium, Low and High or XX Low).

2.7 *Statistical data evaluation*

The concentration-response relationship, measured using the CAL samples, was fitted to an unweighted 4-parameter algorithm using SoftMax Pro GxP software (version 5.2). In addition, in each individual experiment, a limited number of O.D. values from the standard lines could be masked in order to fulfil the requirements as described in paragraph 2.5 with respect to the back-calculated nominal concentration in each individual calibration sample.
The resulting calibration curve was used to back-calculate the T4 concentrations in all Quality Control samples (QC high, QC medium, QC low and QC XX low), and all individual study samples.
Ancova/Anova & Dunnett was used for statistical analysis of the results of the T4 hormone concentrations.

3 Results

3.1 Overview of experiments

A summary of all experiments is given Table 1.

Table 1: Overview of experiments

Date	Experiment	Remark
3-1-2018	Preparation of QC samples for T4 ELISA run 1	Prepared from 24 study samples
3-1-2018	Preparation of standards for run 1	8 standards for T4
3-1-2018	ELISA T4 run 1	QC's + 64 study samples + 8 standards
3-1-2018	Preparation of QC samples for T4 ELISA run 2	Prepared from 24 study samples
3-1-2018	Preparation of standards for run 2	8 standards for T4
3-1-2018	ELISA T4 run 2	QC's + 64 study samples + 8 standards Run rejected due to mistake in performance as indicated by the technician.
4-1-2018	Preparation of QC samples for T4 ELISA run 2 Repeat	Prepared from 24 study samples
4-1-2018	Preparation of standards for run 2 Repeat	8 standards for T4
4-1-2018	ELISA T4 run 2 Repeat	QC's + 64 study samples + 8 standards
4-1-2018	Preparation of QC samples for T4 ELISA run 3	Prepared from 24 study samples
4-1-2018	Preparation of standards for run 3	8 standards for T4
4-1-2018	ELISA T4 run 3	QC's + 21 study samples + 8 standards

3.2 *Analysis of study samples*

T4 was analysed in the rat serum samples from the control group (0 ppm), the low-dose group (250 ppm), the mid-dose group (750 ppm), and the high-dose group (1500 ppm). For each dose level, 3 groups of animals were defined (male generation F0, male generation F1 and female generation F1).
For T4 analysis, all study serum samples were analysed in a two-fold dilution (in case the measured concentration in a two-fold dilution was too high and thereby out of range of the ELISA quantification, the analysis was repeated with a four-fold diluted sample).
Each ELISA plate contained calibration samples, QC samples and randomly chosen study samples.

In Table 2 the results for the analysis on T4 are presented in male serum samples from generation F0.
In Table 3 the results for the analysis on T4 are presented in male serum samples from generation F1 (day 13).
In Table 4 the results for the analysis on T4 are presented in female serum samples from generation F1 (day 13).
Ancova/Anova & Dunnett was used for statistical analysis of the results of the T4 hormone concentrations.

Table 2 Concentrations of T4 in male serum samples from generation F0 (concentrations are expressed as rounded values)

Dose-Group 1	Animal no.	T4 (ng/ml)
Males	2	510.8
0 ppm	4	414.6
	6	740.3
	8	411.4
	10	290.5
	12	670.8
	14	536.8
	16	314.4
	18	509.4
	20	866.1
	22	569.5
	24	424.9
	Mean	521.6
	SD	170.8
	CV	32.7%
	Count	12

Dose-Group 2	Animal no.	T4 (ng/ml)
Males	26	496.9
250 ppm	28	331.7
	30	259.9
	32	371.7
	34	455.0
	36	408.9
	38	480.1
	40	607.6
	42	828.7
	44	531.6
	46	518.4
	48	778.2
	Mean	505.7
	SD	168.2
	CV	33.3%
	Count	12

Sanitized [redacted]

Dose-Group 3 Males 750 ppm	Animal no.	T4 (ng/ml)
	50	487.0
	52	459.4
	54	743.5
	56	561.0
	58	744.6
	60	349.6
	62	365.7
	64	265.8
	66	392.4
	68	349.8
	70	723.0
	72	183.3
	Mean	468.8
	SD	188.9
	CV	40.3%
	Count	12

Dose-Group 4 Males 1500 ppm	Animal no.	T4 (ng/ml)
	74	308.3
	76	442.4
	78	460.1
	80	323.9
	82	412.5
	84	480.2
	86	419.3
	88	403.4
	90	506.2
	92	741.1
	94	443.6
	96	598.6
	Mean	461.6
	SD	116.8
	CV	25.3%
	Count	12

Table 3 Concentrations of T4 in male serum samples from generation F1 (13 d) (concentrations are expressed as rounded values)

Dose-Group 1	Animal no.	T4 (ng/ml)
Males F1	1-2	76.6
0 ppm	3-1	136.1
	5-1	85.9
	7-1	56.1
	9-1	106.7
	11-1	41.7
	13-1	39.1
	15-1	105.6
	17-1	55.9
	19-1	82.7
	21-1	103.5
	23-1	82.3
	Mean	81.0
	SD	29.2
	CV	36.1%
	Count	12

Dose-Group 2	Animal no.	T4 (ng/ml)
Males F1	25-1	53.6
250 ppm	27-1	126.5
	29-1	82.2
	31-1	54.6
	33-1	64.9
	35-1	86.9
	37-1	65.1
	39-1	90.9
	41-1	61.9
	43-1	44.5
	45-1	99.6
	47-1	138.3
	Mean	80.8
	SD	29.4
	CV	36.4%
	Count	12

Dose-Group 3	Animal no.	T4 (ng/ml)
Males F1	49-1	78.9
750 ppm	51-1	51.8
	53-1	94.4
	55-1	73.5
	57-1	105.7
	61-1	51.8
	63-1	93.3
	65-1	48.8
	69-1	54.1
	71-1	106.7
	Mean	75.9
	SD	23.3
	CV	30.6%
	Count	10

Dose-Group 4	Animal no.	T4 (ng/ml)
Males F1	75-1	66.4
1500 ppm	77-1	73.0
	79-1	55.8
	81-1	117.8
	83-1	43.3
	85-1	52.8
	89-1	54.1
	91-1	86.3
	93-1	91.1
	95-1	55.5
	Mean	69.6
	SD	22.8
	CV	32.8%
	Count	10

Table 4 Concentrations of T4 in female serum samples from generation F1 (13d) (concentrations are expressed as rounded values)

Dose-Group 1 Females F1 0 ppm	Animal no.	T4 (ng/ml)
	1-5	111.4
	3-5	50.0
	5-5	66.6
	7-5	113.8
	9-5	39.1
	11-5	140.3
	13-5	80.4
	15-5	105.4
	17-5	102.7
	19-5	55.0
	21-5	58.6
	23-5	41.1
	Mean	80.4
	SD	33.4
	CV	41.5%
	Count	12

Dose-Group 2 Females F1 250 ppm	Animal no.	T4 (ng/ml)
	25-5	87.7
	27-5	69.2
	29-5	37.1
	31-6	113.3
	33-5	109.1
	35-5	52.1
	37-5	94.2
	39-5	76.9
	41-5	94.4
	43-5	85.2
	45-6	42.9
	47-5	65.3
	Mean	77.3
	SD	24.7
	CV	31.9%
	Count	12

Sanitized [redacted]

Dose-Group 3	Animal no.	T4 (ng/ml)
Females F1	49-2	57.7
750 ppm	51-5	110.2
	53-5	62.0
	55-6	45.0
	57-4	103.2
	61-5	93.8
	63-5	48.8
	65-5	96.2
	69-5	85.5
	71-4	33.1
	Mean	73.6
	SD	27.4
	CV	37.2%
	Count	10

Dose-Group 4	Animal no.	T4 (ng/ml)
Females F1	75-7	59.3
1500 ppm	77-6	65.4
	79-3	94.0
	81-5	91.3
	83-5	134.8
	85-3	71.3
	89-5	93.3
	91-6	101.7
	93-3	98.9
	95-5	44.0
	Mean	85.4
	SD	26.0
	CV	30.4%
	Count	10

3.3 Analysis of QC and Calibration samples

In Table 5 below data from the QC samples are summarized and weighed versus the acceptance criteria as described in paragraph 2.6 of this report with respect to repeatability and precision. For all QC samples measured, the % CV BCC (repeatability) were within the limits of the acceptance criterion of 30 %. With respect to precision, the recoveries (%) as calculated from the QC high, QC low and QC XX-low samples versus values obtained for QC medium samples, were within the limits of the acceptance criterion of 40%.

Table 5 Summary of CV values (% BCC) and recoveries (%) of QC samples

	Target	Run	Mean Back Calculated Concentration (ng/ml)	% CV BCC	Repeatability Requirement	Recovery %	Precision Requirement
QC med	T4	1	238.2 (*)	3.4	yes	100	
QC high	T4	1	349.2	2.4	yes	73.3	yes
QC low	T4	1	120.0 (*)	11.6	yes	100.8	yes
QC xx low	T4	1	51.5 (*)	11.8	yes	86.5	yes
QC med	T4	2 repeat	316.3 (*)	5.1	yes	100	
QC high	T4	2 repeat	768.4	12.8	yes	121.4	yes
QC low	T4	2 repeat	116.4 (*)	7.1	yes	73.6	yes
QC xx low	T4	2 repeat	53.9 (*)	19.0	yes	68.2	yes
QC med	T4	3	204.9 (*)	6.0	yes	100	
QC high	T4	3	386.6	13.6	yes	94.3	yes
QC low	T4	3	106.6 (*)	8.4	yes	104.0	yes
QC xx low	T4	3	46.6 (*)	7.0	yes	91.0	yes

(*): The mean back-calculated concentrations for QC Medium, Low and XX-Low for T4 were multiplied by a factor of 2, 4 and 8, respectively in order to calculate the % recovery (precision).

Table 6 Summary of CV values (% and bias (%) of standard samples

T4 (ng/ml)	Target	Run	Mean O.D	% CV (O.D.)	Repeatability Requirement	Average back calculated conc. (ng/ml)	Bias (%)
300	T4	1	0.4242	4.3	yes	289.42	- 3.5
100	T4	1	0.8092	0.6	yes	106.99	7.0
50	T4	1	1.1974	1.1	yes	49.53	- 0.9
25	T4	1	1.6180	0.8	yes	23.52	- 5.9
12.5	T4	1	1.9607	4.7	yes	12.92	3.4
6.25	T4	1	2.3239	2.4	yes	6.40	2.4
3.12	T4	1	2.6296	0.3	yes	3.15	0.9
1.56	T4	1	2.8703	2.1	yes	1.53	- 2.0
300	T4	2 repeat	0.4411	5.2	yes	324.44	8.1
100	T4	2 repeat	0.8103 (*)	0.0 (*)	(*)	86.77	-13.2
50	T4	2 repeat	1.0516	1.3	yes	49.83	- 0.3
25	T4	2 repeat	1.3841	1.2	Yes	26.27	5.1
12.5	T4	2 repeat	1.8215	1.2	yes	12.02	- 3.8
6.25	T4	2 repeat	2.1162	4.3	yes	6.89	10.2
3.12	T4	2 repeat	2.5193	0.0	Yes	2.57	-17.7
1.56	T4	2 repeat	2.6307	2.1	yes	1.77	13.7
300	T4	3	0.4254	4.9	yes	294.36	- 1.9
100	T4	3	0.8197	1.1	yes	104.24	4.2
50	T4	3	1.2238	6.5	yes	49.35	- 1.3
25	T4	3	1.6589	2.6	yes	24.17	- 3.3
12.5	T4	3	2.0316	5.6	yes	13.15	5.2
6.25	T4	3	2.4068 (*)	0.0 (*)	(*)	6.40	2.4
3.12	T4	3	2.7346 (*)	0.0 (*)	(*)	2.76	-11.7
1.56	T4	3	2.8696 (*)	0.0 (*)	(*)	1.68	7.6

(*): In run 2 repeat and run 3 individual O.D. values were masked

4 Conclusions

The ELISA’s for T4 were performed according to the protocols as described in the validation-study plans and the validation report for this type of assays (P20776/V20776). From the results as presented in Table 2 (male parental F0-generation animals), and Table 3 and 4 (male and female F1-generation pups of postnatal day 13, respectively) it was concluded that no statistically significant effects were observed on T4- hormones.

5 References

1: Triskelion report V 20776:
Validation of an ELISA assay for the quantification of Thyroxine (T4) in rat serum

The clinical signs listed below are derived from the lexicon which is part of the computer programme used for the recording of clinical observations.

RESPIRATION
Sniffing
Grunting
Increased rate
Decreased rate
Irregular
Dyspnoea
Shallow
Sneezing
Mouth breathing

GENERAL
Thin
Emaciated
Obese
Weakened
Unconscious
Pale
Red
Jaundice
Cyanosis
Warm
Cold
Dehydrated
Increased muscle tension

MOUTH
Malocclusion of incisors
Lower incisors light color
Lower incisors white
Upper incisors light color
Haemorrhagic discharge
Salivation
Stomatitis
Wart-like lesion(s)
Encrustation(s)
Chewing movement

ABDOMEN
Distension
Tense/firm
Blue/grey
Nodule(s)
Umbilical hernia

FAECES
Increased defaecation
Decreased defaecation
Hard
Soft
Diarrhoea
Pale
Haemorrhagic
Black

BEHAVIOUR
Muscle weakness
Lethargic
Hunched posture
Excessive scratching
Hyperactive
Hypoactive
Aggressive
Stereotypy
Tremors
Convulsions
Ataxia
Circling movements
Vomiting
Vocalisation
Chattering
Excessive grooming
Prone position
Myoclonic jerks

SKIN/FUR
Alopecic area(s)
Sparsely haired area(s)
Piloerection
Soiled fur
Depigmented fur
Oedema
Abscess(es)
Pimple(s)
Subcutaneous nodule(s)
Erythema
Scaly
Haematoma
Haematoma iatrogenic
Encrustation(s)
Wound(s)
Shaving wound(s)
Scar tissue
Sc. color inj. site
Color ventral of inj. site
Red iatrogenic
Scaly iatrgenic

INJECTION SITE
Small nodule
Small red sc nodule
Redness
Swollen
Warm
Shaving wound/encrustation
Haematoma sc
Red nodule with white core
Red sc nodule with wound

HEAD
Tilted
Local/general swelling
Trimmed whiskers
Erythema between ears

NOSE
Encrustation(s)
Wound
Haemorrhagic discharge
Discharge-other than red
Crooked
Swollen
Itching
Skin protrusion

EYES
Discharge
Encrustation(s)
Blepharospasm
Blepharitis
Redness conjunctivae
Microphthalmia
Macrophthalmia
Exophthalmus
Dark red
Pale
Corneal opacity/keratitis
Cataract
Panophthalmitis
Complete degeneration
Protruding nictitant membrane

EARS
Encrustration(s)
Wound(s)
Ear canal greased
Ear canal haemorrhagic
Haematoma iatrogenic
Necrotizing ear pinna
Ear pinna (partly) gone
Nodule
Swollen
Erythema

PENIS
Prolapse
Purulent discharge
Haemorrhagic discharge
Swollen preputium

PERINEUM
Soiled with urine
Soiled with faeces
Soiled with blood
Erythema
Vaginal blood
Vaginal pus
Vaginal occlusion
Membrane present
Prolapsus ani -et recti
Vulva red
Vulva swollen
Vulva nodule

EXTREMITIES (LEG(S))
Encrustation(s)
Wound(s)
Swollen leg
Broken leg
Leg(s) gone
Stiffness
Muscle weakness
Lameness
Hard skin
Pododermatitis
Swollen toe(s)
Toe(s) gone
Nail(s) gone
Popliteal lymph node enlarged

TAIL
Ringtail
Kink
(Partially) discolored
Encrustation(s)
Wound(s)
Scaly
Local thickening
Tip of tail missing
Short and thick

TESTES
Cryptorchidism
Small
Large
Firm
Soft

URETHRA
Urethritis

URINE
Haematuria

Abbreviations: inj. site = injection site sc = subcutaneous

Sanitized [redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

STUDY PLAN

[redacted]

Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

DATE	26 September 2017
AUTHOR(S)	J.G. Theuns – van Vliet J.J. van Triel A.J. Kleinnijenhuis
SPONSOR	[redacted]
TRISKELION PROJECT NUMBER	
TRISKELION STUDY CODE	
STATUS	Final
NUMBER OF PAGES	27

TRISKELION B.V. A TNO COMPANY | Utrechtseweg 48, 3704 HE Zeist | P.O. Box 844, 3700 AV Zeist | The Netherlands | T +31 88 866 2800
info@triskelion.nl | www.triskelion.nl | DUNS 490012042 | IBAN NL10INGB0654470189 | BIC/SWIFT INGBNL2A | VAT NL823253193B01

Sanitized

[redacted]

Approval of the Study Plan

Study director

Josianne / Vliet

J.G. Theuns – van Vliet

26 September 2017.

day-month-year

Program manager

M.J. Appel

26 September 2017

day-month-year

Sponsor

[redacted]

day-month-year

Contents

Contents ... **3**

Abbreviations and definitions ... **4**

1 General ... **5**
1.1 Study Sponsor ... 5
1.2 Test facility ... 5
1.3 Responsible personnel ... 5
1.4 Good Laboratory Practice and Quality Assurance ... 5
1.5 Time schedule ... 6

2 Introduction ... **7**
2.1 Objective ... 7
2.2 Applicable guidelines ... 7
2.3 Animal welfare ... 7

3 Amendments and deviations ... **8**

4 Materials and methods ... **9**
4.1 Safety measures ... 9
4.2 Characterization of the test substance ... 9
4.3 Administration of the test substance ... 10
4.4 Experimental design, groups and dose levels ... 10
4.5 Characterization of the test system ... 11
4.6 Animal allocation ... 11
4.7 Identification ... 12
4.8 Animal husbandry ... 12
4.9 Exposure equipment ... 13
4.10 Generation of the test atmosphere ... 13
4.11 Monitoring of the exposure conditions ... 14
4.12 Observations, analyses and measurements ... 15
4.13 Statistical analysis of the results ... 20

5 Reporting ... **22**

6 Archiving ... **23**

7 References ... **24**

8 Annexes ... **25**

Annex 1 Distribution list ... 26

Annex 2 – Listing of clinical signs ... 27

[redacted]

Abbreviations and definitions

AGD	Ano Genital Distance
AWB	Animal Welfare Body
d	day
GD	Gestation Day
GLP	Good Laboratory Practice
LD	Lactation Day
N or n	Number of units (cages or animals)
NOAEL	No Observed Adverse Effect Level
OECD	Organisation for Economic Co-operation and Development
pc	Post-Coitum
PD	Paring Day
PM	Pre-Mating
PN or PND	Postnatal Day
QA	Quality Assurance
QAU	Quality Assurance Unit
S.d. or SD	Standard Deviation
SPF	specific pathogen free
T4	Thyroid hormone 4 (thyroxine hormone)

Pairing date	= date of placing male and female together
Mating date	= date of copulation, positive sperm finding
Littering date	= date of delivery

Pre-mating period	data are relative to the start of exposure
Gestation period	data are relative to the mating date
Lactation period	data are relative to the littering date

Sanitized

[redacted]

1 General

1.1 Study Sponsor

Sponsor: [redacted]

Monitor:
Phone:
E-mail: [redacted]

1.2 Test facility

Triskelion B.V.	www.triskelion.nl
Postal address:	P.O. Box 844 3700 AV Zeist The Netherlands
Location:	Utrechtseweg 48 3704 HE Zeist The Netherlands
Phone:	+31 88 866 2800

1.3 Responsible personnel

Study director:	J.G. Theuns – van Vliet, M.Sc. Josianne.theuns@triskelion.nl Phone: +31 88 866 4354
Scientific contributor(s):	J.J. van Triel, M.Sc. (inhalation exposure) A.L. Menke, Ph.D. (study pathologist) A.J. Kleinnijenhuis Ph.D. (chemical analysis) G. van Duijn, Ph.D. (hormone analysis)

1.4 Good Laboratory Practice and Quality Assurance

All study activities performed by Triskelion will be conducted according to the Organisation for Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP), as revised in 1997, Paris, ENV/MC/CHEM(98)17. The OECD principles of Good Laboratory Practice are accepted by Regulatory Authorities throughout the European Commission, USA and Japan. Chemical analysis for the verification of the identity and properties of the test substance will not be performed for this study.

The QAU of Triskelion will audit the study plan, the conduct of the study, the raw data and the report. Experimental activities not audited in this study will be audited in other studies. The statement of the QAU will specify the items, the dates of audits and the dates of reports to management and to the study director. This statement will also show dates of audits of other studies for study activities not audited in the present study. Representatives of the sponsor or regulatory authorities may conduct additional inspections of the test facility and/or the raw data.

1.5 Time schedule

Arrival of the animals:	20 September 2017
Start of pre-treatment period:	29 September 2017
Start of exposure (premating period):	16 October 2017
Start of mating period:	30 October 2017
Necropsy:	20 November 2017 (males)
	From 5 December 2017 onwards (females with litters)
Unaudited draft report:	12 March 2018, unless major extension of the histopathology to the animals of the mid and low concentration groups will be necessary. Within a period of six weeks after sending the unaudited draft report, we request you to send comments on the draft report. After this period, Triskelion will finalize the report based on the comments received, unless the sponsor has indicated by letter or e-mail that an extra time period will be required to review the study report.
Final report:	26 April 2018, provided that any remarks of the study monitor on the draft report are timely available.

[redacted]

2 Introduction

2.1 Objective

The objectives of this study are to provide data on the possible effects of the test substance [redacted] on reproductive performance and development of pups by inhalation exposure during a premating period of 2 weeks, during mating and post-mating period up to 28 days in total for male rats and during a premating period of 2 weeks and mating, gestation and lactation until (or shortly after) postnatal day 13 (PN 13) for female rats.

2.2 Applicable guidelines

This study plan has been drafted in accordance with the OECD Guideline for the Testing of Chemicals 421; Reproduction/developmental toxicity screening test, adopted 29 July 2016.
With respect to the inhalation exposure, the study plan has been drafted – as far as applicable – in accordance with OECD guideline 412 (Subacute Inhalation Toxicity: 28-Day Study, adopted 7 September 2009).

2.3 Animal welfare

The welfare of the animals will be maintained in accordance with the general principles governing the use of animals in experiments of the European Communities (Directive 2010/63/EU) and Dutch legislation (The revised Experiments on Animals Act, 2014). This includes licensing of the project by the Central Committee on Animal Experimentation (project license 2016602) and approval of the study by the Triskelion Animal Welfare Body (AWB number TRIS-306).
To reduce the number of animals used for research, any remaining live animals may be used for training purposes.

3 Amendments and deviations

Intended changes to the authorized study plan will be documented in study plan amendments.

Unintended deviations from the study plan will be documented in the study file and in the final report.

[redacted]

4 Materials and methods

4.1 Safety measures

In handling the test substance, no other precautions need to be taken than those described in the General Safety Instructions of the testing facility. Standard safety and hygienic measures to exclude inhalation or contact with the skin or eyes should be observed when handling the test substance.

4.2 Characterization of the test substance

Name[1]	: [redacted]
Chemical name[1]	: 2,3,3,3-tetrafluoro-2-(trifluoromethyl)propanenitrile
Identification container label[1]	: [redacted]
Molecular formula[1]	: C_4F_7N
CAS Reg No.[1]	: 42532-60-5
Molecular weight[1]	: 195.04 g/mol
Melting point[1]	: -118°C
Boiling point[1]	: -4.7°C
Solubility in water[1]	: 0.272 mg/L at 20°C
Vapor pressure[1]	: 253300 Pa at 20°C
Hygroscopy[1]	: slight
Batch number[1]	: [redacted]
Appearance	: colorless gas
Purity[1]	: >99.5%
Storage conditions[1]	: Ambient temperature (15-25°C)
Quantity	: ~450 kg
Date of receipt	: 10 August 2017 ([redacted]) and 29 August 2017 ([redacted])
Expiration date[1]	: 31-03-2019
Supplier	: Sponsor
Triskelion dispense number	: to be specified in the study report

[1] Information provided by the sponsor

Impurity

Name[1]	: [redacted]
Chemical name[1]	: 2, 2, 3, 3, 4, 4, 4-heptafluorobutanenitrile
Identification container label[1]	: [redacted]
Molecular formula[1]	: C_4F_7N
CAS Reg No.[1]	: 375-00-8
Molecular weight[1]	: 195.04
Boiling point[1]	: 2-5 °C
Vapor pressure[1]	: 137895 Pa at 20°C
Hygroscopy[1]	: slight
Batch number[1]	: Synquest item #3137-2-04, lot 28500
Appearance	: colorless gas in lecture bottle
Purity[1]	: >99.3%
Storage conditions[1]	: Ambient temperature (15-25°C)
Quantity	: 23 g

Date of receipt	: 04 August 2017
Approved for use until[1]	: 12 June 2019
Supplier	: Sponsor
Triskelion dispense number	: 170207

[1] Information provided by the sponsor

The sponsor will be responsible for the data concerning the characterization, storage conditions, any known hazards, or any specification details of the test material. A Certificate of Analysis pertaining to the batch used in this study (as provided by the sponsor) will be included in the study report.

Remaining test substance will be returned to the sponsor after completion of all studies with this material.

4.3 Administration of the test substance

The inhalation route will be used because this is a possible route for human exposure.
The animals will be exposed to the test substance by whole-body exposure during 6 hours per exposure day. The exposure during the different study phases is as follows:

Pre exposure period:	male and females will not be exposed.
Premating period:	male and female animals will be exposed during 2 weeks prior to mating to the test substance for 5 days/week (i.e. 10 exposure days in total)
Mating period:	male and female rats will be exposed daily until mating occurs. Subsequently, male rats and non-mated female rats will be exposed daily until sacrifice.
Gestation period:	Female animals will be exposed daily from successful mating (i.e. the finding of a sperm positive vaginal smear is considered gestation day 0) up to and including gestation day 19.
Lactation period:	Females will be exposed daily starting lactation day 5 up to and including lactation day 13.

From gestation day 20 up to and including lactation day 4 exposure will be paused in order to allow the animals to deliver their litter with minimal litter disturbance.

4.4 Experimental design, groups and dose levels

The study will comprise 4 groups of 12 male and 12 female animals each, three test groups exposed to different concentrations of the test substance and one control group exposed to clean air. The animals of the control group will be handled in the same manner as those of the other groups, except for exposure to the test material.

Concentrations were selected in consultation with the sponsor and based on the results of a 28-day study with the test substance in Sprague Dawley rats and a 14-day range finding study (Triskelion study [redacted]) in Wistar Han rats with the same concentrations. Body weight data showed an exposure-related and concentration-dependent reduced growth in all groups of exposed males, whereas in females no effects on body weight were observed. Based on the treatment-related effects in males, these concentrations were selected for the OECD 421 study.

[redacted]

The various groups are presented in the table below:

Group	Color code	Target concentration test substance (ppm)	Number of rats	
			♂♂	♀♀
1 Control	White	0	12	12
2 Low-concentration	Blue	250	12	12
3 Mid-concentration	Green	750	12	12
4 High-concentration	Red	1500	12	12

During fourteen days in the pre-treatment period, vaginal smears will be made in every female rat (including surplus females) for monitoring the estrous cycle. Female rats that do not show a typical 4-5 day estrous cycle after the 2-week pre-treatment period may not be allocated to the experimental groups.

Subsequently the exposure will start. After a two-week premating period, each female will be caged with one male from the same group. Animals will be caged together until mating occurs or until 1 week has elapsed. If the number of mated females would be less than 10 per group after one week of mating, the mating period may be extended with maximally another week until there are at least 10 mated females per group. A male from a non-mated couple will then be replaced by a male from the same group that already successfully mated.

Mating pairs will be clearly identified. Every consecutive morning during the mating period, vaginal smears will be made for determination of the presence of sperm. The day on which sperm is detected in the vaginal smear will be considered as gestation day (GD) 0. Upon evidence of copulation the females will be caged individually for the birth and rearing of their pups.

If a male dies before successful copulation, it will be replaced by another male from the same group (preferably a male that already successfully mated with another female).

4.5 Characterization of the test system

The study will be conducted with albino rats. The rat will be used because this species is considered suitable for this type of study, and is usually required by regulatory agencies. Male and female Wistar Han IGS rats (Crl:WI(Han)) will be obtained from a colony maintained under SPF-conditions at Charles River Deutschland, Sulzfeld, Germany. This rat strain will be used because it is routinely used at the test facility for this type of studies.

In the study, the female rats will be about 9 weeks old and the male rats about 10 weeks old at arrival (corresponding to about 11(♀)/12(♂) weeks at the start of pre-treatment period and about 13(♀)/14(♂) weeks at the start of the treatment . The age difference between males and females is deliberate, to avoid mating of siblings. Body weight at allocation should be within ±20% of the mean weight for each sex.

4.6 Animal allocation

Upon arrival, the animals will be housed in quarantine and checked for overt signs of ill health and anomalies. During the quarantine period, serological investigation of the microbiological status will be carried out in a few randomly chosen rats of the lot delivered. If the results of

[redacted]

serology are satisfactory, the animals will be transferred to their definitive animal room (or the quarantine room will be cleared for use as experimental room). During the study additional serological investigations of the microbiological status may be conducted if considered necessary. The rats will be acclimatized to the laboratory conditions for at least 5 days. After acclimatization, the fourteen-day pre-treatment period will be started (in which the rats are not yet treated). During this fourteen day period, daily vaginal smears will be made in every female rat (including surplus females) for monitoring the estrous cycle. Female rats that do not show a typical 4-5 day estrous cycle after the 2-week pre-treatment period may not be allocated to the treatment groups. At the end of the pre-treatment period, the animals (males and females separately) will be allocated to the various groups by computer randomization proportionately to body weight and taking into account the estrous cyclicity of the females. Surplus animals will be kept in the animal room as sentinel animals (or used in the study if necessary).
Any remaining surplus animals may be used for training purposes at the end of the in-life phase of the study.

4.7 Identification

The study will be identified as Triskelion study number [redacted].
During the pre-treatment period, prior to randomization, all the rats will be identified by a temporary tail mark. After allocation to the different treatment groups the individual animals will be uniquely identified with a number that is programmed in a transponder which will be subcutaneously implanted. During the study each group of rats will be coded by a number and a color. Each cage will be provided with a card showing the color code, the animal identification numbers, the group number and the study number.
Pups will be individually identified within the litter by paw marks (tattoo).

4.8 Animal husbandry

4.8.1 Animal room

The animals will be housed under conventional conditions in one animal room. No other test systems will be housed in the same room during the study. The room will be ventilated with about 10 air changes per hour and will be targeted at a temperature of 20-24ºC and a relative humidity of 45-65%. Lighting will be artificial with a sequence of 12 hours light and 12 hours dark.

4.8.2 Caging

During exposure, the animals will be housed individually in the inhalation unit. After each exposure, the animals will be returned to their home cages. Animals will be housed in Makrolon cages with a bedding of wood shavings (Lignocel, Rettenmaier & Söhne GmbH & Co, Rosenberg, Germany) and strips of paper (Enviro-dri, Shepherd Specialty Papers, Michigan, USA) and a wooden block (ABEDD, Vienna, Austria) as environmental enrichment.
After allocation, the animals will be housed four rats to a cage (separated by sex).
For mating, one male and one female will be housed together.
Mated females will be housed individually in Makrolon cages, which will be placed in another cage rack. The location of the mated females in the new cage racks will be determined by the date of mating (females found sperm-positive on the same date will be considered a ‘lot’) and by the animal number (within each lot the mated females will be housed in the order of animal number).

4.8.3 Food and drinking water

Food and drinking water will be provided ad libitum from the arrival of the rats until the end of the study, except during exposure and unless precluded by the performance of certain laboratory investigations.
From their arrival, the rats will receive a cereal-based (closed formula) rodent diet (VRF1 (FG)) from a commercial supplier (SDS Special Diets Services, Witham, England). Each batch of diet is analysed by the supplier for nutrients and contaminants. The certificate of analysis pertaining to the batch(es) used in this study will be included in the study report. The food will be provided as a powder in stainless steel cans, covered by a perforated stainless steel plate to prevent spillage. The food in the cans will be refreshed at least once weekly.
Each cage will be supplied with domestic mains tap-water suitable for human consumption (quality guidelines according to Dutch legislation based on EC Council Directive 98/83/EC). The water will be given in polypropylene bottles, which will be cleaned weekly and filled as needed. Results of the routine physical, chemical and microbiological examination of drinking water as conducted by the supplier are made available to the test facility. In addition, the supplier periodically (twice per year) analyses water samples taken at the premises for a limited number of physical, chemical and microbiological variables. The results of the samples taken during or close to the conduct of this study will be given in the report.

4.9 Exposure equipment

The animals will be exposed to the test atmosphere in 2.2 m^3 whole body exposure units. The test atmosphere will be introduced at the top and exhausted at the bottom of the chamber. During exposure, animals will be individually housed in Type II Macrolon cages. Each whole body chamber can accommodate 60 cages. Places that will not be filled with animal cages, may be filled with plastic blocks to reduce the chamber volume and thereby the amount of test material required.

The whole body chambers will be illuminated externally by normal laboratory fluorescent tube lighting. The total air flow through the units will be monitored at least 3 times/day. The ventilation rate will be at least 10 times/hour. The atmosphere in the chambers will be maintained at a temperature of 22 ± 3ºC and a relative humidity between 30 and 70%, if possible.

4.10 Generation of the test atmosphere

The inhalation equipment is designed to expose the animals to a continuous supply of fresh test atmosphere. To generate the test atmosphere, a mass flow controlled stream of gaseous test material will be mixed with a controlled flow of clean air available as a laboratory source of (non-pressurized) HEPA-filtered air. A mass flow controlled stream of oxygen may be added to ensure an oxygen concentration of at least 19%. The resulting test atmosphere will be led to the inlet of the exposure chamber. The exposure unit for the control animals will be supplied with a controlled flow of clean filtered air only. The test atmosphere generation will be started after placing the animals in the exposure chamber; the exposure period will be determined by the start and stop of the test atmosphere generation. Details of the method will be described in the raw data and in the study report.

4.11 Monitoring of the exposure conditions

4.11.1 Actual concentration

The actual concentration of the test material in the atmosphere will be measured by total carbon analysis (TCA) at least once each hour during exposure. Test atmosphere will be sampled in the breathing zone of the animals at the center of the exposure chamber. Homogeneity of the test atmosphere concentration in the whole body chamber will be confirmed before the start of exposure by analysis of samples taken at five different locations in each exposure chamber (deviations of individual values from the mean of all five samples should not exceed 10%).
The TCA will be calibrated before the start of the study by measuring known concentrations of test material in air, prepared at approximately 80, 100 and 120% of each target concentration. The calibrations will be checked weekly during the study at each target concentration. If the measured concentration deviates more than 5% from the calculated concentration, the calibration check will be repeated. If the deviation is more than 5% at the re-check, a complete re-calibration will be carried out. The details of the method used will be included in the study report.

4.11.2 Time to attain chamber equilibration (T_{95})

The time to reach 95% of the steady state concentration (T_{95}) will be calculated as: 3V/F. This follows from the formula $C = C_\infty (1 - e^{-(FT/V)})$, describing the increase in concentration C in a perfectly stirred chamber with volume V [L] and flow F [L/min], where T [min] is the time and C_∞ is the steady state concentration.

4.11.3 Generation efficiency

The generation efficiency will be calculated from the weighed amount of test substance used (measured daily) and the calculated amount of test substance used (efficiency = calculated amount as percentage of measured amount). The calculated amount of test substance used will be based on the measured concentration and the flow of the test atmospheres.

4.11.4 Total flow, temperature, relative humidity, oxygen and carbon dioxide concentration

The total flow, temperature and relative humidity of each test atmosphere will be recorded at least hourly during exposure. The concentration of oxygen and carbon dioxide during exposure will be measured at least twice for each group. Oxygen concentration should be at least 19% and carbon dioxide should be less than 1%.

4.11.5 Chemical analysis

The concentration of [redacted] (2,2,3,3,4,4,4-heptafluorobutanenitrile, product code [redacted], an impurity of the test material present in a concentration of 0.23-0.25% (based on the Certificates of Analysis provided by the sponsor), will be determined in test atmosphere samples by Gas Chromatography – Mass Spectrometry (GC-MS). Representative test atmosphere samples will be obtained from the animals' breathing zone by passing mass flow controlled amounts of test atmosphere through glass impingers filled with a suitable impinger liquid. Samples will be obtained twice a week during the study (four samples per day: one control and 3 dose levels) resulting in a total number of about 64 samples taken during the entire exposure period. Prior to method validation, a suitable GC-MS method for the quantification of [redacted] will be implemented. [redacted] (Synquest item # 3137-2-04, lot 28500, provided by the sponsor) will be used as reference standard. Details of the method will be described in the study report.

Method validation samples will be analyzed in triplicate per concentration level (at 0%, 50%, 100% and 150% of the test substance concentration in impinger liquid to be used during the study) after simulation of the experimental test atmosphere sampling conditions. The analytical method will be validated to conform to the following criteria:

• Linearity: the correlation coefficients of the calibration curves should be ≥ 0.996.
• Recovery: the mean recovery of [redacted] from test atmosphere should be between 85% and 115% at each of the tested concentration levels.
• Repeatability: the relative standard deviation in the percentage recovery should be ≤ 10% at each of the tested concentration levels.
• Specificity: study sample results will be corrected for the blank signal when the signal obtained with blank samples is > 5% of the signal obtained with low-concentration validation samples.

Samples will be stored at room temperature until analysis. Sample stability will be assessed to cover the experimental conditions. Details of the analytical method and the results will be described in an annex to the study report.

4.12 Observations, analyses and measurements

4.12.1 General clinical signs

Each animal will be observed daily in the morning hours by cage-side observations and, if necessary, handled to detect signs of toxicity. All cages will be checked again in the afternoon for dead or moribund animals to minimize loss of animals from the study. The observations include, but are not restricted to, the signs listed in Annex 2. The animals will also be observed about halfway through the 6-hour exposure period, in particular to monitor any breathing abnormalities and restlessness. All abnormalities, signs of ill health or reactions to treatment will be recorded. Any animal showing signs of severe debility or intoxication, particularly if death appears imminent, will be humanely killed to prevent loss of tissues by cannibalism or autolytic degeneration.

4.12.2 Body weight

The body weight of each animal will be recorded at least once during the acclimatization period and at initiation of treatment (day 0). Subsequently, males will be weighed weekly. Females will be weighed once per week during the premating and mating period. Mated females will be weighed on days 1, 7, 14 and 20 during presumed gestation and on day 0, 4, 7 and 13 of lactation. Non-mated females will be weighed once per week after the mating period. Body weight changes will be calculated over the different weighing days.
In addition, the animals will be weighed on their scheduled necropsy date in order to calculate the correct organ to body weight ratios.

4.12.3 Food consumption

The food in the feeders will be refreshed once per week. The food consumption will be measured per cage over the same periods as the body weight are measured, except during the mating period when food intake will not be recorded. The results will be expressed in g per animal per day.

4.12.4 Estrous cycle evaluations

Vaginal smears to evaluate the estrus cycle length and normality will be made daily from the start of the pre-treatment period until confirmation of mating. Smears will be made, stained and examined in all females. An additional vaginal smear will be made at the day of sacrifice. These smears will only be analysed and reported in case of inconclusive results of histopathology of uterus and vagina.

4.12.5 Blood sampling for hormone determinations

During necropsy blood will be taken from the aorta under pentobarbital anaesthesia from all adult male and female animals. Blood will be collected in tubes with clot activator SST II. Serum will be stored in a freezer (at ≤ -18 ^{o}C). In addition, blood samples will be collected from the surplus pups per litter at culling on lactation day 4 (pooled, PND 4 pups will be sacrificed by decapitation for blood collection) and from two pups per litter at sacrifice on or shortly after lactation day 13 (individual blood will be collected from the heart whilst under CO_2/O_2 anaesthesia). Serum samples will be discarded after analysis or after issuing the final report.

4.12.6 Hormone determinations (T4)

The serum samples from the adult males and two pups per litter (LD13) will be analysed for T4 hormone levels.
Analysis will be performed with commercially available ELISA kits of Cloud-Clone Corp (kit CEA452Ge). The ELISA will be performed according to a validated method based on the manufacturer's protocol and will be described in detail, together with the results of the measurements, in an Annex to the report.

When relevant, and in consultation with the sponsor, specified in an amendment and at additional costs, T4 in blood samples from the dams and the day 4 pups will be analysed.

4.12.7 Blood sampling for possible toxicokinetic evaluations

During necropsy blood will be taken from the aorta under pentobarbital anaesthesia from all adult male and female animals. Blood will be collected in tubes with clot activator SST II. Serum will be stored in a freezer (at ≤ -18 ^{o}C) for possible future bioanalysis and toxicokinetic evaluation. Samples will be discarded after finalization of the report.

4.12.8 Sacrifice, blood samples, gross necropsy and histology of adult animals

The animals will be sacrificed by exsanguination from the abdominal aorta under pentobarbital anesthesia (intraperitoneal injection of sodium pentobarbital) at necropsy and then subjected to macroscopic examination for pathological changes.

On the day of necropsy of all adult females a vaginal smear will be taken to determine the stage of the estrous cycle. These smears will only be analysed and reported in case of inconclusive results of histopathology of uterus and vagina.

- Adult male animals will be sacrificed after at least 28 days of treatment.
- Parental female animals will be sacrificed on day 14 of lactation.
- Pups will be sacrificed on day 13 of lactation.
- Adult female animals that failed to mate or appeared not pregnant after mating will be sacrificed at least 21 days after the last mating date or at least 25 days after the presumed mating date, respectively.

A necropsy will also be performed on animals that die intercurrently (if not precluded by autolysis) or that have to be killed because they are moribund.

At scheduled necropsy, the organs of the adult animals indicated in the table below will be weighed (paired organs together) as soon as possible after dissection to avoid drying.
Samples of the following tissues and organs (see table below) of the adult animals will be preserved in a neutral aqueous phosphate-buffered 4% solution of formaldehyde; except for the testes and epididymides which will be preserved in Bouin's fixative).

The reproductive organs of all male and female animals will be preserved. The number of implantation sites in the uterus will be counted.
The other organs/tissues (see table below) will be preserved in five adult animals/sex/group (surviving males with the lowest identification numbers in each cage; females with a litter will be selected).
In addition to the organs and tissues in the table, all gross lesions will be preserved.

Tissue / Organ	**Organ weight**	**Tissue fixation**	
Male reproductive organs			
Epididymides	☒	☒	All males
Prostate (dorsolateral and ventral)	☒	☒	All males
Seminal vesicles and coagulation glands	☒	☒	All males
Testes[1]	☒	☒	All males
Levator ani plus bulbocavernosus muscle complex, Cowper's glands and glans penis	☒	☒*	All males
Female reproductive organs			
Ovaries	☒	☒	All females
Uterus, including cervix[2]	☒	☒	All females
Vagina	☐	☒	All females
Other organs			
All gross lesions	☐	☒	All males and females
Noses	☐	☒	All males and females
Thyroid gland[3]	☒	☒	All males and females
Lungs with trachea and larynx	☒	☒*	All males and females
Pups on postnatal day 13			
Thyroid gland[3]	☒	☒	2 selected pups per litter, preferably one male and one female pup.

* Will be preserved after weighing but not further examined.
1 Organ fixation: The tunica albuginea will be gently and shallowly punctured at the both poles of the organ with a needle to permit rapid penetration of the fixative.
2 The number of implantation sites and resorptions will be counted in the uterus. If necessary the implantation sites will be made visible following *Salewski, E (1964), Arch. Exp. Path. Pharmacol. 247, 367*.
3 The weight of the thyroid gland will be determined by direct weighing (not after fixation as suggested in the guidelines).

[redacted]

Tissues for microscopic examination will be embedded in paraffin wax, sectioned, and stained with haematoxylin and eosin, except for sections of the testes which will be stained with PAS haematoxylin.
Histopathological examination (by light microscopy) will be performed on the preserved organs and tissues of all animals of the control (group 1) and high-dose group (group 4). Organs marked with an asterisk (the levator ani plus bulbocavenosus muscle complex, Cowper's glands and glans penis) will be preserved after weighing but not further examined. The thyroid glands in the pups will only be examined if considered necessary.
If treatment-related changes are observed in a specific organ or tissue in the high-dose group, the histopathology on this organ or tissue will be extended to the intermediate-dose groups (2 and 3), in consultation with the sponsor, and specified in an amendment.
In addition, reproductive organs (ovaries, uterus, testes, epididymides, seminal vesicles and prostate) of males that failed to sire (did not mate or mated females were not pregnant) and females that were non-mated or non-pregnant, of the low- and mid-dose groups, will be microscopically examined.
Furthermore, organs showing gross lesions of animals of all groups will be microscopically examined. Histopathology will be subjected to a peer review system.

4.12.9 Parturition

At the end of the gestation period (GD 21), females will be examined twice daily for signs of parturition. Any difficulties occurring during parturition will be recorded.

4.12.10 Litter evaluation

Litters will be evaluated on the day of birth (i.e. day 0 of lactation). To keep nest disturbance to a minimum the litters will be examined only once daily for dead pups.

4.12.11 Reproductive performance

The following data will be presented for each group:
- number of adult females with normal or abnormal estrous cycle and cycle duration
- number of females placed with males and vice versa
- number of females mated and number of males mated
- number of females pregnant
- number of males that became sire
- duration of gestation
- number of females completing delivery
- number of females with liveborn and (all) stillborn pups
- total number of pups delivered (live and stillborn)
- number of live pups at day n
- number of pups lost
- number of pups culled
- number of pups alive after culling
- number of litters lost entirely
- number of male pups at day n
- number of implantation sites
- number of lost implantations

The following parameters are calculated per group:

. Pre-coïtal time (days)	= time between the start of mating and successful copulation
. Duration of gestation	= time between gestation day 0 and day of delivery

Sanitized

[redacted]

. Mating index	= no. of females mated*100/no. of females placed with males
. Male fertility index	= no. of males that became sire*100/no. of males placed with females
. Female fertility index	= no. of females pregnant*100/no. of females placed with males
. Female fecundity index	= no. of females pregnant*100/no. of females mated
. Gestation index	= no. of females with a viable litter *100/ no. of females pregnant

The following parameters are calculated on a litter basis and reported per group:

. Number of lost implantations	= no. of implant sites – no. of liveborn pups
. Post-implantation loss	= no. of implant sites – no. of liveborn *100 /no. of implant sites
. Live birth index	= no. of liveborn pups *100/no. of newborn pups
. Stillborn index	= no. of stillborn pups *100/no. of newborn pups
. Viability index 0 - 4	= no. of live pups on day 4 *100/no. of liveborn pups
. Viability index 4 - 13	= no. of pup live pups on day 13 *100/no. of live pups post cull day 4
. Sex ratio day n	= no. of live male pups on day n *100/no. of live pups on day n
. Pup mortality day n	= no. of dead pups day n*100/total no. of pups on day n

4.12.12 Observations in pups

4.12.12.1 Pup survival, sex and weight

The total litter size and numbers of each sex as well as the number of stillbirths, live- and dead pups, runts (pups that are 25% less in body weight than the mean body weight of the pups in the control group) and grossly malformed pups will be evaluated on days 0, 4, 7 and 13 of lactation. The alive pups will be individually weighed on days 0, 4, 7 and 13 of lactation. Mean pup weight will be calculated per sex and for both sexes combined per dose group.

4.12.12.2 Anogenital distance in pups

At day lactation day 4 the anogenital distance (AGD) will be measured of each pup before culling of the litter. The AGD will be reported corrected for body weight and for the square root of body weight.

4.12.12.3 Blood collection for hormone analysis

<u>Blood collection at culling</u>
On lactation day 4 the litter size will be adjusted by eliminating extra pups by random selection to yield, as nearly as possible, four pups per sex per litter.
Whenever the number of male or female pups prevents having four of each sex per litter, partial adjustment will be acceptable. Preference will be to retain at least four male pups in order to have sufficient male pups for nipple retention determinations on lactation day 13.
Blood samples will be collected from all surplus pups per litter, and serum will be pooled and stored in a freezer (at ≤ - 18 ^{o}C) for possible determination of serum T4 levels. If there is only one pup per litter above the culling target, only one pup will be used for possible hormone determinations. If a litter has no surplus pups, no blood will be collected for possible hormone determinations. Serum samples will be discarded after issuing the final report.

<u>Blood collection at necropsy</u>
Individual blood samples will be collected from two pups per litter at sacrifice on or shortly after lactation day 13 (collected from the heart whilst under CO_2/O_2 anaesthesia). Serum will be

[redacted]

prepared and stored in a freezer (at ≤ -18 °C) for determination of serum T4 levels. Serum samples will be discarded after analysis.

4.12.12.4 Hormone determinations (T4) in pups

See § 4.12.6.

4.12.12.5 Nipple retention in male pups

On postnatal day 13 all surviving male pups will be examined for the presence and number of nipples or areolas.

4.12.12.6 Signs and sacrifice, gross necropsy and pathology of pups

Any abnormal behavior of pups will be recorded on day 0, 4, 7 and 13 of lactation. Grossly malformed pups will be sacrificed and examined. A necropsy will be performed on stillborn pups and pups dying during the study and macroscopic abnormalities will be recorded. At necropsy of the dams and litter, at or shortly after day 13 of lactation, pups will be examined externally for gross abnormalities and will be sacrificed whilst under CO_2/O_2 anaesthesia and necropsied. The thyroids preserved in 2 selected pups per litter will only be examined microscopically if considered necessary.

4.13 Statistical analysis of the results

The statistical procedures for analysis of data in this study are described below. Other statistical tests may be performed when considered appropriate.

- Body weight data collected after initiation of treatment: “AnCova & Dunnett’s Test” with automatic data transformation. Day 0 body weight data are used as covariate unless removed during data preprocessing. The “AnCova & Dunnett’s Test” is an automatic decision tree consisting of:
  (1) Data preprocessing tests. These tests start with transformation “None”. First, suitability of the covariate is checked (criteria: sufficient cases, at least 2; variability of covariate non-zero; covariate effects sufficiently parallel over the groups, significance level parallelism test 0.01). Next, normality of data distribution (Shapiro-Wilks test; significance level 0.05) and homogeneity of variances (Levene test; significance level 0.05) are checked. If any of these three checks fail they are repeated using Log transformation.
  If checks on log-transformed, covariate-adjusted data fail, the covariate is removed and the normality and homogeneity checks are repeated. If these checks pass on transformations “None” or “Log”, data are analyzed without covariate. If they fail, data are rank-transformed and the covariate is reinstated.
  (2) A group test assessing whether or not group means are all equal (one-way analysis of covariance [Ancova], or one-way analysis of variance [Anova] if the covariate is removed). If the group test shows no significant non-homogeneity of group means ($p \geq 0.05$), group summary tables do not show whether or not a covariate is used in the analysis.
  (3) Post-hoc analysis. If the group test shows significant ($p<0.05$) non-homogeneity of group means, pairwise comparisons with the control group are conducted by Dunnett’s multiple comparison test (significance levels 0.01 and 0.05).
- Pretreatment body weight data, body weight changes, clinical pathology (hematology, and clinical chemistry) and organ weight data: “Generalized Anova Test” with automatic data transformation. This test is an automatic decision tree consisting of:

(1) Data preprocessing tests. First, normality of data distribution (Shapiro-Wilks test) and homogeneity of variances (Levene test) are checked (initial transformation “None”). If any of these checks fail ($p<0.05$) they are repeated using Log transformation. If checks on log-transformed data fail, data are rank-transformed.
(2) A group test assessing whether or not group means are all equal (parametric for untransformed or log-transformed data: one-way analysis of variance [Anova]; non-parametric for rank transformed data: Kruskal-Wallis test).
(3) Post-hoc analysis. If the group test shows significant ($p<0.05$) non-homogeneity of group means, pairwise comparisons with the control group are conducted by Dunnett’s multiple comparison test (parametric after Anova, non-parametric after Kruskal-Wallis; significance levels 0.01 and 0.05).

- Food/ water consumption: Dunnett’s multiple comparison test.
- Incidences of histopathological changes: Fisher’s exact probability test.

[redacted]

5 Reporting

The final report will specify:
- Summary
- The objective of the study
- The characterization and administration of the test substance
- The test facility
- Responsible personnel
- The time frame of the study
- The test system
- Observations and measurements
- Materials and methods
- Statistical methods
- Deviations from the study plan
- Results
- Evaluation of the results
- Discussion and conclusions
- Location and retention periods of documents and materials related to the study
- A statement by the QAU
- A statement on GLP compliance signed by the study director.

Should any doubt arise from the publication of the Triskelion report in an electronic form, the authorized printed version shall be considered authentic.

[redacted]

6 Archiving

The following study specific materials will be archived for 5 years:
- Raw data (or true copies if unstable)
- Tissue specimens and paraffin blocks

The following study specific materials will be archived for 15 years
- Original study plan and final report, and any amendments thereof
- Microscopic slides

General raw data will be retained for at least 25 years, after which they may be destroyed without further notice. These may include, but are not necessarily limited to:
- Facility-based documents
- System calibration and quality control data
- General registrations potentially used for more than one study

At the end of the archiving period tissue specimens and paraffin blocks will be discarded.
The sponsor will be asked whether the study plan, final report, amendments, raw data, including microscopic slides, and correspondence should be discarded, retained for an additional period, or transferred to the archives of the sponsor.

All materials will be retained in the archives of TNO, Utrechtseweg 48, 3704 HE Zeist, The Netherlands. The archiving period starts on the cover date of the final report.

7 References

Triskelion B.V. preliminary data of study [redacted] 'A 14-day range finding study with [redacted] in rats' - J.J. van Triel (2017)

[redacted]

8 Annexes

The following documents are attached to this study plan:
Annex 1 – Distribution list
Annex 2 – Listing of clinical signs

Annex 1 Distribution list

Sponsor:
- Monitor[1]

Test facility:
- TNO archives (signed original)[1]

- Study director[2]
- Quality Assurance[2]
- Animal welfare officer[2]
- Animal facility[2]
- Test material information services[2]
- Operational managers[2]
- Project assistant[2]
- Histopathology[2]
- Inhalation toxicology[2]
- Scientific contributor pathology[2]
- Scientific contributor hormone analysis[2]
- Scientific contributor chemical analysis[2]
- Scientific contributor inhalation toxicology[2]
- Finance, Planning & Control[2]

[1] Sent by study director
[2] Copies to be distributed by TNO archives

Annex 2 – Listing of clinical signs

The clinical signs listed below are derived from the lexicon which is part of the computer programme used for the recording of clinical observations

RESPIRATION
Sniffing
Grunting
Increased rate
Decreased rate
Irregular
Dyspnea
Shallow
Sneezing
Mouth breathing

GENERAL
Thin
Emaciated
Obese
Weakened
Unconscious
Pale
Red
Jaundice
Cyanosis
Warm
Cold
Dehydrated
Increased muscle tension

MOUTH
Malocclusion of incisors
Lower incisors light color
Lower incisors white
Upper incisors light color
Hemorrhagic discharge
Salivation
Stomatitis
Wart-like lesion(s)
Encrustation(s)
Chewing movement

ABDOMEN
Distension
Tense/firm
Blue/grey
Nodule(s)
Umbilical hernia

FAECES
Increased defecation
Decreased defecation
Hard
Soft
Diarrhea
Pale
Hemorrhagic
Black

BEHAVIOR
Muscle weakness
Lethargic
Hunched posture
Excessive scratching
Hyperactive
Hypoactive
Aggressive
Stereotypy
Tremors
Convulsions
Ataxia
Circling movements
Vomiting
Vocalization
Chattering
Excessive grooming
Prone position
Myoclonic jerks

SKIN/FUR
Alopecic area(s)
Sparsely haired area(s)
Piloerection
Soiled fur
Depigmented fur
Edema
Abscess(es)
Pimple(s)
Subcutaneous nodule(s)
Erythema
Scaly
Hematoma
Hematoma iatrogenic
Encrustation(s)
Wound(s)
Shaving wound(s)
Scar tissue
Sc. color inj. site
Color ventral of inj. site
Red iatrogenic
Scaly iatrogenic

INJECTION SITE
Small nodule
Small red sc nodule
Redness
Swollen
Warm
Shaving wound/encrustation
Hematoma sc
Red nodule with white core
Red sc nodule with wound

HEAD
Tilted
Local/general swelling
Trimmed whiskers
Erythema between ears

NOSE
Encrustation(s)
Wound
Hemorrhagic discharge
Discharge-other than red
Crooked
Swollen
Itching
Skin protrusion

EYES
Discharge
Encrustation(s)
Blepharospasm
Blepharitis
Redness conjunctivae
Microphthalmia
Macrophthalmia
Exophthalmus
Dark red
Pale
Corneal opacity/keratitis
Cataract
Panophthalmitis
Complete degeneration
Protruding nictitant membrane

EARS
Encrustation(s)
Wound(s)
Ear canal greased
Ear canal hemorrhagic
Hematoma iatrogenic
Necrotizing ear pinna
Ear pinna (partly) gone
Nodule
Swollen
Erythema

PENIS
Prolapse
Purulent discharge
Hemorrhagic discharge
Swollen preputium

PERINEUM
Soiled with urine
Soiled with feces
Soiled with blood
Erythema
Vaginal blood
Vaginal pus
Vaginal occlusion
Membrane present
Prolapsus ani -et recti
Vulva red
Vulva swollen
Vulva nodule

EXTREMITIES (LEG(S))
Encrustation(s)
Wound(s)
Swollen leg
Broken leg
Leg(s) gone
Stiffness
Muscle weakness
Lameness
Hard skin
Pododermatitis
Swollen toe(s)
Toe(s) gone
Nail(s) gone
Popliteal lymph node enlarged

TAIL
Ringtail
Kink
(Partially) discolored
Encrustation(s)
Wound(s)
Scaly
Local thickening
Tip of tail missing
Short and thick

TESTES
Cryptorchidism
Small
Large
Firm
Soft

URETHRA
Urethritis

URINE
Hematuria

Abbreviations: inj. site = injection site; sc = subcutaneous

Sanitized [redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

Study plan amendment

Study plan no: [redacted]	Amendment no: 1
Title of study: Inhalation reproduction and developmental toxicity screening test with [redacted] in rats	
Date amendment: 23-04-2018 (dd-mm-yyyy)	**Study director:** J.G. Theuns – van Vliet

Planned change 1:
Paragraph 1.3 Responsible personnel:
Scientific contributor(s): J.J. van Triel, M.Sc. (inhalation exposure)
A.J. Kleinnijenhuis, Ph.D. (chemical analysis)
G. van Duijn, Ph.D. (hormone analysis)
Pathology:
A.L. Menke, PhD (study pathologist)
J.P. Bruijntjes

Reason for change 1
Clarification for histopathological examinations.

Planned change 2:
Paragraph 4.2 Characterization of the test substance [redacted]:

Batch number[1]	: [redacted]
Purity[1]	: 98.95%
Date of receipt	:10 and 29 August 2017 (9 cylinders per shipment, both [redacted])
Triskelion dispense number	: 1701F4 (received Aug 10th 2017), 170241 (received Aug 29th 2017)

[1]Information provided by the sponsor

Reason for change 2:
Although received on different days, all cylinders were from [redacted].

Planned change 3:
Paragraph 4.11.5 Chemical analysis
No method for the chemical analysis of the concentration [redacted] as impurity in the [redacted] tested in this study could be validated.
A limited number of study samples was measured during method development.
The remaining scheduled study samples were not measured.
A description of the process of method development and the results of a limited number of study samples measured during method development will be reported in an Annex to the report.

Sanitized [redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

Reason for change 3:
No method could be developed and validated and therefore only a limited number of study samples was measured during method development.

Planned change 4:
Paragraph 4.12.8 Sacrifice, blood samples, gross necropsy and histology of adult animals
Microscopic examination of the noses is extended to the intermediate concentration groups.

Reason for change 4:
Based on the effects observed on the olfactory ephithelium in animals in the high concentration group, histopathological examination of the nose is extended to the intermediate concentration groups.

Planned change 5:
Paragraph 4.12.11 Reproductive performance will be replaced with the following text:

The following data was presented for each group:
- number of adult females with normal or abnormal estrous cycle and cycle duration
- number of females placed with males (and *vice versa*)
- number of females (not) mated and number of males (not) mated
- number of females (not) pregnant
- number of males that became sire
- number of females killed moribund or found dead
- number of females completing delivery

- number of females with liveborn pups
- number of females with (all) stillborn pups

- total and mean number of pups delivered (liveborn + stillborn)
- total number of liveborn pups
- total number of stillborn pups

- total and mean number of live pups(/litter) at day n
- total number of culled pups
- total number of pups lost (dead, missing, cannibalized) (period)
- number and incidence of litters lost entirely (period)
- total and mean number of live male pups at day n
- total and mean number of implantation sites

The following parameters are calculated per group:

. Pre-coïtal time (period)	= time between the start of mating and successful copulation
. Duration of gestation	= time between gestation day 0 and day of delivery (=gestation days)
. Male mating index	= no. of males mated*100/no. of males placed with females
. Female mating index	= no. of females mated*100/no. of females placed with males
. Male fertility index	= no. of males that became sire*100/no. of males placed with females
. Female fertility index	= no. of females pregnant*100/no. of females placed with males
. Female fecundity index	= no. of females pregnant*100/no. of females mated
. Gestation index	= no. of females with a viable litter *100/ no. of females pregnant

[redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

The following parameters are calculated on a litter basis and reported per group:

- Number of lost implantations = no. of implant sites – no. of liveborn pups
- Post-implantation loss = no. of implant sites – no. of liveborn *100 /no. of implant sites
- Live birth index = no. of liveborn pups *100/no. of newborn pups
- Stillborn index = no. of stillborn pups *100/no. of newborn pups
- Viability index 0 - 4 = no. of live pups on day 4 *100/no. of liveborn pups
- Viability index 4 - 13 = no. of pup live pups on day 13 *100/no. of live pups post cull day 4
- Sex ratio (day n) = no. of live male pups on day n *100/no. of live pups on day n

Reason for change 5:
The PDS computer programme for reproduction parameters was replaced by a Provantis programme. The parameters presented in the study plan were (partly) based on PDS, while the study was conducted using Provantis.

Planned change 6:
Paragraph 4.13 Statistical analysis of the results
The following text replaced the description in the study plan:

The statistical procedures for analysis of the various parameters of this study are described in the tables below. Other statistical tests may be performed when considered appropriate. Details of the applied statistical tests are described in a separate table (see Annex 5).

Parameters

General parameters:

Parameter	Statistical test as named in Provantis
Pretreatment body weight, body weight changes, clinical pathology (hematology, clinical chemistry, organ weights.	Ancova/Anova & Dunnett (or Kruskal-Wallis & Dunnett on Ranks)
Body weight after initiation of treatment	Ancova/Anova & Dunnett {Covariate: Bodyweight day 0}
Food consumption	Dunnett
Incidences of histopathological changes	Chi-Squared & Fisher's Exact

Parameters specific for reproductive toxicity studies:

Parameter	Statistical test as named in Provantis
Pup body weight, (T4) hormone analysis.	Ancova/Anova & Dunnett (or Kruskal-Wallis & Dunnett on Ranks)
Pre-coital time, gestation days (=duration of gestation), total number of pups delivered, live pups per litter on specified day, incidence of post implantation loss.	Kruskal-Wallis & Wilcoxon

Sanitized [redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

Pre-coital time during specified period, females pregnant, females with liveborn pups, females with stillborn pups, females with all stillborn pups, number of live newborn pups, number of stillborn pups, number of litters lost entirely at specified day.	Chi-Squared & Fisher's Exact

In addition, the following Annex 5 "*Details of statistical tests*" should be added to the study plan:

Details of statistical tests

Statistical test as named in Provantis	**Statistical test**	**Procedure**
Ancova/Anova & Dunnett or Kruskal-Wallis & Dunnett on Ranks	Generalized ANOVA followed by Dunnett's multiple comparison tests.	First, normality of data distribution and homogeneity of variances are checked with the Shapiro-Wilks test and Levene test, respectively (significance level 0.05). If any of these checks fail, they are repeated using log transformation of the data. If the checks on log-transformed data fail, the data are rank transformed. For parameters with a known normal distribution of the data, the Shapiro-Wilks test and Levene test may be omitted. Next, it is assessed whether or not group means are all equal (significance level 0.05) by means of the one-way analysis of variance (ANOVA), or the Kruskal-Wallis test when the data are rank-transformed. If the group test shows significant ($p < 0.05$) non-homogeneity of group means, pairwise comparisons with the control group are conducted by Dunnett's multiple comparisons test (significance level 0.05). When the data require rank-transformation, the Kruskal-Wallis & Dunnett on Ranks test assumes continuous data (which rank-transformed data is not). Consequently, the p-values will be slightly different than what would be obtained with the more appropriate Kruskal-Wallis & Wilxocon test. Markers in the tables include * for $p < 0.05$, ** for $p < 0.01$ and # for $p < 0.001$.
Ancova/Anova & Dunnett {Covariate: Bodyweight day 0}	Generalized ANCOVA with body weight day 0 as covariate followed by Dunnett's multiple comparison	First, suitability of the covariate is checked (criteria: sufficient cases (≥2); variability of covariate non-zero; covariate effects sufficiently parallel over the groups (significance level 0.01)). Next, normality of data distribution and homogeneity of variances are checked with the Shapiro-Wilks test and Levene test, respectively (significance level 0.05).

Sanitized [redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

	tests.	If any of these three checks fail, they are repeated using log transformation of the data. If the checks on log-transformed, covariate-adjusted data fail, the covariate is removed and the normality and homogeneity checks are repeated with the non-transformed data (significance level 0.05). If these checks fail, they are repeated using log transformation of the data. If the checks pass on non-transformed or log-transformed data, the analysis is continued without the covariate. If the checks fail, data are rank-transformed and the covariate is reinstated. Next, it is assessed whether or not group means are all equal (significance level 0.05) by means of the one-way analysis of covariance (ANCOVA), or one-way analysis of variance (ANOVA) when the covariate is removed. Group summary tables do not show whether or not a covariate is used in the analysis. If the group test shows significant ($p < 0.05$) non-homogeneity of group means, pairwise comparisons with the control group are conducted by Dunnett's multiple comparisons test (significance level 0.05). When the data require rank-transformation, the Kruskal-Wallis & Dunnett on Ranks test is performed as described below. Markers in the tables include * for $p < 0.05$, ** for $p < 0.01$ and # for $p < 0.001$.
Kruskal-Wallis & Wilcoxon.	Kruskal-Wallis non-parametric analysis of variance followed by Wilcoxon multiple comparison test.	The Kruskal-Wallis & Wilcoxon test is applied to categorical or rank-transformed data. In case of semi-quantitative data, the data first need to be rank-transformed. Next, it is assessed whether or not group means are all equal (significance level 0.05). If the group test shows significant ($p < 0.05$) non-homogeneity of group means, pairwise comparisons with the control group are conducted by Wilcoxon multiple comparison test (significance level 0.05). Markers in the tables include * for $p < 0.05$, ** for $p < 0.01$ and # for $p < 0.001$.
Dunnett	Dunnett's multiple comparison test	This Dunnett's multiple comparison test is part of the generalized ANOVA, but the significance level for whether or not group means are all equal is set at 1. This test is applied to data with a normal or log-normal distribution. First, normality of data distribution and homogeneity of variances are checked with the Shapiro-Wilks test and Levene test, respectively (significance level 0.05).

Sanitized [redacted]

TRISKELION
RESEARCH FOR BETTER LIVING

		If any of these checks fail, they are repeated using log transformation of the data. Next, pairwise comparisons with the control group are conducted by Dunnett's multiple comparisons test (significance level 0.05). Markers in the tables include * for $p < 0.05$, ** for $p < 0.01$ and # for $p < 0.001$.
Chi-Squared & Fisher's Exact.	Pearson Chi-Square & Fisher Exact analysis followed by multiple comparison test	The Exact Pearson Chi-Square test is applied to incidence data (yes/no; 1/0). First, it is assessed whether or not group total counts are all equal (significance level 0.05). If the group test shows significant ($p < 0.05$) difference in the total number of counts, pairwise comparisons with the control group are conducted by the Fisher Exact test (significance level 0.05) Markers in the tables include * for $p < 0.05$, ** for $p < 0.01$ and # for $p < 0.001$.

References

Box, G.E. (1953), "Non-normality and Tests on Variance," Biometrika, 40, 318 – 335
Duncan, D.B. (1975), ""t Tests and Intervals for Comparisons Suggested by the Data, Biometrics, 31, 339 - 359.
Kutner, M.H. (1974), "Hypothesis Testing in Linear Models (Eisenhart Model)," American Statistician, 28, 98 - 100.
Searle, S.R. (1971), Linear Models, New York: John Wiley & Sons, Inc.
Montgomery D.C. (2001). Design and Analysis of Experiments. New York: John Wiley & Sons, Inc.

Reason for change 6:

Statistical procedures for reproductive endpoints used in the Provantis programme were not yet described in the study plan.

Study Director[1]

J.G. Theuns – van Vliet

Signature:

Date: 23.april.2018 (dd-mm-yyyy)

Sponsor

Name company: [redacted]

Signature:

Name contact person: [redacted]

Date: .... (dd-mm-y

Appendices

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.1.1: Clinical observations males during the study pre-exposure

0 ppm Sex: Male	Observation Type: All Types	From Day -3 (Start Date) to 35 (Start Date)
2	DEAD Killed scheduled	35
4	SKIN Sparsely haired area(s)	0 to 23
	DEAD Killed scheduled	35
6	DEAD Killed scheduled	35
8	EARS Encrustration(s), Left	21 to 23,29 to 34
	DEAD Killed scheduled	35
10	DEAD Killed scheduled	35
12	DEAD Killed scheduled	35
14	DEAD Killed scheduled	35
16	DEAD Killed scheduled	35
18	DEAD Killed scheduled	35
20	DEAD Killed scheduled	35
22	SKIN Sparsely haired area(s)	14 to 23,34 to 35
	DEAD Killed scheduled	35
24	DEAD Killed scheduled	35

[redacted]

Values=Clin Obs Range

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.1.1: Clinical observations males during the study pre-exposure

250 ppm Sex: Male	Observation Type: All Types	From Day -3 (Start Date) to 35 (Start Date)
26	DEAD Killed scheduled	35
28	DEAD Killed scheduled	35
30	DEAD Killed scheduled	35
32	DEAD Killed scheduled	35
34	DEAD Killed scheduled	35
36	DEAD Killed scheduled	35
38	DEAD Killed scheduled	35
40	DEAD Killed scheduled	35
42	DEAD Killed scheduled	35
44	DEAD Killed scheduled	35
46	DEAD Killed scheduled	35
48	DEAD Killed scheduled	35

[redacted]

Values=Clin Obs Range

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.1.1: Clinical observations males during the study pre-exposure

750 ppm Sex: Male	Observation Type: All Types	From Day -3 (Start Date) to 35 (Start Date)
50	DEAD Killed scheduled	35
52	DEAD Killed scheduled	35
54	DEAD Killed scheduled	35
56	DEAD Killed scheduled	35
58	DEAD Killed scheduled	35
60	DEAD Killed scheduled	35
62	DEAD Killed scheduled	35
64	DEAD Killed scheduled	35
66	DEAD Killed scheduled	35
68	DEAD Killed scheduled	35
70	DEAD Killed scheduled	35
72	DEAD Killed scheduled	35

Values=Clin Obs Range

[redacted]

Sanitized

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.1.1: Clinical observations males during the study pre-exposure

1500 ppm Sex: Male	Observation Type: All Types	From Day -3 (Start Date) to 35 (Start Date)
74	SKIN Piloerection	17 to 18,25
	DEAD Killed scheduled	35
76	DEAD Killed scheduled	35
78	SKIN Piloerection	23
	DEAD Killed scheduled	35
80	SKIN Piloerection	18
	DEAD Killed scheduled	35
82	DEAD Killed scheduled	35
84	SKIN Piloerection	15
	DEAD Killed scheduled	35
86	SKIN Piloerection	18,22
	DEAD Killed scheduled	35
88	DEAD Killed scheduled	35
90	DEAD Killed scheduled	35
92	DEAD Killed scheduled	35
94	SKIN Piloerection	17 to 18
	DEAD Killed scheduled	35
96	SKIN Piloerection	23
	DEAD Killed scheduled	35

Values=Clin Obs Range

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.1.2: Clinical observations males during the study post-exposure

0 ppm Sex: Male	Observation Type: All Types	From Day 0 (Start Date) to 34 (Start Date)
4	SKIN Sparsely haired area(s)	0 to 4,7 to 11,14 to 23
8	EARS Encrustration(s), Left	21 to 23,29 to 34
22	SKIN Sparsely haired area(s)	14 to 23,33 to 34

750 ppm Sex: Male	Observation Type: All Types	From Day 0 (Start Date) to 34 (Start Date)
54	SKIN Piloerection	21
68	SKIN Piloerection	21

1500 ppm Sex: Male	Observation Type: All Types	From Day 0 (Start Date) to 34 (Start Date)
74	SKIN Piloerection	3,9,16 to 18,21 to 24
76	SKIN Piloerection	9,21,24
78	SKIN Piloerection	15,23
80	SKIN Piloerection	17 to 18,22
84	SKIN Piloerection	0,14 to 15
86	SKIN Piloerection	17 to 18,21 to 22
90	SKIN Piloerection	14,24
92	SKIN Piloerection	18,23
94	SKIN Piloerection	0,4,9,15 to 18,21,23
96	SKIN Piloerection	21

Values=Clin Obs Range

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.2.1: Clinical observations females premating pre-exposure

0 ppm Sex: Female	Observation Type: All Types	From Day -3 (Start Date (A)) to -1 (Mating)
5	SKIN Sparsely haired area(s)	0 to 16

750 ppm Sex: Female	Observation Type: All Types	From Day -3 (Start Date (A)) to -1 (Mating)
67	DEAD Killed scheduled	53

1500 ppm Sex: Female	Observation Type: All Types	From Day -3 (Start Date (A)) to -1 (Mating)
73	SKIN Piloerection	19 to 22,50
	DEAD Killed scheduled	53

[redacted]

Values=Clin Obs Range

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.2.2: Clinical observations females premating post-exposure

0 ppm Sex: Female	Observation Type: All Types	From Day 0 (Start Date (A)) to -1 (Mating)
5	SKIN Sparsely haired area(s)	0 to 4,7 to 11,14 to 16

750 ppm Sex: Female	Observation Type: All Types	From Day 0 (Start Date (A)) to -1 (Mating)
49	SKIN Piloerection	14
51	SKIN Piloerection	14
57	SKIN Piloerection	14

1500 ppm Sex: Female	Observation Type: All Types	From Day 0 (Start Date (A)) to -1 (Mating)
73	SKIN Piloerection	9,18 to 23,49
77	SKIN Piloerection	0,3,15
83	SKIN Piloerection	3,8
91	SKIN Piloerection	17
93	SKIN Piloerection	3

[redacted]

Values=Clin Obs Range

30/Jan/2018 13:48:28

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.3.1: Clinical observations females gestation pre-exposure

0 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to -1 (Littering)
5 P	SKIN Sparsely haired area(s)	0 to 7,10 to 21
	SKIN Encrustation(s)	12 to 13

250 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to -1 (Littering)
25 P	EARS Encrustration(s), Left	4 to 21
27 P	EARS Encrustration(s), Right	0

750 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to -1 (Littering)
49 P	SKIN Piloerection	0 to 1
51 P	SKIN Piloerection	5 to 7,19 to 20
67 NM		

1500 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to -1 (Littering)
73 NM		
75 P	SKIN Piloerection	1
77 P	SKIN Piloerection	1 to 4,6 to 7,9 to 10
87 NP	DEAD Killed scheduled	32
89 P	SKIN Piloerection	4
91 P	SKIN Piloerection	0 to 1
93 P	SKIN Piloerection	1

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.3.2: Clinical observations females gestation post-exposure

0 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to 19 (Mating)
5 P	SKIN Sparsely haired area(s)	0 to 7,10 to 19
	SKIN Encrustation(s)	12 to 13

250 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to 19 (Mating)
25 P	EARS Encrustration(s), Left	3 to 19
27 P	EARS Encrustration(s), Right	0

750 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to 19 (Mating)
49 P	SKIN Piloerection	0
51 P	SKIN Piloerection	4 to 7,18 to 19
67 NM		

1500 ppm Sex: Female	Observation Type: All Types	From Day 0 (Mating (A)) to 19 (Mating)
73 NM		
75 P	SKIN Piloerection	0 to 1,7
77 P	SKIN Piloerection	1 to 2,4 to 6,8 to 9
81 P	SKIN Piloerection	7
83 P	SKIN Piloerection	4
89 P	SKIN Piloerection	3
91 P	SKIN Piloerection	0
93 P	SKIN Piloerection	0,5

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

30/Jan/2018 13:48:58

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.4.1: Clinical observations females lactation pre-exposure

0 ppm Sex: Female	Observation Type: All Types	From Day 0 (Littering (A)) to 14 (Littering)
1 P	DEAD Killed scheduled	14
3 P	SKIN Piloerection	10
	DEAD Killed scheduled	14
5 P	SKIN Sparsely haired area(s)	0 to 10,14
	SKIN Piloerection	13
	DEAD Killed scheduled	14
7 P	DEAD Killed scheduled	14
9 P	DEAD Killed scheduled	14
11 P	DEAD Killed scheduled	14
13 P	SKIN Piloerection	13
	DEAD Killed scheduled	14
15 P	DEAD Killed scheduled	14
17 P	SKIN Encrustation(s)	4 to 14
	DEAD Killed scheduled	14
19 P	DEAD Killed scheduled	14
21 P	DEAD Killed scheduled	14
23 P	DEAD Killed scheduled	14
	SKIN Piloerection	14

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

30/Jan/2018 13:48:58

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.4.1: Clinical observations females lactation pre-exposure

250 ppm Sex: Female	Observation Type: All Types	From Day 0 (Littering (A)) to 14 (Littering)
25 P	EARS Encrustration(s), Left	0 to 12
	DEAD Killed scheduled	14
27 P	DEAD Killed scheduled	14
29 P	DEAD Killed scheduled	14
31 P	DEAD Killed scheduled	14
33 P	DEAD Killed scheduled	14
35 P	DEAD Killed scheduled	14
37 P	DEAD Killed scheduled	14
39 P	DEAD Killed scheduled	14
41 P	DEAD Killed scheduled	14
43 P	DEAD Killed scheduled	14
	SKIN Piloerection	14
45 P	DEAD Killed scheduled	14
47 P	DEAD Killed scheduled	14

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.4.1: Clinical observations females lactation pre-exposure

750 ppm Sex: Female	Observation Type: All Types	From Day 0 (Littering (A)) to 14 (Littering)
49 P	DEAD Killed scheduled	14
51 P	SKIN Piloerection	7 to 8,11 to 12,14
	DEAD Killed scheduled	14
53 P	SKIN Piloerection	11
	DEAD Killed scheduled	14
55 P	DEAD Killed scheduled	14
57 P	DEAD Killed scheduled	14
59 P	DEAD Killed scheduled	13
61 P	DEAD Killed scheduled	14
63 P	DEAD Killed scheduled	14
65 P	DEAD Killed scheduled	14
67 NM		
69 P	DEAD Killed scheduled	14
71 P	DEAD Killed scheduled	14

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Sanitized

30/Jan/2018 13:48:58

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.4.1: Clinical observations females lactation pre-exposure

1500 ppm Sex: Female	Observation Type: All Types	From Day 0 (Littering (A)) to 14 (Littering)
73 NM		
75 P	DEAD Killed scheduled	14
77 P	DEAD Killed scheduled	14
	SKIN Piloerection	14
79 P	DEAD Killed scheduled	14
81 P	DEAD Killed scheduled	14
83 P	DEAD Killed scheduled	14
85 P	DEAD Killed scheduled	14
87 NP		
89 P	SKIN Piloerection	8 to 9
	DEAD Killed scheduled	14
91 P	SKIN Piloerection	9
	DEAD Killed scheduled	14
93 P	DEAD Killed scheduled	14
95 P	DEAD Killed scheduled	14

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

30/Jan/2018 09:05:40

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.4.2: Clinical observations females lactation post-exposure

0 ppm Sex: Female	Observation Type: All Types	From Day 5 (Littering (A)) to 13 (Littering)
3 P	SKIN Piloerection	9
5 P	SKIN Sparsely haired area(s)	5 to 10
	SKIN Piloerection	12 to 13
7 P	SKIN Piloerection	9
9 P	SKIN Piloerection	9,11
13 P	SKIN Piloerection	12
17 P	SKIN Encrustation(s)	5 to 13
19 P	SKIN Piloerection	8
23 P	SKIN Piloerection	13

250 ppm Sex: Female	Observation Type: All Types	From Day 5 (Littering (A)) to 13 (Littering)
25 P	EARS Encrustration(s), Left	5 to 12
29 P	SKIN Piloerection	9
37 P	SKIN Piloerection	10,12
43 P	SKIN Piloerection	11,13

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

30/Jan/2018 09:05:40

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 1.4.2: Clinical observations females lactation post-exposure

750 ppm Sex: Female	Observation Type: All Types	From Day 5 (Littering (A)) to 13 (Littering)
49 P	SKIN Piloerection	11
51 P	SKIN Piloerection	5 to 8,10 to 13
53 P	SKIN Piloerection	10
57 P	SKIN Piloerection	8
65 P	SKIN Piloerection	9
67 NM		

1500 ppm Sex: Female	Observation Type: All Types	From Day 5 (Littering (A)) to 13 (Littering)
73 NM		
75 P	SKIN Piloerection	5,12
77 P	SKIN Piloerection	6
83 P	SKIN Piloerection	11
85 P	SKIN Piloerection	5
87 NP		
89 P	SKIN Piloerection	7 to 9
91 P	SKIN Piloerection	8
93 P	SKIN Piloerection	8

Values=Clin Obs Range
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

30/Jan/2018 16:27:37

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.1: Body weight males during the study

Sex: Male Day(s) Relative to Start Date

0 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14	21	28	34
2	305.3	309.8	314.2	316.8	318.3	329.7	333.6
4	323.3	329.9	338.9	346.6	353.1	369.3	376.6
6	336.4	345.1	346.0	356.4	360.7	369.5	378.6
8	351.5	356.4	369.2	388.7	396.5	411.6	423.3
10	370.9	379.2	389.5	404.6	412.0	427.3	436.9
12	358.9	365.8	382.1	403.5	411.6	430.7	445.1
14	330.6	335.4	344.7	356.7	355.5	367.0	378.3
16	310.4	315.9	324.1	330.1	333.0	336.2	341.5
18	317.7	324.4	331.7	340.7	344.5	350.0	354.8
20	346.1	357.0	375.0	385.7	383.9	399.0	411.7
22	322.2	328.6	335.2	346.3	351.1	358.9	365.6
24	344.9	353.7	364.0	378.9	378.4	390.2	399.6
Mean	334.85	341.77	351.22	362.92	366.55	378.28	387.13
SD	20.14	21.16	24.19	28.83	30.07	33.61	36.46
N	12	12	12	12	12	12	12

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.1: Body weight males during the study

Sex: Male Day(s) Relative to Start Date

250 ppm	Bodywt day -x (g) -3	Bodywt (g) 0	Bodywt (g) 2	Bodywt (g) 7	Bodywt (g) 14	Bodywt (g) 21	Bodywt (g) 28	Bodywt (g) 34
26	320.7	323.8	-	331.5	338.7	334.6	338.4	344.7
28	294.8	285.7	298.0*	296.3	301.3	302.4	306.1	311.3
30	344.5	351.9	-	356.3	359.4	356.4	367.2	375.7
32	330.1	336.9	-	349.7	353.6	360.1	362.0	369.3
34	371.1	382.5	-	399.6	417.2	423.2	440.0	452.3
36	346.5	352.9	-	357.6	364.2	370.8	382.4	390.3
38	351.8	363.1	-	376.7	385.8	388.7	394.9	404.9
40	311.0	316.7	-	320.2	327.8	329.1	337.9	347.2
42	357.6	367.3	-	375.8	391.1	387.3	418.4	432.4
44	325.9	306.8	320.8*	328.2	335.3	335.5	341.4	346.4
46	316.6	304.9	314.4*	315.1	322.7	324.2	328.3	338.1
48	335.4	307.7	326.9*	332.2	341.0	333.4	346.6	353.7
Mean	333.83	333.35	315.03	344.93	353.18	353.81	363.63	372.19
SD	21.63	30.16	12.44	29.78	32.62	34.03	39.10	41.25
N	12	12	4	12	12	12	12	12

* = Body weight was weighed on day 2 of exposure. These data are excluded from statistics in Table 3.1

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.1: Body weight males during the study

Sex: Male Day(s) Relative to Start Date

750 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14	21	28	34
50	327.0	333.4	327.5	327.2	324.1	327.3	332.6
52	342.1	345.3	343.3	352.6	354.0	368.4	381.6
54	349.1	352.9	356.2	360.4	362.5	371.0	381.1
56	374.0	386.7	387.4	394.1	398.4	406.0	414.0
58	318.0	323.1	323.4	327.9	323.6	328.8	337.8
60	300.9	304.9	301.8	303.6	301.6	310.0	314.4
62	358.3	366.8	368.2	373.2	374.8	386.3	395.8
64	351.0	356.9	357.5	356.9	359.4	366.6	375.8
66	328.2	337.4	339.8	344.6	348.6	355.9	364.1
68	312.4	315.7	308.8	307.3	294.9	301.5	310.7
70	331.2	336.4	333.1	334.5	329.3	342.9	349.3
72	307.3	315.7	310.7	309.2	304.3	300.9	309.4
Mean	333.29	339.60	338.14	340.96	339.63	347.13	355.55
SD	22.13	23.62	25.85	27.93	31.90	34.14	35.12
N	12	12	12	12	12	12	12

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.1: Body weight males during the study

Sex: Male Day(s) Relative to Start Date

1500 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14	21	28	34
74	333.9	337.6	337.2	346.5	347.2	355.3	361.9
76	366.9	377.0	366.6	374.2	379.4	385.3	397.1
78	329.3	338.5	334.5	345.4	354.5	356.7	362.8
80	353.1	354.9	348.7	347.3	344.5	353.5	357.8
82	339.5	344.3	347.6	351.4	354.1	359.2	364.3
84	320.3	326.4	329.5	332.9	341.0	349.5	358.2
86	349.3	359.2	359.6	364.4	362.9	365.0	374.5
88	354.4	358.9	354.4	357.0	354.3	362.2	369.6
90	317.3	323.7	314.1	311.6	303.3	307.2	316.3
92	304.3	307.1	303.4	302.2	303.5	307.7	315.0
94	307.1	320.3	314.5	313.1	309.0	318.6	329.3
96	326.2	336.5	332.1	329.2	324.8	328.9	340.7
Mean	333.47	340.37	336.85	339.60	339.88	345.76	353.96
SD	19.72	19.71	19.50	22.22	24.56	24.54	24.36
N	12	12	12	12	12	12	12

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.2: Body weight females premating

Sex: Female Day(s) Relative to Start Date

0 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14
1	232.0	228.4	240.7	249.5
3	208.3	218.0	222.0	221.5
5	217.0	221.9	225.4	225.3
7	215.1	221.9	221.6	221.5
9	203.0	210.6	211.6	215.5
11	224.7	235.8	240.7	241.3
13	226.7	235.4	234.3	252.3
15	213.9	223.1	221.8	222.7
17	206.6	203.1	214.2	215.3
19	211.9	216.1	217.8	218.4
21	211.3	211.5	216.6	221.6
23	218.3	223.8	222.6	229.7
Mean	215.73	220.80	224.11	227.88
SD	8.59	9.75	9.65	12.80
N	12	12	12	12

30/Jan/2018 16:16:09

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.2: Body weight females premating

Sex: Female Day(s) Relative to Start Date

250 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14
25	208.3	219.3	215.2	214.5
27	206.0	212.5	213.9	215.9
29	212.1	218.7	214.7	212.5
31	222.8	234.0	229.9	231.1
33	200.1	202.6	213.2	216.9
35	216.9	228.3	226.6	226.5
37	222.2	229.5	232.7	235.9
39	210.0	208.6	216.9	217.7
41	215.7	228.8	228.8	231.0
43	233.2	238.4	236.1	234.7
45	231.2	237.0	237.6	241.6
47	214.1	230.6	231.1	234.8
Mean	216.05	224.03	224.73	226.09
SD	9.91	11.56	9.29	10.06
N	12	12	12	12

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.2: Body weight females premating

Sex: Female Day(s) Relative to Start Date

750 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14	21	28	35	42	49
49	218.2	221.4	212.6	214.9	-	-	-	-	-
51	211.7	214.3	217.1	215.6	-	-	-	-	-
53	215.8	225.9	219.7	219.2	-	-	-	-	-
55	227.3	232.2	226.2	232.2	-	-	-	-	-
57	205.8	207.4	202.6	210.9	-	-	-	-	-
59	209.1	215.0	207.2	211.9	-	-	-	-	-
61	223.5	228.1	218.9	226.5	-	-	-	-	-
63	216.3	216.5	212.9	218.9	-	-	-	-	-
65	213.1	223.2	220.2	223.1	-	-	-	-	-
67	232.2	224.6	229.8	233.3	234.6	231.4	244.4	238.4	237.4
69	208.2	220.6	221.7	221.3	-	-	-	-	-
71	204.3	216.5	220.9	218.2	-	-	-	-	-
Mean	215.46	220.48	217.48	220.50	234.60	231.40	244.40	238.40	237.40
SD	8.66	6.88	7.65	7.23	-	-	-	-	-
N	12	12	12	12	1	1	1	1	1

Sanitized

30/Jan/2018 16:16:09

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.2: Body weight females premating

Sex: Female Day(s) Relative to Start Date

1500 ppm	Bodywt day -x (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	-3	0	7	14	21	28	35	42	49
73	211.4	215.7	208.3	214.8	231.7	219.2	217.4	214.7	216.9
75	214.8	217.9	229.1	231.6	-	-	-	-	-
77	206.2	208.8	206.4	203.5	-	-	-	-	-
79	217.2	221.0	221.3	213.1	-	-	-	-	-
81	197.7	211.6	205.0	203.8	-	-	-	-	-
83	219.6	232.2	213.8	210.6	-	-	-	-	-
85	211.3	222.3	224.6	217.2	-	-	-	-	-
87	215.6	220.1	216.4	214.2	-	-	-	-	-
89	232.2	233.8	222.9	226.0	-	-	-	-	-
91	207.3	214.0	209.0	212.3	-	-	-	-	-
93	225.5	227.1	221.3	220.0	-	-	-	-	-
95	222.4	222.5	219.7	223.7	-	-	-	-	-
Mean	215.10	220.58	216.48	215.90	231.70	219.20	217.40	214.70	216.90
SD	9.29	7.71	7.90	8.43	-	-	-	-	-
N	12	12	12	12	1	1	1	1	1

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.3: Body weight females gestation

Sex: Female Day(s) Relative to Mating (Litter: A)

0 ppm	Bodywt (g) 1	Bodywt (g) 7	Bodywt (g) 14	Bodywt (g) 20
1 P	254.0	272.8	300.2	362.4
3 P	226.6	243.4	270.0	314.4
5 P	228.4	237.6	262.6	311.6
7 P	234.6	251.1	274.7	342.1
9 P	223.1	235.4	256.2	316.0
11 P	247.7	261.0	291.3	350.5
13 P	247.3	260.3	284.1	345.4
15 P	235.0	249.0	264.7	313.2
17 P	221.3	236.5	260.3	319.2
19 P	224.7	243.3	262.8	317.7
21 P	226.0	236.5	266.3	321.0
23 P	231.3	241.2	260.4	319.2
Mean	233.33	247.34	271.13	327.73
SD	10.81	11.92	13.80	17.37
N	12	12	12	12

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.3: Body weight females gestation

Sex: Female Day(s) Relative to Mating (Litter: A)

250 ppm	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	1	7	14	20
25 P	226.7	241.0	264.0	331.5
27 P	223.2	234.5	254.8	313.0
29 P	217.9	229.9	249.4	300.2
31 P	234.5	248.0	272.0	328.4
33 P	220.5	235.6	261.3	318.9
35 P	239.2	251.5	270.0	331.4
37 P	241.5	252.4	267.7	324.4
39 P	224.3	242.1	262.3	314.2
41 P	234.6	261.8	287.1	344.1
43 P	246.7	260.9	279.0	353.6
45 P	252.8	273.5	294.5	363.5
47 P	238.1	260.5	285.1	335.9
Mean	233.33	249.31	270.60	329.93
SD	10.94	13.22	13.59	17.84
N	12	12	12	12

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.3: Body weight females gestation

Sex: Female Day(s) Relative to Mating (Litter: A)

750 ppm	Bodywt (g) 1	Bodywt (g) 7	Bodywt (g) 14	Bodywt (g) 20
49 P	216.4	231.0	249.7	288.9
51 P	218.3	229.1	246.2	303.2
53 P	220.6	240.6	259.0	301.1
55 P	235.1	255.2	278.7	340.9
57 P	212.7	230.4	250.5	299.8
59 P	210.3	222.1	233.1	249.6
61 P	234.9	249.5	275.5	324.7
63 P	222.0	230.6	245.6	291.9
65 P	220.0	235.8	255.7	301.2
67 NM	-	-	-	-
69 P	231.1	243.7	267.2	325.0
71 P	225.0	238.2	254.6	289.9
Mean	222.40	236.93	255.98	301.47
SD	8.38	9.76	13.53	23.93
N	11	11	11	11

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

30/Jan/2018 15:57:57

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.3: Body weight females gestation

Sex: Female Day(s) Relative to Mating (Litter: A)

1500 ppm	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	1	7	14	20
73 NM	-	-	-	-
75 P	217.0 E¹	231.1	247.9	294.6
77 P	203.4	216.4	235.7	263.1
79 P	218.7	226.7	249.6	294.2
81 P	204.8	219.5	238.4	293.7
83 P	212.6	216.0	233.1	271.7
85 P	219.2	228.2	250.0	290.6
87 NP	216.0 E	225.6 E	225.0 E	218.8 E
89 P	225.6	233.6	255.9	309.0
91 P	214.0	216.9	239.2	276.1
93 P	224.4	243.8	255.6	284.1
95 P	223.6	242.1	254.9	300.9
Mean	216.26	227.43	246.03	287.80
SD	8.19	10.34	8.68	14.03
N	9	10	10	10

E = Exclude; NP females excluded from statistics

E¹ = Exclude; Female retrospectively declared mated, body weight measured after whole body exposure

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

05/Feb/2018 11:29:54

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.4: Body weight females lactation

Sex: Female Day(s) Relative to Littering (Litter: A)

0 ppm	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	0	4	7	13
1 P	272.1	296.3	305.5	316.9
3 P	257.4	272.6	284.7	299.7
5 P	242.9	260.9	271.1	281.7
7 P	243.6	255.2	269.5	283.6
9 P	244.2	264.6	272.5	284.1
11 P	258.0	278.4	291.6	298.0
13 P	260.3	288.0	295.1	302.4
15 P	246.6	283.0	293.1	302.9
17 P	242.4	240.6	257.1	282.0
19 P	242.1	264.0	277.4	292.3
21 P	255.1	267.2	279.8	290.9
23 P	233.4	261.3	270.2	275.0
Mean	249.84	269.34	280.63	292.46
SD	10.75	15.29	13.73	11.94
N	12	12	12	12

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.4: Body weight females lactation

Sex: Female Day(s) Relative to Littering (Litter: A)

250 ppm	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	0	4	7	13
25 P	238.2	255.5	261.0	278.1
27 P	233.9	258.1	260.3	270.4
29 P	225.6	262.4	254.4	270.8
31 P	245.2	279.7	283.7	291.7
33 P	243.3	258.1	269.1	281.3
35 P	251.5	263.7	273.7	285.2
37 P	266.4	275.0	284.9	293.9
39 P	243.0	265.4	272.3	285.1
41 P	261.4	289.7	292.4	312.9
43 P	268.8	283.8	298.7	308.6
45 P	278.6	295.7	299.4	304.8
47 P	265.9	283.8	289.6	295.0
Mean	251.82	272.58	278.29	289.82
SD	16.23	13.75	15.36	13.98
N	12	12	12	12

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

05/Feb/2018 11:29:54

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.4: Body weight females lactation

Sex: Female Day(s) Relative to Littering (Litter: A)

750 ppm	Bodywt (g)	Bodywt (g)	Bodywt (g)	Bodywt (g)
	0	4	7	13
49 P	232.9	259.0	262.6	273.1
51 P	221.9	249.5	255.6	267.5
53 P	245.8	258.6	269.8	279.2
55 P	260.9	269.2	277.5	289.4
57 P	233.5	254.0	261.4	275.8
59 P	229.4	225.4	221.6	221.8 *
61 P	252.7	273.4	271.7	283.7
63 P	234.4	252.4	263.8	273.7
65 P	235.3	257.9	261.5	268.9
67 NM	-	-	-	-
69 P	243.6	277.8	279.3	291.8
71 P	242.1	257.3	259.3	260.0
Mean	239.32	257.68	262.19	271.35
SD	11.09	13.92	15.42	18.95
N	11	11	11	11

* = Body weight was measured on day 12

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted]

05/Feb/2018 11:29:54

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 2.4: Body weight females lactation

Sex: Female Day(s) Relative to Littering (Litter: A)

1500 ppm	Bodywt (g) 0	Bodywt (g) 4	Bodywt (g) 7	Bodywt (g) 13
73 NM	-	-	-	-
75 P	227.3	242.0	249.6	263.0
77 P	203.9	235.0	227.0	238.4
79 P	223.8	241.3	252.6	262.2
81 P	223.7	236.9	247.9	269.4
83 P	216.8	228.1	237.8	248.9
85 P	225.7	245.9	251.3	261.5
87 NP	-	-	-	-
89 P	236.6	259.6	255.5	272.2
91 P	220.2	239.2	253.4	261.5
93 P	245.3	254.4	254.7	265.9
95 P	225.2	257.2	259.5	270.6
Mean	224.85	243.96	248.93	261.36
SD	11.01	10.26	9.62	10.40
N	10	10	10	10

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.1: Food consumption males during the study

Sex: Male Daily Food Cons Per Animal (Gram)

0 ppm	No. in Cage	Day(s) Relative to Animal Start Date 0 - 7	7 - 14	21 - 28	28 - 34
2	4	19.72	20.15	19.83	19.31
4	4	22.60	22.29	21.71	22.16
6	4	20.83	20.42	20.86	19.83
	Mean	21.1	21.0	20.8	20.4
	SD	1.5	1.2	0.9	1.5
	N	3	3	3	3

250 ppm	No. in Cage	Day(s) Relative to Animal Start Date 0 - 7	7 - 14	21 - 28	28 - 34
8	4	18.48	17.00	18.30	17.55
10	4	21.96	21.13	20.54	20.88
12	4	22.13	20.75	21.12	21.18
	Mean	20.9	19.6	20.0	19.9
	SD	2.1	2.3	1.5	2.0
	N	3	3	3	3

N=Number of cages

Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.1: Food consumption males during the study

Sex: Male Daily Food Cons Per Animal (Gram)

750 ppm	No. in Cage	Day(s) Relative to Animal Start Date			
		0 - 7	7 - 14	21 - 28	28 - 34
14	4	17.24	17.89	18.98	19.61
16	4	17.42	17.39	18.36	18.83
18	4	16.70	16.46	17.41	18.32
	Mean	17.1	17.2	18.3	18.9
	SD	0.4	0.7	0.8	0.6
	N	3	3	3	3

1500 ppm	No. in Cage	Day(s) Relative to Animal Start Date			
		0 - 7	7 - 14	21 - 28	28 - 34
20	4	17.34	17.35	19.31	19.77
22	4	18.45	17.94	18.80	18.69
24	4	15.86	15.23	17.03	17.85
	Mean	17.2	16.8	18.4	18.8
	SD	1.3	1.4	1.2	1.0
	N	3	3	3	3

N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.2: Food consumption females premating

[redacted]

Sex: Female Daily Food Cons Per Animal (Gram)

0 ppm	No. in Cage	Day(s) Relative to Animal Start Date 0 - 7	7 - 14
1	4	15.42	14.33
3	4	15.60	14.61
5	4	15.81	14.46
	Mean	15.6	14.5
	SD	0.2	0.1
	N	3	3

250 ppm	No. in Cage	Day(s) Relative to Animal Start Date 0 - 7	7 - 14
7	4	14.48	13.52
9	4	14.64	13.95
11	4	15.75	15.24
	Mean	15.0	14.2
	SD	0.7	0.9
	N	3	3

N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.2: Food consumption females premating

Sex: Female Daily Food Cons Per Animal (Gram)

750 ppm	No. in Cage	Day(s) Relative to Animal Start Date 0 - 7	7 - 14
13	4	13.48	13.06
15	4	12.30	13.05
17	4	13.22	13.44
	Mean	13.0	13.2
	SD	0.6	0.2
	N	3	3

1500 ppm	No. in Cage	Day(s) Relative to Animal Start Date 0 - 7	7 - 14
19	4	12.52	11.79
21	4	12.63	10.79
23	4	13.01	13.08
	Mean	12.7	11.9
	SD	0.3	1.1
	N	3	3

N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

Appendix 3.3: Food consumption females gestation

Sex: Female   Daily Food Cons Per Animal

0 ppm	Day(s) Relative to Mating (Litter: A)		
	0 - 7	7 - 14	14 - 20
1 P	19.24	20.50	21.75
3 P	15.17	17.80	18.88
5 P	16.71	18.37	20.58
7 P	18.14	17.96	21.78
9 P	15.60	15.87	19.95
11 P	17.84	19.66	19.20
13 P	17.23	18.49	21.85
15 P	16.00	16.13	17.90
17 P	18.53	19.81	19.92
19 P	16.66	16.04	19.77
21 P	15.87	17.77	20.45
23 P	15.80	16.44	19.25
Mean	16.90	17.90	20.11
SD	1.30	1.56	1.24
N	12	12	12

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.3: Food consumption females gestation

Sex: Female Daily Food Cons Per Animal

250 ppm	Day(s) Relative to Mating (Litter: A)		
	0 - 7	7 - 14	14 - 20
25 P	18.60	18.26	20.55
27 P	16.87	17.77	21.18
29 P	14.74	16.04	17.60
31 P	17.20	19.61	21.55
33 P	16.51	17.09	20.00
35 P	17.11	19.66	20.87
37 P	16.20	19.39	19.42
39 P	16.86	17.46	19.62
41 P	18.56	20.27	22.57
43 P	19.61	18.57	22.37
45 P	19.50	19.73	22.75
47 P	17.90	20.70	19.75
Mean	17.47	18.71	20.68
SD	1.42	1.42	1.52
N	12	12	12

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

31/Jan/2018 12:09:24

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.3: Food consumption females gestation

Sex: Female Daily Food Cons Per Animal

[redacted]

750 ppm	Day(s) Relative to Mating (Litter: A)		
	0 - 7	7 - 14	14 - 20
49 P	14.07	16.11	18.33
51 P	14.90	16.89	18.67
53 P	17.61	19.41	22.18
55 P	16.09	16.49	19.27
57 P	16.24	17.04	19.63
59 P	15.43	15.23	16.85
61 P	18.54	20.84	21.70
63 P	15.17	14.80	17.45
65 P	14.50	16.61	18.47
67 NM	.	.	.
69 P	16.51	19.57	22.25
71 P	15.41	17.14	18.62
Mean	15.86	17.29	19.40
SD	1.33	1.88	1.86
N	11	11	11

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.3: Food consumption females gestation

Sex: Female Daily Food Cons Per Animal

1500 ppm	Day(s) Relative to Mating (Litter: A)		
	0 - 7	7 - 14	14 - 20
73 NM	.	.	.
75 P	*	13.96	15.85
77 P	13.50	13.40	15.12
79 P	14.49	16.01	18.07
81 P	15.79	16.44	18.25
83 P	13.41	12.84	15.83
85 P	13.24	14.40	18.57
87 NP	14.63 E	14.90 E	12.53 E
89 P	14.50	16.96	18.77
91 P	13.30	15.06	16.25
93 P	16.20	17.01	19.08
95 P	18.61	16.67	18.97
Mean	14.78	15.28	17.48
SD	1.80	1.55	1.53
N	9	10	10

* = Female 75 was retrospectively declared mated, therefore no food consumption was measured
E = Exclude; NP females excluded from statistics
Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.4: Food consumption females lactation

Sex: Female Daily Food Cons Per Animal

0 ppm	Day(s) Relative to Littering (Litter: A)		
	0 - 4	4 - 7	7 - 13
1 P	30.65	41.13	47.22
3 P	31.63	36.80	43.80
5 P	31.35	41.03	41.88
7 P	27.68	36.07	45.37
9 P	32.08	39.93	45.93
11 P	32.00	40.83	49.27
13 P	33.98	38.57	42.82
15 P	29.90	37.20	40.57
17 P	25.20	35.53	48.35
19 P	31.10	39.33	42.52
21 P	28.03	39.17	43.83
23 P	29.48	33.57	40.27
Mean	30.25	38.26	44.32
SD	2.38	2.43	2.94
N	12	12	12

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.4: Food consumption females lactation

Sex: Female Daily Food Cons Per Animal

250 ppm	Day(s) Relative to Littering (Litter: A)		
	0 - 4	4 - 7	7 - 13
25 P	34.60	36.87	43.35
27 P	30.25	35.77	41.22
29 P	35.50	34.27	43.05
31 P	32.43	39.87	44.43
33 P	27.43	37.97	42.50
35 P	32.68	36.40	42.78
37 P	25.50	36.80	42.43
39 P	31.25	36.67	41.20
41 P	27.95	37.33	46.78
43 P	29.30	39.70	45.07
45 P	35.15	39.50	47.85
47 P	31.73	38.10	44.53
Mean	31.15	37.44	43.77
SD	3.18	1.69	2.06
N	12	12	12

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.4: Food consumption females lactation

Sex: Female Daily Food Cons Per Animal

750 ppm	Day(s) Relative to Littering (Litter: A)		
	0 - 4	4 - 7	7 - 13
49 P	29.90	31.90	35.38
51 P	34.05	35.60	42.33
53 P	26.25	33.90	36.77
55 P	26.23	37.90	40.20
57 P	34.68	39.27	44.93
59 P	12.35	8.87	10.82 *
61 P	29.45	37.00	42.43
63 P	30.60	34.47	38.93
65 P	28.50	30.77	37.38
67 NM	.	.	.
69 P	35.15	39.67	45.88
71 P	25.30	28.23	36.42
Mean	28.40	32.51	40.07
SD	6.34	8.61	3.70
N	11	11	10

* = Food consumption was measured on day 12, not included in statistics
Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 3.4: Food consumption females lactation

Sex: Female Daily Food Cons Per Animal

1500 ppm	Day(s) Relative to Littering (Litter: A)		
	0 - 4	4 - 7	7 - 13
73 NM	.	.	.
75 P	28.10	33.13	39.82
77 P	22.53	27.37	32.07
79 P	28.45	34.80	40.47
81 P	25.15	33.20	39.83
83 P	21.08	30.20	33.35
85 P	24.55	30.73	34.83
87 NP	.	.	.
89 P	30.25	30.60	38.30
91 P	30.43	35.17	39.53
93 P	21.55	21.30	29.17
95 P	30.33	33.07	38.88
Mean	26.24	30.96	36.63
SD	3.73	4.13	3.97
N	10	10	10

[redacted]

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant
N=Number of cages
Consumption was measured per cage over the periods shown and expressed as g/animal/day

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pretreatment)

Predestined group 1

SMEAR#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	#	L	C/A	P
pre animal #	Female #																		
2028	1	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	3	4	C	
2023	3	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2046	5	DI	PRO	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2040	7	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2039	9	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2049	11	DI	DI	EST	MET	XX	XX	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2030	13	XX	XX	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2038	15	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2052	17	PRO	EST	MET	DI	DI	EST	MET	DI	PRO	EST	MET	DI	DI	EST	3	4	C	
2043	19	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2042	21	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	XX	EST	3	4	C	
2019	23	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	

DI	= DIESTRUS	PRO	= PROESTRUS	#	= number of cycles during 14 day test period
EST	= ESTRUS	MET	= METESTRUS	L	= length of longest cycle in days
XX	= TOO FEW CELLS			C/A	= cyclic (C) or acyclic (A)
--	= UNABLE TO SCORE			P	= prolonged estrus period

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pretreatment)

Predestined group 2

SMEAR#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	#	L	C/A	P
pre animal #	Female #																		
2011	25	MET	DI	PRO	EST	MET	DI	PRO	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2031	27	DI	PRO	EST	MET	DI	DI	EST	MET	DI	PRO	EST	MET	DI	DI	2	4	C	
2027	29	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2012	31	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	2	4	C	
2032	33	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	3	4	C	
2017	35	DI	DI	EST	MET	DI	DI	EST	MET	DI	PRO	EST	MET	DI	DI	2	4	C	
2014	37	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2004	39	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	EST	3	4	C	
2035	41	DI	DI	EST	DI	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2050	43	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2044	45	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2001	47	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	2	4	C	

DI	= DIESTRUS	PRO	= PROESTRUS	#	= number of cycles during 14 day test period
EST	= ESTRUS	MET	= METESTRUS	L	= length of longest cycle in days
XX	= TOO FEW CELLS			C/A	= cyclic (C) or acyclic (A)
--	= UNABLE TO SCORE			P	= prolonged estrus period

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pretreatment)

Predestined group 3

SMEAR#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	#	L	C/A	P
pre animal #	Female #																		
2022	49	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2024	51	DI	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2036	53	DI	DI	EST	MET	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	2	4	C	
2025	55	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	3	4	C	
2053	57	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2034	59	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2003	61	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2054	63	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	2	4	C	
2015	65	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2033	67	PRO	EST	MET	XX	DI	XX[1]	MET	DI	DI	EST	MET	DI	DI	EST	3	4	C	
2005	69	DI	DI	EST	MET	XX	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2007	71	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE
PRO = PROESTRUS
MET = METESTRUS
\# = number of cycles during 14 day test period
L = length of longest cycle in days
C/A = cyclic (C) or acyclic (A)
P = prolonged estrus period

[1] Considered as EST

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pretreatment)

Predestined group 4

SMEAR#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	#	L	C/A	P
pre animal #	Female #																		
2008	73	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2018	75	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	2	4	C	
2047	77	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2020	79	EST	MET	DI	DI	EST	DI	DI	DI	EST	MET	DI	DI	EST	DI	3	4	C	
2048	81	DI	DI	EST	MET	DI	DI	EST	MET	DI	PRO	EST	MET	DI	DI	2	4	C	
2029	83	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2041	85	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	EST	DI	DI	DI	2	4	C	
2002	87	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2021	89	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	EST	DI	3	4	C	
2009	91	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2010	93	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	
2045	95	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	

[redacted]

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE
PRO = PROESTRUS
MET = METESTRUS
# = number of cycles during 14 day test period
L = length of longest cycle in days
C/A = cyclic (C) or acyclic (A)
P = prolonged estrus period

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pretreatment)

non-selected females

SMEAR#		1	2	3	4	5	6	7	8	9	10	11	12	13	14	#	L	C/A	P
pre animal #	Female #																		
2006		EST	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	2	4	C	
2013		MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	PRO*	MET	DI	2	4	C	
2016		MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	PRO*	MET	DI	2	4	C	
2026		DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	DI	DI	DI	2	4	C	
2037		PRO*	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	3	4	C	
2051		MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	2	4	C	

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE
PRO = PROESTRUS
MET = METESTRUS
# = number of cycles during 14 day test period
L = length of longest cycle in days
C/A = cyclic (C) or acyclic (A)
P = prolonged estrus period

* Used for cycle length determination

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pre-treatment after allocation)

group 1, pretreatment

SMEAR#		1	2	3
pre animal #	Female #			
2028	1	MET	DI	DI
2023	3	EST	MET	DI
2046	5	MET	DI	DI
2040	7	DI	EST	MET
2039	9	PRO	EST	DI
2049	11	MET	DI	DI
2030	13	PRO	EST	MET
2038	15	PRO	EST	MET
2052	17	MET	DI	PRO
2043	19	DI	EST	MET
2042	21	MET	DI	DI
2019	23	DI	EST	MET

DI = DIESTRUS
PRO = PROESTRUS
EST = ESTRUS
MET = METESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pre-treatment after allocation)

group 2, pretreatment

SMEAR#		1	2	3
pre animal #	Female #			
2011	25	PRO	EST	MET
2031	27	EST	MET	DI
2027	29	PRO	EST	MET
2012	31	EST	MET	DI
2032	33	MET	DI	XX
2017	35	EST	MET	DI
2014	37	EST	MET	DI
2004	39	MET	DI	DI
2035	41	MET	MET	DI
2050	43	PRO	EST	MET
2044	45	PRO	EST	MET
2001	47	EST	MET	DI

DI = DIESTRUS
PRO = PROESTRUS
EST = ESTRUS
MET = METESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pre-treatment after allocation)

group 3, pretreatment

SMEAR#		1	2	3
pre animal #	Female #			
2022	49	PRO	EST	MET
2024	51	EST	MET	DI
2036	53	DI	DI	EST
2025	55	DI	DI	EST
2053	57	PRO	EST	MET
2034	59	PRO	EST	MET
2003	61	DI	EST	MET
2054	63	PRO	EST	MET
2015	65	EST	MET	DI
2033	67	MET	DI	DI
2005	69	EST	MET	DI
2007	71	EST	MET	DI

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE
PRO = PROESTRUS
MET = METESTRUS

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (pre-treatment after allocation)

group 4, pretreatment

SMEAR#		1	2	3
pre animal #	Female #			
2008	73	PRO	EST	MET
2018	75	EST	MET	DI
2047	77	PRO	EST	MET
2020	79	DI	DI	EST
2048	81	EST	MET	DI
2029	83	PRO	EST	MET
2041	85	EST	MET	DI
2002	87	EST	MET	DI
2021	89	DI	DI	EST
2009	91	PRO	EST	MET
2010	93	PRO	EST	MET
2045	95	PRO	EST	MET

DI = DIESTRUS PRO = PROESTRUS
EST = ESTRUS MET = METESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (premating)

GROUP 1

SMEAR#	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	#	L	C/A	P
FEMALE#																										
1	EST	MET	DI	DI	EST	MET	MET	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM						3	4	C	
3	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
5	PRO	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
7	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
9	DI	DI	EST	MET	XX	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
11	DI	EST	MET	XX	XX	EST	DI	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
13	DI	DI	DI	MET	DI	XX	EST	MET	DI	DI	DI	DI	DI	XX	DI	XX	XX	EST/SPERM							A	
15	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
17	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM						3	4	C	
19	DI	DI	EST	MET	XX	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
21	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM						3	4	C	
23	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	

DI	= DIESTRUS	PRO	= PROESTRUS	#	= number of cycles during 14 day test period
EST	= ESTRUS	MET	= METESTRUS	L	= length of longest cycle in days
XX	= TOO FEW CELLS			C/A	= cyclic (C) or acyclic (A)
--	= UNABLE TO SCORE			P	= prolonged estrus period

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (premating)

GROUP 2

SMEAR#	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	#	L	C/A	P
FEMALE#																										
25	DI	DI	EST	MET	DI	PRO	EST	MET	MET	DI	EST	MET	DI	PRO	EST	MET	DI	DI	EST/SPERM				3	4	C	
27	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	MET	DI	EST	MET	DI	PRO	EST/SPERM					3	4	C	
29	DI	DI	EST	MET	DI	PRO	EST	MET	DI	PRO	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
31	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
33	EST	MET	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	XX	EST/SPERM						3	4	C	
35	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
37	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
39	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM						3	4	C	
41	DI	EST	MET	DI	XX	EST	DI	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM					3	4	C	
43	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
45	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				3	4	C	
47	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	XX	EST/SPERM					3	4	C	

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE
PRO = PROESTRUS
MET = METESTRUS
# = number of cycles during 14 day test period
L = length of longest cycle in days
C/A = cyclic (C) or acyclic (A)
P = prolonged estrus period

Sanitized

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (premating)

GROUP 3

SMEAR#	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
FEMALE#																				
49	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	PRO	EST	MET	DI	DI	EST/SPERM				
51	PRO	DI	EST	XX	XX	DI	DI	DI	DI	XX	DI	XX	XX	EST	MET	DI	DI	EST/SPERM		
53	MET	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	PRO	EST/SPERM		
55	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				
57	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	EST/SPERM		
59	DI	DI	EST	MET	DI	XX	EST	DI	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM	
61	DI	DI	EST	MET	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM	
63	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM	
65	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	PRO	EST/SPERM		
67	EST	MET	DI	DI	DI	XX	XX	XX	DI	XX	DI	DI	XX	DI	DI	DI	DI	PRO	PRO	DI
69	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	XX	EST/SPERM		
71	PRO	EST	MET	DI	XX	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM		

GROUP 3 (continue)

SMEAR#	21	22	23	#	L	C/A	P
FEMALE#							
49				2	5	C	
51						A	
53				3	4	C	
55				2	4	C	
57				3	4	C	
59				3	4	C	
61				3	4	C	
63				3	4	C	
65				3	4	C	
67	DI	DI	EST			A	
69				3	4	C	
71				3	4	C	

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE

PRO = PROESTRUS
MET = METESTRUS

# = number of cycles during 14 day test period
L = length of longest cycle in days
C/A = cyclic (C) or acyclic (A)
P = prolonged estrus period

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 4: Estrus cyclicity (premating)

GROUP 4

SMEAR#	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
FEMALE#																				
73	DI	DI	EST	MET	DI	XX	EST	MET	XX	DI	EST	MET	DI	DI	DI	XX	DI	DI	DI	XX
75	DI	EST	MET	DI	DI	XX	DI	DI	XX	XX	DI	DI	DI	XX	XX	XX	EST	MET	DI	XX
77	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	DI	EST	EST/SPERM			
79	MET	DI	DI	DI	DI	XX	XX	XX	XX	XX	XX	XX	DI	DI	DI	DI	PRO	EST/SPERM		
81	DI	EST	MET	DI	DI	EST	MET	XX	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM		
83	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	DI	MET*	DI	DI	EST	MET	DI	DI	EST/SPERM	
85	DI	EST	MET	DI	DI	XX	DI	DI	XX	XX	XX	DI	XX	EST	MET	DI	DI	EST/SPERM		
87	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI
89	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM				
91	DI	DI	EST	MET	DI	XX	DI	DI	XX	XX	DI	XX	DI	XX	DI	MET	DI	DI	EST/SPERM	
93	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST	MET	DI	DI	EST/SPERM	
95	DI	DI	EST	MET	DI	XX	EST	MET	DI	DI	EST	DI	DI	DI	EST	DI	DI	DI	EST/SPERM	

GROUP 4 (continue)

SMEAR#	21	22	23	#	L	C/A	P
FEMALE#							
73	XX	XX	XX			A	
75	XX	XX	XX			A	
77				2	4	C	
79						A	
81				3	4	C	
83				3	5	C	
85						A	
87	DI	EST/SPERM		3	4	C	
89				2	4	C	
91						A	
93				3	4	C	
95				3	4	C	

DI = DIESTRUS
EST = ESTRUS
XX = TOO FEW CELLS
-- = UNABLE TO SCORE
PRO = PROESTRUS
MET = METESTRUS
# = number of cycles during 14 day test period
L = length of longest cycle in days
C/A = cyclic (C) or acyclic (A)
P = prolonged estrus period
* Used for cycle length determination

31/Jan/2018 15:27:51

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Male Day(s) Relative to Start Date

0 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Testes (g)	Epididy mides (g)	Prostate (g)	Seminal vesicles (g)	LABC Muscle (g)	Cowpers Glands (g)	Glans Penis (g)
	35	35	35	35	35	35	35	35	35	35
2	319.7	1.38	0.014	3.46	1.18	0.97	1.38	1.279	0.131	0.113
4	354.3	1.45	0.015	3.33	1.16	0.94	1.25	1.127	0.107	0.112
6	358.1	1.44	0.014	3.91	1.23	1.01	1.99	1.185	0.143	0.201
8	395.9	1.46	0.023	3.50	1.12	0.70	1.17	0.919	0.119	0.211
10	415.4	1.63	0.023	3.56	1.21	0.80	1.36	1.131	0.122	0.147
12	417.7	1.64	0.023	3.53	1.21	1.08	1.37	1.200	0.140	0.138
14	360.9	1.44	0.015	3.44	1.14	0.95	1.30	1.067	0.094	0.219
16	320.0	1.31	0.015	3.39	1.34	0.94	1.54	1.077	0.150	0.104
18	337.6	1.22	0.015	3.50	1.10	0.90	1.31	1.109	0.130	0.108
20	386.6	1.41	0.016	3.20	1.13	0.79	1.15	1.055	0.103	0.143
22	348.8	1.35	0.013	3.60	1.15	0.69	0.99	0.975	0.086	0.127
24	374.5	1.48	0.015	3.42	1.28	1.00	1.32	1.193	0.111	0.132
Mean	365.79	1.434	0.0168	3.487	1.188	0.898	1.344	1.1098	0.1197	0.1463
SD	33.15	0.119	0.0038	0.171	0.070	0.125	0.246	0.1003	0.0201	0.0412
N	12	12	12	12	12	12	12	12	12	12

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Male Day(s) Relative to Start Date

250 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Testes (g)	Epididy mides (g)	Prostate (g)	Seminal vesicles (g)	LABC Muscle (g)	Cowpers Glands (g)	Glans Penis (g)
	35	35	35	35	35	35	35	35	35	35
26	329.2	1.41	0.021	3.20	1.11	0.86	1.23	1.039	0.137	0.102
28	293.0	1.30	0.013	3.31	1.27	0.91	1.38	1.175	0.145	0.127
30	353.6	1.51	0.018	3.99	1.28	0.71	1.16	0.923	0.082	0.121
32	353.2	1.42	0.016	3.25	1.16	0.79	1.39	1.009	0.109	0.105
34	427.4	1.77	0.023	3.36	1.22	0.99	1.83	1.217	0.125	0.235
36	372.9	1.47	0.011	3.19	1.11	0.86	1.55	1.209	0.115	0.138
38	384.7	1.64	0.017	3.72	1.23	1.13	1.34	1.106	0.108	0.078
40	328.1	1.31	0.015	3.71	1.24	0.64	1.35	0.987	0.066	0.108
42	407.4	1.65	0.018	3.14	1.20	0.84	1.64	1.208	0.135	0.115
44	328.6	1.40	0.015	3.65	1.28	0.88	1.15	1.034	0.062	0.130
46	319.9	1.45	0.018	2.97	0.97	0.80	1.26	0.976	0.093	0.224
48	321.2	1.52	0.011	3.12	1.09	0.67	0.83	0.881	0.069	0.126
Mean	351.60	1.488	0.0163	3.384	1.180	0.840	1.343	1.0637	0.1038	0.1341
SD	39.73	0.141	0.0037	0.309	0.095	0.136	0.257	0.1171	0.0292	0.0473
N	12	12	12	12	12	12	12	12	12	12

[redacted]

Sanitized

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Male Day(s) Relative to Start Date

750 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Testes (g)	Epididy mides (g)	Prostate (g)	Seminal vesicles (g)	LABC Muscle (g)	Cowpers Glands (g)	Glans Penis (g)
	35	35	35	35	35	35	35	35	35	35
50	311.8	1.36	0.024	3.27	1.07	0.64	1.05	0.893	0.086	0.084
52	360.7	1.46	0.022	3.42	1.16	0.77	1.24	0.881	0.116	0.120
54	356.6	1.32	0.013	3.65	1.07	0.63	1.10	0.925	0.076	0.098
56	388.9	1.78	0.022	4.31	1.48	0.96	1.47	1.267	0.119	0.185
58	318.1	1.39	0.018	2.91	0.97	1.09	0.19	0.964	0.104	0.113
60	298.3	1.40	0.016	3.19	1.16	0.80	1.08	0.721	0.059	0.098
62	380.4	1.46	0.020	3.16	1.14	0.65	1.26	0.995	0.087	0.136
64	357.5	1.39	0.012	3.55	1.04	0.72	1.43	0.980	0.101	0.201
66	342.1	1.34	0.013	3.65	1.09	0.78	1.33	0.952	0.089	0.129
68	292.5	1.27	0.016	3.31	1.08	0.63	1.15	0.801	0.126	0.135
70	331.2	1.43	0.018	3.38	1.19	1.09	1.29	0.927	0.069	0.121
72	290.6	1.29	0.012	3.10	1.10	0.85	0.86	0.900	0.074	0.148
Mean	335.73	1.408	0.0172	3.408	1.129	0.801	1.121	0.9338	0.0922	0.1307
SD	33.85	0.132	0.0042	0.361	0.126	0.168	0.339	0.1303	0.0212	0.0345
N	12	12	12	12	12	12	12	12	12	12

31/Jan/2018 15:27:51

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Male Day(s) Relative to Start Date

1500 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Testes (g)	Epididy mides (g)	Prostate (g)	Seminal vesicles (g)	LABC Muscle (g)	Cowpers Glands (g)	Glans Penis (g)
	35	35	35	35	35	35	35	35	35	35
74	340.2	1.46	0.020	3.55	1.09	0.79	1.01	0.951	0.088	0.118
76	370.4	1.63	0.019	3.53	1.19	0.98	1.50	1.028	0.104	0.122
78	345.4	1.45	0.015	3.16	1.15	0.78	1.41	1.030	0.119	0.105
80	333.5	1.42	0.007	3.12	1.02	0.80	0.96	0.838	0.101	0.105
82	345.0	1.54	0.013	3.28	1.15	0.78	1.04	0.947	0.079	0.102
84	336.6	1.43	0.007	3.44	1.11	0.72	1.06	0.929	0.091	0.096
86	352.5	1.41	0.034	3.21	1.00	0.48	1.08	0.794	0.095	0.113
88	351.1	1.49	0.017	3.69	1.25	0.98	1.20	0.867	0.089	0.145
90	296.5	1.33	0.016	3.23	1.10	0.93	1.24	0.840	0.079	0.204
92	297.3	1.36	0.004	3.63	1.24	0.90	1.58	1.020	0.105	0.149
94	305.8	1.43	0.015	3.42	1.14	0.59	0.98	0.850	0.099	0.121
96	315.0	1.33	0.016	3.43	1.04	1.02	0.70	1.103	0.079	0.178
Mean	332.44	1.440	0.0153	3.391	1.123	0.813	1.147	0.9331	0.0940	0.1298
SD	23.62	0.086	0.0077	0.189	0.080	0.163	0.252	0.0971	0.0123	0.0332
N	12	12	12	12	12	12	12	12	12	12

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

0 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Ovaries (g)	Uterus (g)
	14	14	14	14	14
1 P	281.5	1.31	0.014	0.092	0.776
3 P	266.8	1.38	0.027	0.098	0.524
5 P	240.2	1.21	0.008	0.090	0.498
7 P	251.0	1.25	0.015	0.093	0.541
9 P	248.5	1.20	0.015	0.096	0.294
11 P	264.2	1.29	0.019	0.096	0.626
13 P	264.0	1.16	0.022	0.090	0.603
15 P	260.2	1.28	0.015	0.093	0.618
17 P	245.9	1.32	0.018	0.099	0.518
19 P	251.8	1.28	0.016	0.077	0.370
21 P	254.9	1.25	0.014	0.091	0.530
23 P	248.1	1.21	0.010	0.104	0.496
Mean	256.43	1.262	0.0161	0.0933	0.5328
SD	11.39	0.061	0.0051	0.0066	0.1230
N	12	12	12	12	12

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

250 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Ovaries (g)	Uterus (g)
	14	14	14	14	14
25 P	243.3	1.23	0.026	0.092	0.589
27 P	230.1	1.18	0.020	0.101	0.597
29 P	236.1	1.18	0.017	0.093	0.475
31 P	254.1	1.26	0.013	0.080	0.384
33 P	253.1	1.19	0.021	0.105	0.447
35 P	248.8	1.16	0.013	0.115	0.575
37 P	259.3	1.25	0.013	0.096	0.491
39 P	251.5	1.23	0.014	0.098	0.352
41 P	271.7	1.37	0.017	0.098	0.597
43 P	263.6	1.32	0.018	0.116	0.605
45 P	278.8	1.36	0.026	0.111	0.650
47 P	264.5	1.16	0.024	0.113	0.483
Mean	254.58	1.241	0.0185	0.1015	0.5204
SD	14.13	0.074	0.0049	0.0109	0.0954
N	12	12	12	12	12

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

31/Jan/2018 15:27:59

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

750 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Ovaries (g)	Uterus (g)
	14	14	14	14	14
49 P	237.8	1.22	0.013	0.067	0.363
51 P	232.9	1.11	0.014	0.079	0.608
53 P	255.4	1.29	0.014	0.079	0.715
55 P	271.5	1.18	0.012	0.090	0.536
57 P	238.9	1.18	0.010	0.075	0.473
59 P	206.3	1.18	0.016	0.106	0.942
61 P	255.8	1.27	0.015	0.095	0.370
63 P	241.9	1.25	0.019	0.101	0.398
65 P	246.4	1.15	0.019	0.086	0.382
67 NM	219.4 E	1.23 E	0.016 E	0.119 E	1.004 E
69 P	260.4	1.26	0.015	0.091	0.518
71 P	238.6	1.27	0.016	0.080	0.480
Mean	244.17	1.215	0.0148	0.0863	0.5259
SD	17.15	0.058	0.0027	0.0117	0.1757
N	11	11	11	11	11

E = Exclude; NM females excluded from statistics
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 5: Absolute organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

1500 ppm	Terminal body wgt (g)	Lungs (g)	Thyroid (g)	Ovaries (g)	Uterus (g)
	14	14	14	14	14
73 NM	205.3 E	1.01 E	0.014 E	0.131 E	0.740 E
75 P	233.2	1.22	0.014	0.059	0.363
77 P	217.7	1.13	0.015	0.078	0.399
79 P	229.5	1.14 [1]	0.024	0.110	0.329
81 P	232.5	1.20	0.021	0.087	0.409
83 P	219.1	1.21	0.014	0.062	0.382
85 P	232.7	1.20	0.010	0.071	0.393
87 NP	205.8 E	1.10 E	0.009 E	0.107 E	0.401 E
89 P	237.0	1.33	0.010	0.099	0.730
91 P	229.3	1.12	0.013	0.088	0.418
93 P	241.3	1.29	0.014	0.076	0.374
95 P	233.0	1.20	0.019	0.084	0.392
Mean	230.53	1.204	0.0154	0.0814	0.4189
SD	7.28	0.067	0.0046	0.0158	0.1122
N	10	10	10	10	10

E = Exclude; NM and NP females excluded from statistics

[1] Weight without larynx

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

31/Jan/2018 15:27:51

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Male Day(s) Relative to Start Date

0 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Testes rel.wgt (g/kg body wgt)	Epididy rel.wgt (g/kg body wgt)	Prostate rel.wgt (g/kg body wgt)	Sem ves rel.wgt (g/kg body wgt)	LABC Muscle rel.wgt (g/kg body wgt)	Cowpers Gl. rel.wgt (g/kg body wgt)	Glans Penis rel.wgt (g/kg body wgt)
	35	35	35	35	35	35	35	35	35	35
2	319.7	4.32	0.044	10.82	3.69	3.03	4.32	4.001	0.410	0.353
4	354.3	4.09	0.042	9.40	3.27	2.65	3.53	3.181	0.302	0.316
6	358.1	4.02	0.039	10.92	3.43	2.82	5.56	3.309	0.399	0.561
8	395.9	3.69	0.058	8.84	2.83	1.77	2.96	2.321	0.301	0.533
10	415.4	3.92	0.055	8.57	2.91	1.93	3.27	2.723	0.294	0.354
12	417.7	3.93	0.055	8.45	2.90	2.59	3.28	2.873	0.335	0.330
14	360.9	3.99	0.042	9.53	3.16	2.63	3.60	2.956	0.260	0.607
16	320.0	4.09	0.047	10.59	4.19	2.94	4.81	3.366	0.469	0.325
18	337.6	3.61	0.044	10.37	3.26	2.67	3.88	3.285	0.385	0.320
20	386.6	3.65	0.041	8.28	2.92	2.04	2.97	2.729	0.266	0.370
22	348.8	3.87	0.037	10.32	3.30	1.98	2.84	2.795	0.247	0.364
24	374.5	3.95	0.040	9.13	3.42	2.67	3.52	3.186	0.296	0.352
Mean	365.79	3.928	0.0454	9.602	3.273	2.476	3.712	3.0604	0.3303	0.3989
SD	33.15	0.204	0.0070	0.968	0.389	0.429	0.817	0.4271	0.0697	0.1041
N	12	12	12	12	12	12	12	12	12	12

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Male Day(s) Relative to Start Date

250 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Testes rel.wgt (g/kg body wgt)	Epididy rel.wgt (g/kg body wgt)	Prostate rel.wgt (g/kg body wgt)	Sem ves rel.wgt (g/kg body wgt)	LABC Muscle rel.wgt (g/kg body wgt)	Cowpers Gl. rel.wgt (g/kg body wgt)	Glans Penis rel.wgt (g/kg body wgt)
	35	35	35	35	35	35	35	35	35	35
26	329.2	4.28	0.064	9.72	3.37	2.61	3.74	3.156	0.416	0.310
28	293.0	4.44	0.044	11.30	4.33	3.11	4.71	4.010	0.495	0.433
30	353.6	4.27	0.051	11.28	3.62	2.01	3.28	2.610	0.232	0.342
32	353.2	4.02	0.045	9.20	3.28	2.24	3.94	2.857	0.309	0.297
34	427.4	4.14	0.054	7.86	2.85	2.32	4.28	2.847	0.292	0.550
36	372.9	3.94	0.029	8.55	2.98	2.31	4.16	3.242	0.308	0.370
38	384.7	4.26	0.044	9.67	3.20	2.94	3.48	2.875	0.281	0.203
40	328.1	3.99	0.046	11.31	3.78	1.95	4.11	3.008	0.201	0.329
42	407.4	4.05	0.044	7.71	2.95	2.06	4.03	2.965	0.331	0.282
44	328.6	4.26	0.046	11.11	3.90	2.68	3.50	3.147	0.189	0.396
46	319.9	4.53	0.056	9.28	3.03	2.50	3.94	3.051	0.291	0.700
48	321.2	4.73	0.034	9.71	3.39	2.09	2.58	2.743	0.215	0.392
Mean	351.60	4.244	0.0465	9.726	3.390	2.400	3.812	3.0427	0.2967	0.3837
SD	39.73	0.236	0.0092	1.304	0.446	0.373	0.549	0.3548	0.0890	0.1319
N	12	12	12	12	12	12	12	12	12	12

Sanitized

31/Jan/2018 15:27:51

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Male   Day(s) Relative to Start Date

750 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Testes rel.wgt (g/kg body wgt)	Epididy rel.wgt (g/kg body wgt)	Prostate rel.wgt (g/kg body wgt)	Sem ves rel.wgt (g/kg body wgt)	LABC Muscle rel.wgt (g/kg body wgt)	Cowpers Gl. rel.wgt (g/kg body wgt)	Glans Penis rel.wgt (g/kg body wgt)
	35	35	35	35	35	35	35	35	35	35
50	311.8	4.36	0.077	10.49	3.43	2.05	3.37	2.864	0.276	0.269
52	360.7	4.05	0.061	9.48	3.22	2.13	3.44	2.442	0.322	0.333
54	356.6	3.70	0.036	10.24	3.00	1.77	3.08	2.594	0.213	0.275
56	388.9	4.58	0.057	11.08	3.81	2.47	3.78	3.258	0.306	0.476
58	318.1	4.37	0.057	9.15	3.05	3.43	0.60	3.030	0.327	0.355
60	298.3	4.69	0.054	10.69	3.89	2.68	3.62	2.417	0.198	0.329
62	380.4	3.84	0.053	8.31	3.00	1.71	3.31	2.616	0.229	0.358
64	357.5	3.89	0.034	9.93	2.91	2.01	4.00	2.741	0.283	0.562
66	342.1	3.92	0.038	10.67	3.19	2.28	3.89	2.783	0.260	0.377
68	292.5	4.34	0.055	11.32	3.69	2.15	3.93	2.738	0.431	0.462
70	331.2	4.32	0.054	10.21	3.59	3.29	3.89	2.799	0.208	0.365
72	290.6	4.44	0.041	10.67	3.79	2.92	2.96	3.097	0.255	0.509
Mean	335.73	4.208	0.0513	10.185	3.380	2.409	3.323	2.7817	0.2755	0.3891
SD	33.85	0.318	0.0122	0.856	0.361	0.564	0.925	0.2540	0.0655	0.0926
N	12	12	12	12	12	12	12	12	12	12

Sanitized

31/Jan/2018 15:27:51

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Male Day(s) Relative to Start Date

1500 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Testes rel.wgt (g/kg body wgt)	Epididy rel.wgt (g/kg body wgt)	Prostate rel.wgt (g/kg body wgt)	Sem ves rel.wgt (g/kg body wgt)	LABC Muscle rel.wgt (g/kg body wgt)	Cowpers Gl. rel.wgt (g/kg body wgt)	Glans Penis rel.wgt (g/kg body wgt)
	35	35	35	35	35	35	35	35	35	35
74	340.2	4.29	0.059	10.44	3.20	2.32	2.97	2.795	0.259	0.347
76	370.4	4.40	0.051	9.53	3.21	2.65	4.05	2.775	0.281	0.329
78	345.4	4.20	0.043	9.15	3.33	2.26	4.08	2.982	0.345	0.304
80	333.5	4.26	0.021	9.36	3.06	2.40	2.88	2.513	0.303	0.315
82	345.0	4.46	0.038	9.51	3.33	2.26	3.01	2.745	0.229	0.296
84	336.6	4.25	0.021	10.22	3.30	2.14	3.15	2.760	0.270	0.285
86	352.5	4.00	0.096	9.11	2.84	1.36	3.06	2.252	0.270	0.321
88	351.1	4.24	0.048	10.51	3.56	2.79	3.42	2.469	0.253	0.413
90	296.5	4.49	0.054	10.89	3.71	3.14	4.18	2.833	0.266	0.688
92	297.3	4.57	0.013	12.21	4.17	3.03	5.31	3.431	0.353	0.501
94	305.8	4.68	0.049	11.18	3.73	1.93	3.20	2.780	0.324	0.396
96	315.0	4.22	0.051	10.89	3.30	3.24	2.22	3.502	0.251	0.565
Mean	332.44	4.339	0.0454	10.249	3.395	2.459	3.462	2.8198	0.2836	0.3966
SD	23.62	0.187	0.0218	0.955	0.352	0.541	0.816	0.3589	0.0391	0.1262
N	12	12	12	12	12	12	12	12	12	12

Appendix 6: Relative organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

0 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Ovaries rel.wgt (g/kg body wgt)	Uterus rel.wgt (g/kg body wgt)
	14	14	14	14	14
1 P	281.5	4.65	0.050	0.327	2.76
3 P	266.8	5.17	0.101	0.367	1.96
5 P	240.2	5.04	0.033	0.375	2.07
7 P	251.0	4.98	0.060	0.371	2.16
9 P	248.5	4.83	0.060	0.386	1.18
11 P	264.2	4.88	0.072	0.363	2.37
13 P	264.0	4.39	0.083	0.341	2.28
15 P	260.2	4.92	0.058	0.357	2.38
17 P	245.9	5.37	0.073	0.403	2.11
19 P	251.8	5.08	0.064	0.306	1.47
21 P	254.9	4.90	0.055	0.357	2.08
23 P	248.1	4.88	0.040	0.419	2.00
Mean	256.43	4.925	0.0624	0.3643	2.068
SD	11.39	0.246	0.0184	0.0310	0.413
N	12	12	12	12	12

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Sanitized

31/Jan/2018 15:27:59

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

250 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Ovaries rel.wgt (g/kg body wgt)	Uterus rel.wgt (g/kg body wgt)
	14	14	14	14	14
25 P	243.3	5.06	0.107	0.378	2.42
27 P	230.1	5.13	0.087	0.439	2.59
29 P	236.1	5.00	0.072	0.394	2.01
31 P	254.1	4.96	0.051	0.315	1.51
33 P	253.1	4.70	0.083	0.415	1.77
35 P	248.8	4.66	0.052	0.462	2.31
37 P	259.3	4.82	0.050	0.370	1.89
39 P	251.5	4.89	0.056	0.390	1.40
41 P	271.7	5.04	0.063	0.361	2.20
43 P	263.6	5.01	0.068	0.440	2.30
45 P	278.8	4.88	0.093	0.398	2.33
47 P	264.5	4.39	0.091	0.427	1.83
Mean	254.58	4.877	0.0727	0.3991	2.047
SD	14.13	0.209	0.0191	0.0407	0.373
N	12	12	12	12	12

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Female Day(s) Relative to Littering (Litter: A)

750 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Ovaries rel.wgt (g/kg body wgt)	Uterus rel.wgt (g/kg body wgt)
	14	14	14	14	14
49 P	237.8	5.13	0.055	0.282	1.53
51 P	232.9	4.77	0.060	0.339	2.61
53 P	255.4	5.05	0.055	0.309	2.80
55 P	271.5	4.35	0.044	0.331	1.97
57 P	238.9	4.94	0.042	0.314	1.98
59 P	206.3	5.72	0.078	0.514	4.57
61 P	255.8	4.96	0.059	0.371	1.45
63 P	241.9	5.17	0.079	0.418	1.65
65 P	246.4	4.67	0.077	0.349	1.55
67 NM	219.4 E	5.61 E	0.073 E	0.542 E	4.58 E
69 P	260.4	4.84	0.058	0.349	1.99
71 P	238.6	5.32	0.067	0.335	2.01
Mean	244.17	4.992	0.0611	0.3557	2.191
SD	17.15	0.360	0.0127	0.0631	0.898
N	11	11	11	11	11

E = Exclude; NM females excluded from statistics
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 6: Relative organ weights

Sex: Female   Day(s) Relative to Littering (Litter: A)

1500 ppm	Terminal body wgt (g)	Lungs rel.wgt (g/kg body wgt)	Thyroid rel.wgt (g/kg body wgt)	Ovaries rel.wgt (g/kg body wgt)	Uterus rel.wgt (g/kg body wgt)
	14	14	14	14	14
73 NM	205.3 E	4.92 E	0.068 E	0.638 E	3.60 E
75 P	233.2	5.23	0.060	0.253	1.56
77 P	217.7	5.19	0.069	0.358	1.83
79 P	229.5	4.97 [1]	0.105	0.479	1.43
81 P	232.5	5.16	0.090	0.374	1.76
83 P	219.1	5.52	0.064	0.283	1.74
85 P	232.7	5.16	0.043	0.305	1.69
87 NP	205.8 E	5.34 E	0.044 E	0.520 E	1.95 E
89 P	237.0	5.61	0.042	0.418	3.08
91 P	229.3	4.88	0.057	0.384	1.82
93 P	241.3	5.35	0.058	0.315	1.55
95 P	233.0	5.15	0.082	0.361	1.68
Mean	230.53	5.222	0.0669	0.3530	1.815
SD	7.28	0.224	0.0200	0.0669	0.463
N	10	10	10	10	10

E = Exclude; NM and NP females excluded from statistics

[1] Weight without larynx

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Animal: 2 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : left lobe; spot; red [lungs : gross finding not confirmed (H)]
thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

epididymides : inflammation; mononuclear, focal, minimal
lungs : gross finding not confirmed [lungs : left lobe; spot; red (G)]
thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 4 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

thymus : discoloration; red, partly [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : discoloration; red, partly (G)]

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 6 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

Animal: 6 (Continued) Group: 1 - Control Sex: Male

Histopathology - The following Tissues were Within Normal Limits (Continued):

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 8 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 10 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 12 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Animal: 12 (Continued) Group: 1 - Control Sex: Male

Histopathology Observations [Correlation]:

prostate gland : inflammation; mononuclear, minimal

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 14 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 16 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 18 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Animal: 18 (Continued) Group: 1 - Control Sex: Male

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; red [lungs : alveolitis; mild (H) | lungs : crystal; haemoglobin, mild (H)]
thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

lungs : alveolitis; mild [lungs : all lobes; spots; red (G)]
lungs : crystal; haemoglobin, mild [lungs : all lobes; spots; red (G)]
thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 20 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

prostate gland : inflammation; mononuclear, minimal
testes : seminiferous tubular atrophy; minimal

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 22 Group: 1 - Control Sex: Male
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Animal: 22 (Continued) Group: 1 - Control Sex: Male

Histopathology - The following Tissues were Not Examined:

None

Animal: 24 Group: 1 - Control Sex: Male

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 1 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 07/Dec/2017 Study Day (Week) of Death: 52 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 3 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 1 : inflammation; mixed, minimal

Animal: 3 (Continued) Group: 1 - Control Sex: Female

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 5 Group: 1 - Control Sex: Female
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

skin/subcutis : sparsely haired [skin/subcutis : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

skin/subcutis : gross finding not confirmed [skin/subcutis : sparsely haired (G)]
nose, level 2 : inflammation; mononuclear, minimal
nose, level 4 : inflammation; mononuclear, mild
nose, level 3 : inflammation; mononuclear, minimal

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 7 Group: 1 - Control Sex: Female
Species: Rat
Dose: 0 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]
adipose tissue : abdominal adipose tissue; nodules; yellow [adipose tissue : necrosis; fatty, focal, mild (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
adipose tissue : necrosis; fatty, focal, mild [adipose tissue : abdominal adipose tissue; nodules; yellow (G)]

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 9 Group: 1 - Control Sex: Female
Species: Rat
Dose: 0 ppm

Animal:	9 (Continued)	Group:	1 - Control	Sex:	Female
		Removal Reason:	Killed Terminal		
Necropsy Date:	09/Dec/2017	Study Day (Week) of Death:	54 (7)		

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer [stomach : gross finding not confirmed (H)]
thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

stomach : gross finding not confirmed [stomach : glandular stomach; ulcer (G)]
thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal:	11	Group:	1 - Control	Sex:	Female
Species:	Rat				
		Dose:	0 ppm		
		Removal Reason:	Killed Terminal		
Necropsy Date:	09/Dec/2017	Study Day (Week) of Death:	54 (7)		

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal:	13	Group:	1 - Control	Sex:	Female
Species:	Rat				
		Dose:	0 ppm		
		Removal Reason:	Killed Terminal		
Necropsy Date:	08/Dec/2017	Study Day (Week) of Death:	53 (7)		

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Animal: 13 (Continued) Group: 1 - Control Sex: Female

Histopathology - The following Tissues were Not Examined:

None

Animal: 15 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 10/Dec/2017 Study Day (Week) of Death: 55 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 17 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 07/Dec/2017 Study Day (Week) of Death: 52 (7)

Gross Pathology Observations [Correlation]:

skin/subcutis : encrustations [skin/subcutis : dermatitis; focal, moderate (H)]

Histopathology Observations [Correlation]:

skin/subcutis : dermatitis; focal, moderate [skin/subcutis : encrustations (G)]
nose, level 1 : inflammation; mixed, minimal
nose, level 2 : inflammation; mononuclear, mild
nose, level 4 : inflammation; mononuclear, moderate
nose, level 4 : rhinitis; mild
nose, level 3 : inflammation; mononuclear, mild
nose, level 5 : inflammation; mononuclear, mild
nasal associated lymphoid tissue : germinal centre development; mild

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; ureters; uterus; vagina; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 19 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Sanitized [redacted]

Animal: 19 (Continued) Group: 1 - Control Sex: Female

Necropsy Date: 10/Dec/2017 Study Day (Week) of Death: 55 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer; red

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 21 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 07/Dec/2017 Study Day (Week) of Death: 52 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 23 Group: 1 - Control Sex: Female

Species: Rat

Dose: 0 ppm

Removal Reason: Killed Terminal

Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 5 : inflammation; mononuclear, minimal

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2; nose, level 4; nose, level 3; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 26 Group: 2 - Low dose Sex: Male

Species: Rat

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 26 (Continued) Group: 2 - Low dose Sex: Male
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

thymus : spots; red, few [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red, few (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 28 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : spots; white [lungs : haemorrhage(s); alveolar, mild (H)]
thymus : discoloration; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

lungs : haemorrhage(s); alveolar, mild [lungs : spots; white (G)]
lungs : accumulation of alveolar macrophages; minimal
thymus : microhaemorrhage(s) [thymus : discoloration; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 30 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Animal: 30 (Continued) Group: 2 - Low dose Sex: Male

Histopathology - The following Tissues were Not Examined:

None

Animal: 32 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lymph node, mesenteric : discoloration; red [lymph node, mesenteric : sinusoidal blood (H)]
lymph node, mesenteric : enlarged [lymph node, mesenteric : haemorrhage(s); moderate (H)]

Histopathology Observations [Correlation]:

lymph node, mesenteric : haemorrhage(s); moderate [lymph node, mesenteric : enlarged (G)]
lymph node, mesenteric : sinusoidal blood [lymph node, mesenteric : discoloration; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 34 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : left lobe; spots; red
lungs : medial lobe; spots; red [lungs : haemorrhage(s); alveolar, mild (H)]

Histopathology Observations [Correlation]:

lungs : haemorrhage(s); alveolar, mild [lungs : medial lobe; spots; red (G)]
lungs : bone spicule
nose, level 5 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 36 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 36 (Continued) Group: 2 - Low dose Sex: Male

Gross Pathology Observations [Correlation] (Continued):

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 38 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 40 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : left lobe; spot; red [lungs : gross finding not confirmed (H)]
lungs : caudal lobe; spots; dark

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : left lobe; spot; red (G)]
lungs : bone spicule
lungs : alveolitis; minimal
lungs : inflammation; mononuclear, mild
nose, level 4 : inflammation; mononuclear, mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

Animal: 40 (Continued) Group: 2 - Low dose Sex: Male

None

Animal: 42 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 44 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 46 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5

Animal: 46 (Continued) Group: 2 - Low dose Sex: Male

Histopathology - The following Tissues were Not Examined:

None

Animal: 48 Group: 2 - Low dose Sex: Male
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 25 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 27 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

Animal: 27 (Continued) Group: 2 - Low dose Sex: Female

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 29 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 31 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 33 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 07/Dec/2017 Study Day (Week) of Death: 52 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; haemorrhage(s); minimal

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 33 (Continued) Group: 2 - Low dose Sex: Female

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 35 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 37 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : inflammation; mononuclear, mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 39 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 39 (Continued) Group: 2 - Low dose Sex: Female

Histopathology Observations [Correlation] (Continued):

nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5

Histopathology - The following Tissues were Not Examined:

None

Animal: 41 Group: 2 - Low dose Sex: Female

Species: Rat

Dose: 250 ppm

Removal Reason: Killed Terminal

Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

cavity, abdominal : nodule; dark, 1 cm : (comment) attached to liver and stomach [cavity, abdominal : fat necrosis (H)]
lungs : left lobe; spot; dark [lungs : haemorrhage(s); alveolar, mild (H)]
lymph node, cervical/mandibular : enlarged; red [lymph node, cervical/mandibular : sinusoidal blood; mild (H)]

Histopathology Observations [Correlation]:

cavity, abdominal : fat necrosis [cavity, abdominal : nodule; dark, 1 cm : (comment) attached to liver and stomach (G)]
liver : inflammation; mononuclear, focal, marked : (comment) including haemorrhage(s) and brown pigment accumulation
lungs : haemorrhage(s); alveolar, mild [lungs : left lobe; spot; dark (G)]
lymph node, cervical/mandibular : sinusoidal blood; mild [lymph node, cervical/mandibular : enlarged; red (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 43 Group: 2 - Low dose Sex: Female

Species: Rat

Dose: 250 ppm

Removal Reason: Killed Terminal

Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer; black [stomach : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

stomach : gross finding not confirmed [stomach : glandular stomach; ulcer; black (G)]

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

Animal: 43 (Continued) Group: 2 - Low dose Sex: Female

None

Animal: 45 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 47 Group: 2 - Low dose Sex: Female
Species: Rat
Dose: 250 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

No observations found

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3; nose, level 5; nose, level 6

Histopathology - The following Tissues were Not Examined:

None

Animal: 50 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 4 : olfactory epithelium; haemorrhage(s); minimal
nose, level 3 : olfactory epithelium; haemorrhage(s); minimal

Animal: 50 (Continued) Group: 3 - Mid dose Sex: Male

Histopathology Observations [Correlation] (Continued):

nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; haemorrhage(s); minimal
nose, level 6 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Animal: 52 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : left lobe; spot; red [lungs : gross finding not confirmed (H)]
lymph node, cervical/mandibular : discoloration; red [lymph node, cervical/mandibular : sinusoidal blood; mild (H)]

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : left lobe; spot; red (G)]
lymph node, cervical/mandibular : sinusoidal blood; mild [lymph node, cervical/mandibular : discoloration; red (G)]

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; haemorrhage(s); minimal
nose, level 3 : olfactory epithelium; haemorrhage(s); minimal
nose, level 3 : respiratory epithelium; inflammation; mixed, minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; haemorrhage(s); minimal
nose, level 6 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; haemorrhage(s); mild

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Animal: 54 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : caudal lobe; spot; dark [lungs : accumulation of alveolar macrophages; moderate (H)]

Animal: 54 (Continued) Group: 3 - Mid dose Sex: Male

Gross Pathology Observations [Correlation] (Continued):

lungs : left lobe; spots; dark [lungs : accumulation of alveolar macrophages; moderate (H)]

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed
lungs : bone spicule
lungs : accumulation of alveolar macrophages; moderate [lungs : caudal lobe; spot; dark (G) | lungs : left lobe; spots; dark (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 5 : inflammation; mononuclear, minimal
nose, level 6 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 56 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 58 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

seminal vesicles : small [seminal vesicles : decreased content (H)]

Histopathology Observations [Correlation]:

seminal vesicles : decreased content [seminal vesicles : small (G)]

(G) = Gross Pathology, (H) = Histo Pathology

Sanitized [redacted]

Animal: 58 (Continued) Group: 3 - Mid dose Sex: Male

Histopathology Observations [Correlation] (Continued):

nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 60 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; minimal
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 62 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Animal: 64 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 66 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; red [lungs : alveolitis; mild (H)]

Histopathology Observations [Correlation]:

lungs : alveolitis; mild [lungs : all lobes; spots; red (G)]
lungs : inflammation; mononuclear, mild
lungs : accumulation of alveolar macrophages; mild
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 68 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; red [lungs : gross finding not confirmed (H)]

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 68 (Continued) Group: 3 - Mid dose Sex: Male

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : all lobes; spots; red (G)]
lungs : bone spicule
lungs : peri-vascular; inflammation; granulocytic, minimal
nose, level 6 : olfactory epithelium; degeneration; minimal

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; nose, level 4; nose, level 3; nose, level 5

Histopathology - The following Tissues were Not Examined:

None

Animal: 70 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 72 Group: 3 - Mid dose Sex: Male
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3

Histopathology - The following Tissues were Not Examined:

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 72 (Continued) Group: 3 - Mid dose Sex: Male

None

Animal: 49 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 07/Dec/2017 Study Day (Week) of Death: 52 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcers; black [stomach : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

stomach : gross finding not confirmed [stomach : glandular stomach; ulcers; black (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 51 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 53 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

lungs : cranial lobe; spot; red [lungs : haemorrhage(s); alveolar, minimal (H)]

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 53 (Continued) Group: 3 - Mid dose Sex: Female

Gross Pathology Observations [Correlation] (Continued):

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

lungs : haemorrhage(s); alveolar, minimal [lungs : cranial lobe; spot; red (G)]
thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Animal: 55 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 06/Dec/2017 Study Day (Week) of Death: 51 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4; nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 57 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 10/Dec/2017 Study Day (Week) of Death: 55 (7)

Gross Pathology Observations [Correlation]:

stomach : deposition; white [stomach : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

stomach : gross finding not confirmed [stomach : deposition; white (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

[redacted]

Animal: 57 (Continued) Group: 3 - Mid dose Sex: Female

Histopathology Observations [Correlation] (Continued):

nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Animal: 59 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 10/Dec/2017 Study Day (Week) of Death: 55 (7)

Gross Pathology Observations [Correlation]:

lungs : left lobe; discoloration; red, partly [lungs : gross finding not confirmed (H)]
stomach : deposition; white

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : left lobe; discoloration; red, partly (G)]
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

nose, level 4

Histopathology - The following Tissues were Not Examined:

None

Animal: 61 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer; black [stomach : degeneration; epithelial, focal, mild (H)]

Histopathology Observations [Correlation]:

stomach : degeneration; epithelial, focal, mild [stomach : glandular stomach; ulcer; black (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 4 : olfactory epithelium; haemorrhage(s); minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 61 (Continued) Group: 3 - Mid dose Sex: Female

None

Animal: 63 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer; black [stomach : gross finding not confirmed (H)]
thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

stomach : gross finding not confirmed [stomach : glandular stomach; ulcer; black (G)]
thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

None

Histopathology - The following Tissues were Not Examined:

None

Animal: 65 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 67 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Animal: 67 (Continued) Group: 3 - Mid dose Sex: Female

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; red [lungs : haemorrhage(s); alveolar, mild (H)]
ovaries : cyst; unilateral
uterus : swollen [uterus : lumen; dilatation; mild (H)]

Histopathology Observations [Correlation]:

lungs : haemorrhage(s); alveolar, mild [lungs : all lobes; spots; red (G)]
lungs : bone spicule
lungs : peri-vascular; inflammation; granulocytic, minimal
ovaries : cyst(s)
uterus : lumen; dilatation; mild [uterus : swollen (G)]
nose, level 4 : inflammation; mononuclear, minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

thymus; nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 69 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

lungs : cranial lobe; spot; red [lungs : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : cranial lobe; spot; red (G)]
nose, level 4 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 71 Group: 3 - Mid dose Sex: Female
Species: Rat
Dose: 750 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

Animal: 71 (Continued) Group: 3 - Mid dose Sex: Female

Gross Pathology Observations [Correlation] (Continued):

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 74 Group: 4 - High dose Sex: Male
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; red [lungs : haemorrhage(s); alveolar, mild (H)]
lymph node, cervical/mandibular : discoloration; red [lymph node, cervical/mandibular : sinusoidal blood; mild (H)]

Histopathology Observations [Correlation]:

lungs : haemorrhage(s); alveolar, mild [lungs : all lobes; spots; red (G)]
lymph node, cervical/mandibular : sinusoidal blood; mild [lymph node, cervical/mandibular : discoloration; red (G)]

prostate gland : inflammation; mononuclear, minimal
nose, level 2 : inflammation; mononuclear, minimal
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 4 : olfactory epithelium; haemorrhage(s); mild
nose, level 3 : olfactory epithelium; degeneration; moderate
nose, level 3 : respiratory epithelium; haemorrhage(s); minimal
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; haemorrhage(s); minimal

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1

Histopathology - The following Tissues were Not Examined:

None

Animal: 76 Group: 4 - High dose Sex: Male
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Animal: 76 (Continued) Group: 4 - High dose Sex: Male

Gross Pathology Observations [Correlation]:

lungs : left lobe; spots; red [lungs : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : left lobe; spots; red (G)]
lungs : bone spicule
prostate gland : inflammation; mononuclear, mild
nose, level 2 : transitional epithelium; degeneration; minimal
nose, level 4 : olfactory epithelium; degeneration; marked
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 78 Group: 4 - High dose Sex: Male
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 4 : inflammation; mononuclear, mild
nose, level 3 : olfactory epithelium; degeneration; moderate
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 80 Group: 4 - High dose Sex: Male
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : left lobe; spots; red [lungs : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

Animal: 80 (Continued) Group: 4 - High dose Sex: Male

Histopathology Observations [Correlation] (Continued):

lungs : gross finding not confirmed [lungs : left lobe; spots; red (G)]
thyroid gland : inflammation; mononuclear, mild
nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 82 Group: 4 - High dose Sex: Male
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 84 Group: 4 - High dose Sex: Male
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : caudal lobe; spots; red [lungs : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : caudal lobe; spots; red (G)]
lungs : inflammation; mononuclear, mild
nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate

Animal: 84 (Continued) Group: 4 - High dose Sex: Male

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 86 Group: 4 - High dose Sex: Male

Species: Rat

Dose: 1500 ppm

Removal Reason: Killed Terminal

Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

prostate gland : inflammation; mononuclear, mild
thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 4 : inflammation; mononuclear, mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 88 Group: 4 - High dose Sex: Male

Species: Rat

Dose: 1500 ppm

Removal Reason: Killed Terminal

Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; red [lungs : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

lungs : gross finding not confirmed [lungs : all lobes; spots; red (G)]
lungs : bone spicule
prostate gland : inflammation; mononuclear, minimal
nose, level 4 : olfactory epithelium; degeneration; marked
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 6 : olfactory epithelium; degeneration; marked
nose, level 6 : respiratory epithelium; degeneration; minimal

Histopathology - The following Tissues were Within Normal Limits:

Animal:	88 (Continued)	Group:	4 - High dose	Sex:	Male

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal:	90	Group:	4 - High dose	Sex:	Male
Species:	Rat				
		Dose:	1500 ppm		
		Removal Reason:	Killed Terminal		
Necropsy Date:	20/Nov/2017	Study Day (Week) of Death:	35 (5)		

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer [stomach : gross finding not confirmed (H)]
thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

prostate gland : inflammation; mononuclear, minimal
stomach : gross finding not confirmed [stomach : glandular stomach; ulcer (G)]
thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal:	92	Group:	4 - High dose	Sex:	Male
Species:	Rat				
		Dose:	1500 ppm		
		Removal Reason:	Killed Terminal		
Necropsy Date:	20/Nov/2017	Study Day (Week) of Death:	35 (5)		

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

prostate gland : inflammation; mononuclear, mild
nose, level 4 : olfactory epithelium; degeneration; marked
nose, level 4 : respiratory epithelium; degeneration; minimal
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 5 : inflammation; mononuclear, minimal
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 92 (Continued) Group: 4 - High dose Sex: Male

Histopathology - The following Tissues were Not Examined:

None

Animal: 94 Group: 4 - High dose Sex: Male

Species: Rat

Dose: 1500 ppm

Removal Reason: Killed Terminal

Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

lungs : all lobes; spots; white

Histopathology Observations [Correlation]:

lungs : haemorrhage(s); alveolar, minimal
lungs : alveolitis; mild
lungs : accumulation of alveolar macrophages; minimal
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 96 Group: 4 - High dose Sex: Male

Species: Rat

Dose: 1500 ppm

Removal Reason: Killed Terminal

Necropsy Date: 20/Nov/2017 Study Day (Week) of Death: 35 (5)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; marked
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

coagulating glands; epididymides; prostate gland; seminal vesicles; testes; thyroid gland; nose, level 1; nose, level 2; nose, level 3

Histopathology - The following Tissues were Not Examined:

None

Animal: 73 Group: 4 - High dose Sex: Female

Species: Rat

Dose: 1500 ppm

[redacted]

Animal: 73 (Continued) Group: 4 - High dose Sex: Female
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

uterus : lumen; dilatation; mild
nose, level 4 : olfactory epithelium; degeneration; marked
nose, level 3 : olfactory epithelium; degeneration; moderate
nose, level 5 : olfactory epithelium; degeneration; marked
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 75 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 3 : olfactory epithelium; degeneration; moderate
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 77 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 07/Dec/2017 Study Day (Week) of Death: 52 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; moderate

Animal: 77 (Continued) Group: 4 - High dose Sex: Female

Histopathology Observations [Correlation] (Continued):

nose, level 3 : olfactory epithelium; degeneration; moderate
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 79 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 81 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Animal: 81 (Continued) Group: 4 - High dose Sex: Female

Histopathology - The following Tissues were Not Examined:

None

Animal: 83 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcer; black [stomach : degeneration; epithelial, focal, mild (H)]
thymus : spots; red [thymus : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

stomach : degeneration; epithelial, focal, mild [stomach : glandular stomach; ulcer; black (G)]
thymus : gross finding not confirmed [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 85 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

thymus : spots; red [thymus : microhaemorrhage(s) (H)]

Histopathology Observations [Correlation]:

thymus : microhaemorrhage(s) [thymus : spots; red (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 87 Group: 4 - High dose Sex: Female
Species: Rat

 [redacted]

Animal: 87 (Continued) Group: 4 - High dose Sex: Female
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 08/Dec/2017 Study Day (Week) of Death: 53 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 1 : inflammation; granulocytic, minimal
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; mild

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 89 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 06/Dec/2017 Study Day (Week) of Death: 51 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; minimal
nose, level 5 : olfactory epithelium; degeneration; mild
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 91 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 10/Dec/2017 Study Day (Week) of Death: 55 (7)

Gross Pathology Observations [Correlation]:

stomach : deposition; white [stomach : gross finding not confirmed (H)]

Histopathology Observations [Correlation]:

Animal: 91 (Continued) Group: 4 - High dose Sex: Female

Histopathology Observations [Correlation] (Continued):

stomach : gross finding not confirmed [stomach : deposition; white (G)]
nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 93 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 10/Dec/2017 Study Day (Week) of Death: 55 (7)

Gross Pathology Observations [Correlation]:

all organs/tissues : no visible lesions

Histopathology Observations [Correlation]:

nose, level 4 : olfactory epithelium; degeneration; moderate
nose, level 4 : inflammation; mononuclear, minimal
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; moderate

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

Animal: 95 Group: 4 - High dose Sex: Female
Species: Rat
Dose: 1500 ppm
Removal Reason: Killed Terminal
Necropsy Date: 09/Dec/2017 Study Day (Week) of Death: 54 (7)

Gross Pathology Observations [Correlation]:

stomach : glandular stomach; ulcers; black [stomach : degeneration; epithelial, focal, mild (H)]

Histopathology Observations [Correlation]:

stomach : degeneration; epithelial, focal, mild [stomach : glandular stomach; ulcers; black (G)]
nose, level 4 : olfactory epithelium; degeneration; mild
nose, level 3 : olfactory epithelium; degeneration; mild
nose, level 5 : olfactory epithelium; degeneration; moderate
nose, level 6 : olfactory epithelium; degeneration; marked

(G) = Gross Pathology, (H) = Histo Pathology

Animal: 95 (Continued) Group: 4 - High dose Sex: Female

Histopathology - The following Tissues were Within Normal Limits:

ovaries; thyroid gland; uterus; vagina; nose, level 1; nose, level 2

Histopathology - The following Tissues were Not Examined:

None

(G) = Gross Pathology, (H) = Histo Pathology

31/Jan/2018 14:40:09

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 8: Coupling report

Sex: Female (Litter: A)

0 ppm	Pairing Male (1)	Day 0 of Pairing	Day 0 of Pregnancy	Pre-coital time (days)	Day of Delivery	Gestation Days	Day of Necropsy
1 P	2	30/10/2017	01/11/2017	2	23/11/2017	22	07/12/2017
3 P	4	30/10/2017	02/11/2017	3	25/11/2017	23	09/12/2017
5 P	6	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
7 P	8	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
9 P	10	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
11 P	12	30/10/2017	02/11/2017	3	25/11/2017	23	09/12/2017
13 P	14	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
15 P	16	30/10/2017	03/11/2017	4	26/11/2017	23	10/12/2017
17 P	18	30/10/2017	01/11/2017	2	23/11/2017	22	07/12/2017
19 P	20	30/10/2017	03/11/2017	4	26/11/2017	23	10/12/2017
21 P	22	30/10/2017	01/11/2017	2	23/11/2017	22	07/12/2017
23 P	24	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 8: Coupling report

Sex: Female (Litter: A)

250 ppm	Pairing Male (1)	Day 0 of Pairing	Day 0 of Pregnancy	Pre-coital time (days)	Day of Delivery	Gestation Days	Day of Necropsy
25 P	26	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
27 P	28	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
29 P	30	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
31 P	32	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
33 P	34	30/10/2017	01/11/2017	2	23/11/2017	22	07/12/2017
35 P	36	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
37 P	38	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
39 P	40	30/10/2017	01/11/2017	2	24/11/2017	23	08/12/2017
41 P	42	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
43 P	44	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
45 P	46	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
47 P	48	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017

[redacted]

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 8: Coupling report

Sex: Female (Litter: A)

750 ppm	Pairing Male (1)	Day 0 of Pairing	Day 0 of Pregnancy	Pre-coital time (days)	Day of Delivery	Gestation Days	Day of Necropsy
49 P	50	30/10/2017	31/10/2017	1	23/11/2017	23	07/12/2017
51 P	52	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
53 P	54	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
55 P	56	30/10/2017	31/10/2017	1	22/11/2017	22	06/12/2017
57 P	58	30/10/2017	03/11/2017	4	26/11/2017	23	10/12/2017
59 P	60	30/10/2017	03/11/2017	4	27/11/2017	24	10/12/2017
61 P	62	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
63 P	64	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
65 P	66	30/10/2017	02/11/2017	3	25/11/2017	23	09/12/2017
67 NM	68	30/10/2017	.	.	.	.	08/12/2017
69 P	70	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
71 P	72	30/10/2017	02/11/2017	3	25/11/2017	23	09/12/2017

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Sanitized

31/Jan/2018 14:40:09

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 8: Coupling report

Sex: Female (Litter: A)

1500 ppm	Pairing Male (1)	Day 0 of Pairing	Day 0 of Pregnancy	Pre-coital time (days)	Day of Delivery	Gestation Days	Day of Necropsy
73 NM	74	30/10/2017	.	.	.	.	08/12/2017
75 P	76	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
77 P	78	30/10/2017	01/11/2017	2	23/11/2017	22	07/12/2017
79 P	80	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
81 P	82	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
83 P	84	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017
85 P	86	30/10/2017	02/11/2017	3	24/11/2017	22	08/12/2017
87 NP	88	30/10/2017	06/11/2017	7	.	.	08/12/2017
89 P	90	30/10/2017	31/10/2017	1	22/11/2017	22	06/12/2017
91 P	92	30/10/2017	03/11/2017	4	26/11/2017	23	10/12/2017
93 P	94	30/10/2017	03/11/2017	4	26/11/2017	23	10/12/2017
95 P	96	30/10/2017	03/11/2017	4	25/11/2017	22	09/12/2017

[redacted]

Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

15/May/2018 14:09:08

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 9: Delivery report

Sex: Female Day(s): Relative to Littering (Litter: A)

0 ppm	Liveborn Pups	Stillborn Pups	Total number of Pups	Live Males on Day 0	Live Females on Day 0	Live Males on Day 4	Live Females on Day 4	Live Males D4 Post-cull	Live Females D4 Post-cull	Live Males on Day 7	Live Females on Day 7	Live Males on Day 13	Live Females on Day 13	Implant. Sites
1 P	13	0	13	6	7	4	7	4	4	4	4	4	4	13
3 P	10	0	10	4	6	4	6	4	4	4	4	4	4	13
5 P	12	0	12	5	7	5	7	4	4	4	4	4	4	12
7 P	14	0	14	8	6	8	6	4	4	4	4	4	4	14
9 P	10	0	10	5	5	5	5	4	4	4	4	4	4	10
11 P	11	0	11	5	6	5	6	4	4	4	4	4	4	13
13 P	12	0	12	5	7	5	7	4	4	4	4	4	4	13
15 P	10	0	10	4	6	3	6	3	5	3	5	3	5	12
17 P	12	0	12	4	8	4	8	4	4	4	4	4	4	12
19 P	11	0	11	7	4	7	4	4	4	4	4	4	4	11
21 P	11	0	11	4	7	4	7	4	4	4	4	4	4	12
23 P	13	0	13	5	8	5	8	4	4	4	4	4	4	11
Mean	11.6	0.0	11.6	5.2	6.4	4.9	6.4	3.9	4.1	3.9	4.1	3.9	4.1	12.2
SD	1.3	0.0	1.3	1.3	1.2	1.4	1.2	0.3	0.3	0.3	0.3	0.3	0.3	1.1
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 9: Delivery report

Sex: Female Day(s): Relative to Littering (Litter: A)

250 ppm	Liveborn Pups	Stillborn Pups	Total number of Pups	Live Males on Day 0	Live Females on Day 0	Live Males on Day 4	Live Females on Day 4	Live Males D4 Post-cull	Live Females D4 Post-cull	Live Males on Day 7	Live Females on Day 7	Live Males on Day 13	Live Females on Day 13	Implant. Sites
25 P	16	0	16	11	5	11	5	4	4	4	4	4	4	17
27 P	12	0	12	6	6	6	6	4	4	4	4	4	4	12
29 P	12	0	12	4	8	4	8	4	4	4	4	4	4	12
31 P	13	0	13	10	3	10	3	5	3	5	3	5	3	13
33 P	11	0	11	4	7	4	7	4	4	4	4	4	4	12
35 P	13	0	13	6	7	6	7	4	4	4	4	4	4	15
37 P	10	0	10	5	5	5	5	4	4	4	4	4	4	12
39 P	11	0	11	5	6	5	6	4	4	4	4	4	4	11
41 P	11	0	11	7	4	7	4	4	4	4	4	4	4	12
43 P	11	0	11	7	4	7	4	4	4	4	4	4	4	14
45 P	13	0	13	10	3	10	3	5	3	5	3	5	3	15
47 P	12	0	12	6	6	6	6	4	4	4	4	4	4	12
Mean	12.1	0.0	12.1	6.8	5.3	6.8	5.3	4.2	3.8	4.2	3.8	4.2	3.8	13.1
SD	1.6	0.0	1.6	2.4	1.6	2.4	1.6	0.4	0.4	0.4	0.4	0.4	0.4	1.8
N	12	12	12	12	12	12	12	12	12	12	12	12	12	12

Litter: A = First litter

NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Sanitized

15/May/2018 14:09:08

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 9: Delivery report

Sex: Female Day(s): Relative to Littering (Litter: A)

750 ppm	Liveborn Pups	Stillborn Pups	Total number of Pups	Live Males on Day 0	Live Females on Day 0	Live Males on Day 4	Live Females on Day 4	Live Males D4 Post-cull	Live Females D4 Post-cull	Live Males on Day 7	Live Females on Day 7	Live Males on Day 13	Live Females on Day 13	Implant. Sites
49 P	8	0	8	1	7	1	7	1	7	1	7	1	7	9
51 P	12	0	12	5	7	5	7	4	4	4	4	4	4	14
53 P	7	0	7	4	3	4	3	4	3	4	3	4	3	10
55 P	12	0	12	9	3	9	3	5	3	5	3	5	3	12
57 P	11	0	11	3	8	3	8	3	5	3	5	3	5	12
59 P	1	0	1	0	0	.	.	.	.	.	.	.	.	2
61 P	11	0	11	7	4	7	4	4	4	4	4	4	4	12
63 P	11	0	11	5	6	5	6	4	4	4	4	4	4	12
65 P	9	0	9	5	4	5	4	4	4	4	4	4	4	10
67 NM	.	.	.	.	.	.	.	.	.	.	.	.	.	0 E
69 P	12	0	12	5	7	5	7	4	4	4	4	4	4	13
71 P	6	0	6	3	3	3	3	3	3	3	3	3	3	8
Mean	9.1	0.0	9.1	4.3	4.7	4.7	5.2	3.6	4.1	3.6	4.1	3.6	4.1	10.4
SD	3.4	0.0	3.4	2.5	2.5	2.2	2.0	1.1	1.2	1.1	1.2	1.1	1.2	3.3
N	11	11	11	11	11	10	10	10	10	10	10	10	10	11

E = Exclude; NM females excluded from statistics
Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Sanitized

15/May/2018 14:09:08

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 9: Delivery report

Sex: Female Day(s): Relative to Littering (Litter: A)

1500 ppm	Liveborn Pups	Stillborn Pups	Total number of Pups	Live Males on Day 0	Live Females on Day 0	Live Males on Day 4	Live Females on Day 4	Live Males D4 Post-cull	Live Females D4 Post-cull	Live Males on Day 7	Live Females on Day 7	Live Males on Day 13	Live Females on Day 13	Implant. Sites
73 NM	.	.	.	.	.	.	.	.	.	.	.	.	.	0 E
75 P	9	0	9	7	2	7	2	6	2	6	2	6	2	10
77 P	8	0	8	5	3	5	3	5	3	5	3	5	3	8
79 P	11	0	11	2	9	2	9	2	6	2	6	2	6	12
81 P	11	0	11	6	5	6	5	4	4	4	4	4	4	11
83 P	9	0	9	5	4	5	4	4	4	4	4	4	4	9
85 P	9	0	9	2	7	2	7	2	6	2	6	2	6	9
87 NP	.	.	.	.	.	.	.	.	.	.	.	.	.	0 E
89 P	13	0	13	8	5	8	5	4	4	4	4	4	4	13
91 P	10	0	10	7	3	7	3	5	3	5	3	5	3	11
93 P	4	0	4	2	2	2	2	2	2	2	2	2	2	4
95 P	12	0	12	4	8	4	8	4	4	4	4	4	4	13
Mean	9.6	0.0	9.6	4.8	4.8	4.8	4.8	3.8	3.8	3.8	3.8	3.8	3.8	10.0
SD	2.5	0.0	2.5	2.3	2.5	2.3	2.5	1.4	1.4	1.4	1.4	1.4	1.4	2.7
N	10	10	10	10	10	10	10	10	10	10	10	10	10	10

E = Exclude; NM and NP females excluded from statistics
Litter: A = First litter
NM=Not Mated,NP=Not Pregnant,IN=Implant,No Pups,P#=Misjudged to be Not Mated,P=Pregnant

Sanitized

15/May/2018 14:08:28

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 10: Pup sex and status

Group: Control   Day(s): Relative to Littering (Litter: A)

Dam	Measurement	Count	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Pup Sex and Status	13	MM4	MK13	MA	MM4	FK13	FA	FA	FA	MA	MA	FC4	FC4	FC4	.	.	.
3	Pup Sex and Status	10	MK13	MA	MA	MA	FK13	FA	FA	FA	FC4	FC4	.	.	.	.	.	.
5	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	FC4	.	.	.	.
7	Pup Sex and Status	14	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	MC4	FC4	FC4	.	.
9	Pup Sex and Status	10	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	.	.	.	.	.	.
11	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	.	.	.	.	.
13	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	FC4	.	.	.	.
15	Pup Sex and Status	10	MK13	MA	MM4	MA	FK13	FA	FA	FA	FA	FC4	.	.	.	.	.	.
17	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	FC4	FC4	FC4	FC4	.	.	.	.
19	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	.	.	.	.	.
21	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	FC4	FC4	FC4	.	.	.	.	.
23	Pup Sex and Status	13	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	FC4	FC4	.	.	.

Litter: A = First litter
Sex codes: M-Male F-Female U-Unsexed
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Sanitized

15/May/2018 14:08:28

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 10: Pup sex and status

Group: Low dose   Day(s): Relative to Littering (Litter: A)

Dam	Measurement	Count	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Pup Sex and Status	16	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	MC4	MC4	MC4	MC4	FC4
27	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	FC4	FC4	.	.	.	.
29	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	FC4	FC4	FC4	FC4	.	.	.	.
31	Pup Sex and Status	13	MK13	MA	MA	MA	MA	FK13	FA	FA	MC4	MC4	MC4	MC4	MC4	.	.	.
33	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	FC4	FC4	FC4	.	.	.	.	.
35	Pup Sex and Status	13	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	FC4	FC4	FC4	.	.	.
37	Pup Sex and Status	10	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	.	.	.	.	.	.
39	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	.	.	.	.	.
41	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	.	.	.	.	.
43	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	.	.	.	.	.
45	Pup Sex and Status	13	MK13	MA	MA	MA	MA	FK13	FA	FA	MC4	MC4	MC4	MC4	MC4	.	.	.
47	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	FC4	FC4	.	.	.	.

Litter: A = First litter
Sex codes: M-Male F-Female U-Unsexed
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Sanitized

15/May/2018 14:08:28

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 10: Pup sex and status

Group: Mid dose   Day(s): Relative to Littering (Litter: A)

Dam	Measurement	Count	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Pup Sex and Status	8	MK13	FK13	FA	FA	FA	FA	FA	FA	.	.	.	.	.	.	.	.
51	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	FC4	.	.	.	.
53	Pup Sex and Status	7	MK13	MA	MA	MA	FK13	FA	FA	.	.	.	.	.	.	.	.	.
55	Pup Sex and Status	12	MK13	MA	MA	MA	MA	FK13	FA	FA	MC4	MC4	MC4	MC4	.	.	.	.
57	Pup Sex and Status	11	MK13	MA	MA	FK13	FA	FA	FA	FA	FC4	FC4	FC4	.	.	.	.	.
59[1]	Pup Sex and Status	1	UM0	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
61	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	.	.	.	.	.
63	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	.	.	.	.	.
65	Pup Sex and Status	9	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	.	.	.	.	.	.	.
69	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	FC4	FC4	FC4	.	.	.	.
71	Pup Sex and Status	6	MK13	MA	MA	FK13	FA	FA	.	.	.	.	.	.	.	.	.	.

Litter: A = First litter

[1] Female 59 was observed littering, but the litter was lost (cannibalized) before the number of pups was registered.
One missing pup with unknown sex (UM0) was entered, representing the entire litter.

Sex codes: M-Male F-Female U-Unsexed

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Sanitized

15/May/2018 14:08:28

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 10: Pup sex and status

Group: High dose   Day(s): Relative to Littering (Litter: A)

Dam	Measurement	Count	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Pup Sex and Status	9	MK13	MA	MA	MA	MA	MA	FK13	FA	MC4	.	.	.	.	.	.	.
77	Pup Sex and Status	8	MK13	MA	MA	MA	MA	FK13	FA	FA	.	.	.	.	.	.	.	.
79	Pup Sex and Status	11	MK13	MA	FK13	FA	FA	FA	FA	FA	FC4	FC4	FC4	.	.	.	.	.
81	Pup Sex and Status	11	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	FC4	.	.	.	.	.
83	Pup Sex and Status	9	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	.	.	.	.	.	.	.
85	Pup Sex and Status	9	MK13	MA	FK13	FA	FA	FA	FA	FA	FC4	.	.	.	.	.	.	.
89	Pup Sex and Status	13	MK13	MA	MA	MA	FK13	FA	FA	FA	MC4	MC4	MC4	MC4	FC4	.	.	.
91	Pup Sex and Status	10	MK13	MA	MA	MA	MA	FK13	FA	FA	MC4	MC4	.	.	.	.	.	.
93	Pup Sex and Status	4	MK13	MA	FK13	FA	.	.	.	.	.	.	.	.	.	.	.	.
95	Pup Sex and Status	12	MK13	MA	MA	MA	FK13	FA	FA	FA	FC4	FC4	FC4	FC4	.	.	.	.

Litter: A = First litter
Sex codes: M-Male F-Female U-Unsexed
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 11: Pup clinical observations

0 ppm	Day(s) Relative to Littering (A)	Pup ID	Observation Type: All Types
5	13	1 - M	SKIN Sparsely haired area(s)
		2 - M	SKIN Sparsely haired area(s)
		3 - M	SKIN Sparsely haired area(s)
		4 - M	SKIN Sparsely haired area(s)
		5 - F	SKIN Sparsely haired area(s)
		6 - F	SKIN Sparsely haired area(s)
		7 - F	SKIN Sparsely haired area(s)
		8 - F	SKIN Sparsely haired area(s)
23	0	13 - F	SKIN Haematoma

250 ppm	Day(s) Relative to Littering (A)	Pup ID	Observation Type: All Types
27	0	3 - M	SKIN Wound(s)
39	0	8 - F	SKIN Wound(s)
	4	8 - F	SKIN Wound(s)
47	13	1 - M	SKIN Sparsely haired area(s)
		2 - M	SKIN Sparsely haired area(s)
		3 - M	SKIN Sparsely haired area(s)
		4 - M	SKIN Sparsely haired area(s)
		5 - F	SKIN Sparsely haired area(s)
		6 - F	SKIN Sparsely haired area(s)
		7 - F	SKIN Sparsely haired area(s)
		8 - F	SKIN Sparsely haired area(s)

Sex codes: M-Male F-Female U-Unsexed

[redacted]

Sanitized

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Control Day: 0 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Pup Bodyweight	5.7	6.2	6.0	5.7	5.4	5.6	5.7	5.9	6.0	6.2	5.9	5.8	5.1	.	.	.
3	Pup Bodyweight	7.2	7.1	6.6	6.4	6.5	6.2	6.0	6.7	6.6	6.5	.	.	.	.	.	.
5	Pup Bodyweight	6.1	5.8	6.1	5.9	5.5	5.7	5.5	5.7	R4.9	5.0	5.3	5.7	.	.	.	.
7	Pup Bodyweight	6.2	5.9	5.8	6.1	5.8	5.9	5.7	5.6	6.6	5.8	5.6	6.0	6.7	5.5	.	.
9	Pup Bodyweight	6.6	6.7	6.6	6.9	6.2	5.6	5.8	5.8	6.2	6.0	.	.	.	.	.	.
11	Pup Bodyweight	6.9	7.0	7.9	6.9	6.5	7.2	7.2	6.6	7.5	7.4	6.9	.	.	.	.	.
13	Pup Bodyweight	6.6	5.8	6.0	6.1	6.5	5.8	6.1	5.6	6.1	5.6	R4.8	6.0	.	.	.	.
15	Pup Bodyweight	6.8	6.4	6.3	6.6	6.0	6.3	6.6	6.2	6.7	6.7	.	.	.	.	.	.
17	Pup Bodyweight	6.4	5.7	6.5	6.3	6.0	6.2	5.7	6.1	6.1	5.4	6.3	6.0	.	.	.	.
19	Pup Bodyweight	6.6	7.0	6.9	7.3	6.5	5.6	6.3	5.5	6.4	7.0	7.0	.	.	.	.	.
21	Pup Bodyweight	6.3	5.5	5.7	5.6	5.7	5.5	5.5	5.1	5.4	5.1	5.0	.	.	.	.	.
23	Pup Bodyweight	5.9	6.2	6.0	6.2	5.5	5.6	5.4	5.8	5.6	5.4	5.8	6.2	5.1	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

Sanitized

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Low dose   Day: 0 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Pup Bodyweight	5.7	R4.8	5.5	5.3	5.1	5.8	5.1	R4.8	5.5	5.7	5.7	5.9	5.9	5.4	6.0	5.5
27	Pup Bodyweight	6.6	6.4	6.8	6.7	6.3	6.9	6.9	6.8	6.3	6.3	6.3	6.4	.	.	.	.
29	Pup Bodyweight	6.2	6.2	5.7	6.6	R4.7	5.3	5.8	6.2	5.4	5.2	6.0	6.5	.	.	.	.
31	Pup Bodyweight	5.3	6.2	6.3	5.9	6.0	5.4	6.0	5.5	6.7	6.3	6.4	6.4	6.2	.	.	.
33	Pup Bodyweight	6.5	6.4	6.8	6.6	6.3	5.9	6.3	6.6	6.6	5.7	6.1	.	.	.	.	.
35	Pup Bodyweight	5.7	6.3	5.6	6.0	5.7	6.0	5.6	5.2	5.8	5.8	5.4	5.9	5.4	.	.	.
37	Pup Bodyweight	6.0	6.7	6.6	6.3	6.4	6.0	5.7	6.0	6.6	6.2	.	.	.	.	.	.
39	Pup Bodyweight	7.0	6.5	6.9	6.4	6.4	5.2	5.4	6.9	6.0	6.3	5.3	.	.	.	.	.
41	Pup Bodyweight	7.0	7.2	7.6	7.1	5.9	6.2	5.5	6.5	6.9	6.5	6.9	.	.	.	.	.
43	Pup Bodyweight	5.8	6.1	6.3	6.4	6.2	6.3	6.4	5.8	6.4	5.5	6.0	.	.	.	.	.
45	Pup Bodyweight	5.9	6.0	5.9	5.9	5.8	5.9	5.6	5.6	5.8	6.3	5.7	5.8	5.8	.	.	.
47	Pup Bodyweight	5.9	5.3	5.7	5.3	5.1	5.5	5.2	4.9	6.0	5.7	5.3	5.0	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Mid dose Day: 0 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Pup Bodyweight	7.5	6.8	7.2	6.6	7.3	7.2	7.0	6.8	.	.	.	.	.	.	.	.
51	Pup Bodyweight	R5.1	5.5	5.9	6.1	5.8	4.9	5.3	5.1	6.1	5.0	5.0	5.7	.	.	.	.
53	Pup Bodyweight	6.4	6.6	6.1	6.5	6.5	6.4	6.5	.	.	.	.	.	.	.	.	.
55	Pup Bodyweight	5.8	6.3	6.1	5.6	5.9	5.6	6.2	5.7	5.4	6.2	5.9	5.6	.	.	.	.
57	Pup Bodyweight	6.9	7.2	7.0	6.6	6.3	7.3	6.6	6.9	6.5	5.9	6.7	.	.	.	.	.
61	Pup Bodyweight	6.6	6.2	5.7	6.5	6.2	5.7	5.8	6.0	5.5	6.4	6.2	.	.	.	.	.
63	Pup Bodyweight	6.2	5.9	5.4	6.4	5.9	6.0	5.9	5.5	6.5	6.0	6.3	.	.	.	.	.
65	Pup Bodyweight	7.3	7.1	7.0	7.3	6.4	6.5	6.4	6.6	6.6	.	.	.	.	.	.	.
69	Pup Bodyweight	6.6	R5.1	6.6	6.1	6.5	6.2	5.6	5.9	6.2	6.4	5.5	5.6	.	.	.	.
71	Pup Bodyweight	7.6	7.9	8.3	7.4	8.0	7.5	.	.	.	.	.	.	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: High dose   Day: 0 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Pup Bodyweight	7.4	7.1	7.1	7.2	7.2	7.0	7.2	6.9	7.6	.	.	.	.	.	.	.
77	Pup Bodyweight	5.7	5.8	5.4	5.7	5.9	R4.7	5.1	5.1	.	.	.	.	.	.	.	.
79	Pup Bodyweight	5.7	5.8	5.4	6.0	5.2	5.2	5.3	5.8	5.4	5.3	5.0	.	.	.	.	.
81	Pup Bodyweight	5.5	5.8	5.7	6.2	5.3	5.6	5.9	5.5	5.7	6.2	5.8	.	.	.	.	.
83	Pup Bodyweight	6.3	5.9	6.4	5.9	5.8	5.3	5.2	6.0	6.1	.	.	.	.	.	.	.
85	Pup Bodyweight	5.8	6.0	5.4	5.6	5.2	5.4	5.2	5.5	5.6	.	.	.	.	.	.	.
89	Pup Bodyweight	R5.1	5.7	R4.9	5.4	5.6	5.2	5.1	5.1	5.7	5.8	5.4	5.5	5.4	.	.	.
91	Pup Bodyweight	6.6	6.3	6.5	6.7	5.9	6.1	6.5	6.1	6.2	6.4	.	.	.	.	.	.
93	Pup Bodyweight	5.8	7.2	6.8	6.8	.	.	.	.	.	.	.	.	.	.	.	.
95	Pup Bodyweight	5.7	R4.9	5.3	R5.1	5.5	5.5	5.6	5.7	5.0	5.8	5.2	5.7	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Control Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Pup Bodyweight	M	12.1	11.2	M	10.8	10.7	10.8	10.6	11.2	11.2	11.3	11.1	9.3	.	.	.
3	Pup Bodyweight	13.0	13.8	12.6	12.5	12.5	12.4	11.7	12.9	12.9	12.5	.	.	.	.	.	.
5	Pup Bodyweight	11.1	10.9	11.5	10.9	10.1	10.0	10.1	11.0	9.0	9.6	9.5	9.8	.	.	.	.
7	Pup Bodyweight	10.0	10.2	9.2	9.7	9.6	9.4	9.0	9.0	9.7	9.4	R8.5	9.7	10.4	8.9	.	.
9	Pup Bodyweight	12.8	12.4	12.4	13.1	11.7	10.5	12.0	11.5	12.0	11.4	.	.	.	.	.	.
11	Pup Bodyweight	12.5	13.0	13.4	12.9	12.4	13.1	12.8	12.4	13.7	13.3	13.3	.	.	.	.	.
13	Pup Bodyweight	11.5	10.8	11.2	11.3	11.2	10.9	10.9	10.9	11.1	10.6	9.2	10.3	.	.	.	.
15	Pup Bodyweight	12.4	12.1	M	12.2	11.8	12.1	11.9	11.7	12.2	12.1	.	.	.	.	.	.
17	Pup Bodyweight	11.1	9.9	11.1	11.0	10.6	10.6	9.9	10.8	10.8	9.5	10.7	10.4	.	.	.	.
19	Pup Bodyweight	12.2	12.7	12.2	12.5	12.1	10.8	12.0	10.1	11.7	12.6	12.8	.	.	.	.	.
21	Pup Bodyweight	11.7	10.5	10.6	10.6	10.4	10.1	10.7	9.5	9.8	9.0	9.5	.	.	.	.	.
23	Pup Bodyweight	9.6	9.9	9.5	9.5	9.2	9.1	8.7	9.8	9.3	9.1	9.4	9.5	8.4	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

Sanitized

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Low dose Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Pup Bodyweight	9.6	R8.3	9.0	9.4	R7.8	10.5	8.7	R7.9	9.4	9.6	10.3	9.8	9.6	9.5	R8.7	9.9
27	Pup Bodyweight	11.6	10.6	11.7	11.0	10.8	11.0	11.3	10.6	10.9	11.3	11.2	11.0	.	.	.	.
29	Pup Bodyweight	10.9	10.7	10.3	12.0	8.9	10.2	10.6	11.1	9.8	9.6	10.5	11.5	.	.	.	.
31	Pup Bodyweight	9.6	9.8	10.5	10.3	10.2	9.4	10.5	9.7	10.5	10.1	10.7	10.3	10.3	.	.	.
33	Pup Bodyweight	12.0	11.5	11.9	11.4	11.2	10.8	11.4	11.6	11.7	10.5	11.0	.	.	.	.	.
35	Pup Bodyweight	10.5	11.2	10.7	9.3	10.2	9.7	10.2	9.6	10.4	10.4	10.3	10.5	10.6	.	.	.
37	Pup Bodyweight	10.7	11.6	11.0	11.2	11.6	10.8	10.7	10.9	10.9	11.2	.	.	.	.	.	.
39	Pup Bodyweight	12.2	12.0	12.5	11.7	11.8	10.1	10.1	11.9	11.1	11.5	10.0	.	.	.	.	.
41	Pup Bodyweight	11.1	11.8	12.0	11.7	10.2	10.3	9.3	10.8	11.0	11.0	11.4	.	.	.	.	.
43	Pup Bodyweight	11.6	11.3	11.8	12.2	11.4	12.2	12.1	11.3	12.1	10.4	11.2	.	.	.	.	.
45	Pup Bodyweight	11.2	10.9	10.9	10.8	10.6	10.6	10.4	10.6	10.4	11.8	10.7	10.1	10.5	.	.	.
47	Pup Bodyweight	10.7	9.0	9.2	9.5	10.3	9.3	11.3	9.9	11.2	10.3	9.3	9.0	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

[redacted]

Sanitized

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Mid dose Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Pup Bodyweight	12.7	11.7	12.5	11.7	12.4	12.6	12.3	12.0	.	.	.	.	.	.	.	.
51	Pup Bodyweight	10.3	10.9	10.6	10.8	10.4	9.7	10.6	10.5	11.6	10.0	9.9	10.6	.	.	.	.
53	Pup Bodyweight	13.0	13.1	12.3	12.5	12.8	12.4	12.9	.	.	.	.	.	.	.	.	.
55	Pup Bodyweight	9.1	11.0	10.6	10.2	9.9	9.4	11.1	9.5	9.3	9.8	10.0	9.4	.	.	.	.
57	Pup Bodyweight	12.8	13.8	13.6	12.7	12.8	13.6	12.9	13.0	11.9	11.8	12.1	.	.	.	.	.
61	Pup Bodyweight	11.8	11.3	10.0	11.3	10.7	10.5	10.2	10.4	9.3	11.0	11.2	.	.	.	.	.
63	Pup Bodyweight	11.3	10.4	10.0	11.8	11.2	11.5	10.8	10.2	11.9	10.5	10.9	.	.	.	.	.
65	Pup Bodyweight	12.8	12.1	12.8	12.9	12.0	11.7	11.9	12.0	11.9	.	.	.	.	.	.	.
69	Pup Bodyweight	12.0	R8.6	11.9	9.9	11.7	11.3	9.9	11.5	10.7	11.6	10.3	10.8	.	.	.	.
71	Pup Bodyweight	15.2	15.0	14.9	14.4	15.0	14.6	.	.	.	.	.	.	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: High dose   Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Pup Bodyweight	13.3	13.5	12.8	13.4	12.5	12.8	13.1	12.5	13.9	.	.	.	.	.	.	.
77	Pup Bodyweight	9.4	10.0	9.6	9.3	10.0	8.6	9.0	9.4	.	.	.	.	.	.	.	.
79	Pup Bodyweight	10.7	10.6	10.0	11.1	9.8	9.9	10.2	10.8	10.5	10.0	9.7	.	.	.	.	.
81	Pup Bodyweight	10.1	10.5	10.4	11.0	9.7	9.8	10.5	10.6	10.6	10.9	10.4	.	.	.	.	.
83	Pup Bodyweight	10.6	9.2	10.4	10.1	10.2	9.2	9.0	9.8	10.5	.	.	.	.	.	.	.
85	Pup Bodyweight	10.6	10.8	10.2	10.4	9.9	10.2	9.8	9.9	10.1	.	.	.	.	.	.	.
89	Pup Bodyweight	R8.3	9.3	R7.6	9.1	9.3	9.0	9.1	8.8	9.6	9.2	R8.7	9.1	9.0	.	.	.
91	Pup Bodyweight	11.9	12.4	12.4	12.1	11.2	11.7	12.3	11.4	12.0	12.3	.	.	.	.	.	.
93	Pup Bodyweight	12.1	14.3	13.3	13.8	.	.	.	.	.	.	.	.	.	.	.	.
95	Pup Bodyweight	9.9	8.8	9.0	9.0	9.8	9.6	9.7	9.8	9.2	10.2	9.3	9.5	.	.	.	.

[redacted]

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Control Day: 7 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Pup Bodyweight	M	18.5	17.5	M	17.1	16.7	16.9	16.8	18.2	18.0	C	C	C	.	.	.
3	Pup Bodyweight	18.3	19.4	18.0	17.9	17.6	18.0	16.8	18.5	C	C	.	.	.	.	.	.
5	Pup Bodyweight	16.4	16.1	16.6	16.4	14.8	14.0	15.1	16.4	C	C	C	C	.	.	.	.
7	Pup Bodyweight	16.2	16.4	15.1	15.4	15.1	15.5	14.7	14.3	C	C	C	C	C	C	.	.
9	Pup Bodyweight	19.7	19.5	19.3	20.2	18.4	16.9	18.5	18.1	C	C	.	.	.	.	.	.
11	Pup Bodyweight	19.2	19.6	20.2	19.4	19.4	20.1	19.5	18.6	C	C	C	.	.	.	.	.
13	Pup Bodyweight	18.2	16.8	16.8	17.2	17.4	16.8	16.6	16.3	C	C	C	C	.	.	.	.
15	Pup Bodyweight	17.4	18.2	M	17.1	16.6	17.0	16.9	16.7	17.0	C	.	.	.	.	.	.
17	Pup Bodyweight	17.1	15.7	17.2	17.3	16.8	16.8	15.5	17.0	C	C	C	C	.	.	.	.
19	Pup Bodyweight	17.9	18.2	18.2	18.5	17.8	16.7	17.8	15.7	C	C	C	.	.	.	.	.
21	Pup Bodyweight	17.2	15.8	15.4	15.9	15.6	15.6	16.0	14.1	C	C	C	.	.	.	.	.
23	Pup Bodyweight	15.3	15.3	14.7	14.5	14.2	13.8	13.7	15.1	C	C	C	C	C	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Low dose   Day: 7 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Pup Bodyweight	15.7	R13.2	15.4	15.3	R12.5	16.5	13.6	R13.1	C	C	C	C	C	C	C	C
27	Pup Bodyweight	17.5	16.0	17.9	17.1	16.2	16.5	16.5	16.0	C	C	C	C	.	.	.	.
29	Pup Bodyweight	17.1	17.3	16.3	18.5	14.3	16.1	16.7	17.2	C	C	C	C	.	.	.	.
31	Pup Bodyweight	15.5	15.9	16.4	16.5	15.9	15.2	16.8	15.6	C	C	C	C	C	.	.	.
33	Pup Bodyweight	18.3	17.6	18.0	17.1	17.5	16.7	17.0	17.7	C	C	C	.	.	.	.	.
35	Pup Bodyweight	15.7	16.5	16.6	14.5	15.6	15.3	15.7	15.3	C	C	C	C	C	.	.	.
37	Pup Bodyweight	15.6	16.9	16.1	16.2	16.9	15.9	15.8	15.8	C	C	.	.	.	.	.	.
39	Pup Bodyweight	18.0	18.1	18.4	17.5	17.6	15.0	15.5	17.7	C	C	C	.	.	.	.	.
41	Pup Bodyweight	17.5	17.9	18.3	18.5	15.9	16.1	14.5	16.5	C	C	C	.	.	.	.	.
43	Pup Bodyweight	17.1	17.4	17.9	18.0	17.2	18.2	18.1	17.0	C	C	C	.	.	.	.	.
45	Pup Bodyweight	17.5	17.8	17.7	17.3	17.1	17.0	16.5	17.1	C	C	C	C	C	.	.	.
47	Pup Bodyweight	18.0	R13.9	15.0	16.7	17.0	15.1	18.9	15.2	C	C	C	C	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Mid dose   Day: 7 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Pup Bodyweight	17.0	16.0	16.5	15.8	16.5	16.7	16.2	16.1	.	.	.	.	.	.	.	.
51	Pup Bodyweight	15.7	16.4	16.5	16.9	16.0	15.1	16.3	16.1	C	C	C	C	.	.	.	.
53	Pup Bodyweight	17.7	17.8	17.0	17.0	17.5	16.5	17.7	.	.	.	.	.	.	.	.	.
55	Pup Bodyweight	14.4	16.3	16.0	15.8	15.4	14.6	16.5	14.6	C	C	C	C	.	.	.	.
57	Pup Bodyweight	18.7	21.0	19.5	19.2	19.9	19.0	20.0	19.9	C	C	C	.	.	.	.	.
61	Pup Bodyweight	18.0	16.8	15.5	17.4	16.6	15.8	15.4	16.2	C	C	C	.	.	.	.	.
63	Pup Bodyweight	16.4	15.2	14.6	16.6	16.3	16.5	15.7	14.8	C	C	C	.	.	.	.	.
65	Pup Bodyweight	18.0	16.8	17.6	17.3	16.5	16.6	16.6	16.4	C	.	.	.	.	.	.	.
69	Pup Bodyweight	18.5	R13.5	18.5	15.5	18.4	17.3	15.4	17.7	C	C	C	C	.	.	.	.
71	Pup Bodyweight	20.9	20.5	20.4	20.0	20.5	20.5	.	.	.	.	.	.	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

Sanitized

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: High dose Day: 7 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Pup Bodyweight	18.3	18.6	17.6	18.8	17.7	17.8	17.7	17.3	C	.	.	.	.	.	.	.
77	Pup Bodyweight	R13.8	14.7	R14.1	R13.7	14.7	R12.9	R13.5	R13.5	.	.	.	.	.	.	.	.
79	Pup Bodyweight	16.5	16.1	15.2	16.5	15.4	15.2	15.9	15.9	C	C	C	.	.	.	.	.
81	Pup Bodyweight	15.0	15.6	15.2	15.9	14.4	14.7	16.0	15.3	C	C	C	.	.	.	.	.
83	Pup Bodyweight	15.3	R13.4	14.6	14.7	14.4	R13.5	R13.1	14.0	C	.	.	.	.	.	.	.
85	Pup Bodyweight	15.0	15.6	14.7	14.9	14.4	14.8	14.0	14.3	C	.	.	.	.	.	.	.
89	Pup Bodyweight	R13.7	R14.1	R12.4	14.5	14.8	14.6	14.4	R13.4	C	C	C	C	C	.	.	.
91	Pup Bodyweight	17.3	17.6	18.1	17.8	16.2	17.2	17.8	16.5	C	C	.	.	.	.	.	.
93	Pup Bodyweight	17.9	19.7	19.1	20.7	.	.	.	.	.	.	.	.	.	.	.	.
95	Pup Bodyweight	15.3	R13.9	15.0	14.5	15.3	14.7	15.1	15.2	C	C	C	C	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Control Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Pup Bodyweight	M	30.5	30.3	M	29.5	28.7	29.4	29.2	30.5	30.7	C	C	C	.	.	.
3	Pup Bodyweight	30.6	32.1	29.8	29.5	29.1	29.6	28.3	30.1	C	C	.	.	.	.	.	.
5	Pup Bodyweight	25.8	26.1	25.9	25.3	24.4	23.2	23.3	25.0	C	C	C	C	.	.	.	.
7	Pup Bodyweight	27.1	27.2	25.9	26.7	25.0	26.5	25.3	24.8	C	C	C	C	C	C	.	.
9	Pup Bodyweight	32.3	32.0	31.9	32.4	30.0	28.7	31.1	30.9	C	C	.	.	.	.	.	.
11	Pup Bodyweight	31.3	33.1	33.6	33.2	32.8	32.9	32.1	31.7	C	C	C	.	.	.	.	.
13	Pup Bodyweight	30.2	27.6	28.1	28.0	28.3	27.5	27.0	26.5	C	C	C	C	.	.	.	.
15	Pup Bodyweight	26.8	26.7	M	26.7	25.9	26.8	25.9	27.1	27.1	C	.	.	.	.	.	.
17	Pup Bodyweight	29.7	27.6	29.5	30.1	29.0	29.4	27.8	29.7	C	C	C	C	.	.	.	.
19	Pup Bodyweight	29.0	29.2	28.3	28.7	26.9	26.2	28.2	25.9	C	C	C	.	.	.	.	.
21	Pup Bodyweight	28.2	26.1	25.4	26.5	26.4	25.4	26.7	25.0	C	C	C	.	.	.	.	.
23	Pup Bodyweight	24.9	25.3	25.2	24.6	24.1	24.0	23.9	25.1	C	C	C	C	C	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

Sanitized

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Low dose Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Pup Bodyweight	26.3	23.7	26.2	26.6	22.7	27.1	23.9	23.6	C	C	C	C	C	C	C	C
27	Pup Bodyweight	26.8	24.0	27.3	25.9	24.5	25.1	24.7	25.0	C	C	C	C	.	.	.	.
29	Pup Bodyweight	28.2	27.9	26.5	29.0	24.7	26.5	26.1	27.4	C	C	C	C	.	.	.	.
31	Pup Bodyweight	26.9	28.0	27.9	27.7	27.5	26.3	28.2	27.2	C	C	C	C	C	.	.	.
33	Pup Bodyweight	29.8	29.5	30.1	29.3	29.3	28.9	28.2	29.7	C	C	C	.	.	.	.	.
35	Pup Bodyweight	26.2	27.2	27.7	25.0	26.1	25.9	26.8	25.4	C	C	C	C	C	.	.	.
37	Pup Bodyweight	26.2	27.8	27.6	26.8	27.9	26.6	25.9	26.9	C	C	.	.	.	.	.	.
39	Pup Bodyweight	28.8	28.6	29.2	28.1	29.1	24.8	25.9	28.5	C	C	C	.	.	.	.	.
41	Pup Bodyweight	30.5	29.6	30.2	31.0	28.2	28.1	26.5	28.4	C	C	C	.	.	.	.	.
43	Pup Bodyweight	28.7	29.0	29.6	29.5	28.7	29.6	29.8	27.9	C	C	C	.	.	.	.	.
45	Pup Bodyweight	30.0	29.9	29.4	29.6	28.7	30.3	28.0	29.6	C	C	C	C	C	.	.	.
47	Pup Bodyweight	30.2	24.3	27.0	30.2	29.7	25.9	31.2	27.2	C	C	C	C	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: Mid dose Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Pup Bodyweight	26.3	24.2	25.2	24.2	24.9	25.0	24.6	24.0	.	.	.	.	.	.	.	.
51	Pup Bodyweight	26.3	26.9	27.6	27.4	25.8	25.8	27.7	27.2	C	C	C	C	.	.	.	.
53	Pup Bodyweight	28.2	28.3	27.4	27.1	27.6	26.9	27.8	.	.	.	.	.	.	.	.	.
55	Pup Bodyweight	24.3	26.1	26.5	25.8	25.8	24.2	27.3	25.2	C	C	C	C	.	.	.	.
57	Pup Bodyweight	30.9	34.0	31.4	33.4	32.6	33.6	31.0	31.3	C	C	C	.	.	.	.	.
61	Pup Bodyweight	29.0	28.2	26.8	28.5	28.2	27.3	26.3	27.8	C	C	C	.	.	.	.	.
63	Pup Bodyweight	26.4	25.2	24.4	26.9	26.1	26.1	25.8	24.7	C	C	C	.	.	.	.	.
65	Pup Bodyweight	27.8	25.9	27.1	27.4	26.2	25.6	26.1	25.5	C	.	.	.	.	.	.	.
69	Pup Bodyweight	30.3	24.1	30.8	26.0	30.5	28.7	26.8	29.7	C	C	C	C	.	.	.	.
71	Pup Bodyweight	34.5	33.5	34.5	32.9	35.0	34.1	.	.	.	.	.	.	.	.	.	.

[redacted]

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:10

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 12: Pup body weight (g)

Group: High dose Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Pup Bodyweight	28.9	29.6	27.9	29.5	28.0	28.1	28.2	28.6	C	.	.	.	.	.	.	.
77	Pup Bodyweight	R21.8	R22.5	R22.3	R22.4	R23.4	R21.0	R21.9	R21.6	.	.	.	.	.	.	.	.
79	Pup Bodyweight	27.6	27.8	26.5	27.3	26.0	26.4	27.2	27.2	C	C	C	.	.	.	.	.
81	Pup Bodyweight	25.0	25.9	24.6	26.6	24.5	24.8	26.7	25.9	C	C	C	.	.	.	.	.
83	Pup Bodyweight	23.9	R21.8	23.7	23.7	22.7	R22.0	R20.9	22.8	C	.	.	.	.	.	.	.
85	Pup Bodyweight	23.8	24.7	23.5	24.1	24.1	23.7	23.5	23.3	C	.	.	.	.	.	.	.
89	Pup Bodyweight	R21.8	R23.3	R21.2	R23.6	24.2	23.4	22.6	R20.2	C	C	C	C	C	.	.	.
91	Pup Bodyweight	27.2	28.0	30.0	28.2	26.6	28.0	28.0	26.7	C	C	.	.	.	.	.	.
93	Pup Bodyweight	30.7	33.5	31.5	32.7	.	.	.	.	.	.	.	.	.	.	.	.
95	Pup Bodyweight	25.5	R23.5	24.8	24.4	25.1	24.9	25.0	25.5	C	C	C	C	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
R = Runt: 2 SD less weight than the mean of the control

02/Feb/2018 12:26:05

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 13: Pup anogenital distance

Group: Control Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Anogenital Distance	M	5.10	5.20	M	3.10	3.10	3.00	3.00	5.00	5.20	3.30	3.30	2.70	.	.	.
	AGD corrected for BW	.	2.22	2.32	.	1.40	1.41	1.36	1.37	2.23	2.32	1.47	1.48	1.28	.	.	.
3	Anogenital Distance	7.00	7.20	7.00	7.00	4.40	4.00	3.90	3.80	3.70	3.80	.	.	.	.	.	.
	AGD corrected for BW	2.98	3.00	3.01	3.02	1.90	1.73	1.72	1.62	1.58	1.64	.	.	.	.	.	.
5	Anogenital Distance	6.70	6.40	6.10	6.20	3.70	3.90	3.70	3.70	6.40	4.00	3.90	4.00	.	.	.	.
	AGD corrected for BW	3.00	2.89	2.70	2.80	1.71	1.81	1.71	1.66	3.08	1.88	1.84	1.87	.	.	.	.
7	Anogenital Distance	6.40	6.40	6.10	6.10	3.90	4.00	3.90	4.10	6.30	6.40	6.00	6.10	3.80	4.00	.	.
	AGD corrected for BW	2.97	2.95	2.91	2.86	1.84	1.90	1.87	1.97	2.95	3.03	2.94	2.86	1.74	1.93	.	.
9	Anogenital Distance	6.80	6.40	6.80	7.00	4.10	3.70	3.40	3.60	6.80	4.00	.	.	.	.	.	.
	AGD corrected for BW	2.91	2.77	2.94	2.97	1.81	1.69	1.49	1.59	2.97	1.78	.	.	.	.	.	.
11	Anogenital Distance	6.40	6.20	5.90	6.50	4.00	3.80	4.00	3.60	6.50	4.00	3.70	.	.	.	.	.
	AGD corrected for BW	2.76	2.64	2.48	2.77	1.73	1.61	1.71	1.56	2.72	1.69	1.56	.	.	.	.	.
13	Anogenital Distance	6.70	6.10	6.00	6.30	3.90	4.00	4.00	3.90	6.40	3.70	4.00	4.00	.	.	.	.
	AGD corrected for BW	2.97	2.76	2.68	2.81	1.74	1.80	1.80	1.76	2.87	1.68	1.91	1.84	.	.	.	.
15	Anogenital Distance	7.00	7.00	M	6.60	3.80	3.60	4.00	3.80	4.00	4.00	.	.	.	.	.	.
	AGD corrected for BW	3.02	3.05	.	2.87	1.67	1.57	1.75	1.67	1.74	1.74	.	.	.	.	.	.
17	Anogenital Distance	5.20	5.00	4.70	5.40	2.40	2.70	2.90	2.70	2.30	2.60	3.20	3.70	.	.	.	.
	AGD corrected for BW	2.33	2.33	2.11	2.43	1.09	1.23	1.35	1.22	1.04	1.23	1.45	1.70	.	.	.	.
19	Anogenital Distance	6.70	6.60	6.80	6.40	3.80	3.70	4.00	3.80	6.40	6.50	6.50	.	.	.	.	.
	AGD corrected for BW	2.91	2.83	2.95	2.76	1.66	1.67	1.75	1.76	2.82	2.79	2.78	.	.	.	.	.
21	Anogenital Distance	5.00	5.30	4.60	5.10	2.50	2.70	2.40	2.40	2.50	2.50	2.60	.	.	.	.	.
	AGD corrected for BW	2.20	2.42	2.09	2.32	1.15	1.25	1.09	1.13	1.17	1.20	1.23	.	.	.	.	.
23	Anogenital Distance	6.30	6.20	6.00	6.60	3.60	3.20	3.50	3.70	6.00	3.90	3.60	3.80	3.60	.	.	.
	AGD corrected for BW	2.96	2.89	2.83	3.12	1.72	1.53	1.70	1.73	2.85	1.87	1.71	1.79	1.77	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
Anogenital Distance is reported in mm; AGD corrected for BW is reported in mm/g3

Sanitized

02/Feb/2018 12:26:05

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 13: Pup anogenital distance

Group: Low dose Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Anogenital Distance	6.00	5.70	5.80	5.10	3.20	3.80	3.60	3.10	6.00	5.60	5.90	6.10	5.90	5.70	6.20	3.70
	AGD corrected for BW	2.82	2.82	2.79	2.42	1.61	1.74	1.75	1.56	2.84	2.63	2.71	2.85	2.78	2.69	3.01	1.72
27	Anogenital Distance	6.30	6.30	6.10	6.00	4.10	3.80	3.90	4.10	6.50	6.20	4.00	3.80	.	.	.	.
	AGD corrected for BW	2.78	2.87	2.69	2.70	1.85	1.71	1.74	1.87	2.93	2.76	1.79	1.71	.	.	.	.
29	Anogenital Distance	5.90	6.30	6.20	6.30	3.20	4.00	3.80	3.60	4.00	4.00	4.00	3.80	.	.	.	.
	AGD corrected for BW	2.66	2.86	2.85	2.75	1.54	1.84	1.73	1.61	1.87	1.88	1.83	1.68	.	.	.	.
31	Anogenital Distance	6.10	6.90	6.00	6.10	6.00	3.70	3.60	3.60	5.80	5.80	6.00	5.90	5.90	.	.	.
	AGD corrected for BW	2.87	3.22	2.74	2.80	2.77	1.75	1.64	1.69	2.65	2.68	2.72	2.71	2.71	.	.	.
33	Anogenital Distance	5.20	5.20	5.30	5.50	2.70	2.70	2.80	2.80	2.80	2.60	2.60	.	.	.	.	.
	AGD corrected for BW	2.27	2.30	2.32	2.44	1.21	1.22	1.24	1.24	1.23	1.19	1.17	.	.	.	.	.
35	Anogenital Distance	6.00	5.90	6.60	6.00	3.70	3.90	4.00	4.00	5.90	5.90	4.10	4.10	4.00	.	.	.
	AGD corrected for BW	2.74	2.64	3.00	2.85	1.71	1.83	1.84	1.88	2.70	2.70	1.88	1.87	1.82	.	.	.
37	Anogenital Distance	6.10	6.10	6.40	5.80	3.70	3.70	4.00	3.70	6.60	3.60	.	.	.	.	.	.
	AGD corrected for BW	2.77	2.69	2.88	2.59	1.63	1.67	1.82	1.67	2.98	1.61	.	.	.	.	.	.
39	Anogenital Distance	6.60	6.20	6.30	6.00	4.00	3.70	3.60	3.20	6.00	3.60	4.30	.	.	.	.	.
	AGD corrected for BW	2.87	2.71	2.71	2.64	1.76	1.71	1.67	1.40	2.69	1.59	2.00	.	.	.	.	.
41	Anogenital Distance	6.30	6.70	7.00	6.50	4.00	4.10	3.80	4.00	6.70	6.40	6.00	.	.	.	.	.
	AGD corrected for BW	2.82	2.94	3.06	2.86	1.84	1.88	1.81	1.81	3.01	2.88	2.67	.	.	.	.	.
43	Anogenital Distance	6.10	6.30	5.90	5.60	3.90	3.80	3.80	4.00	6.50	6.80	6.20	.	.	.	.	.
	AGD corrected for BW	2.69	2.81	2.59	2.43	1.73	1.65	1.66	1.78	2.83	3.12	2.77	.	.	.	.	.
45	Anogenital Distance	6.70	6.50	6.00	6.20	6.30	3.90	4.00	4.20	5.30	6.30	6.30	7.00	6.50	.	.	.
	AGD corrected for BW	2.99	2.93	2.71	2.80	2.87	1.78	1.83	1.91	2.43	2.77	2.86	3.24	2.97	.	.	.
47	Anogenital Distance	6.90	6.40	6.20	6.00	3.90	4.00	3.90	3.90	6.30	6.80	3.70	4.00	.	.	.	.
	AGD corrected for BW	3.13	3.08	2.96	2.83	1.79	1.90	1.74	1.82	2.82	3.13	1.76	1.92	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
Anogenital Distance is reported in mm; AGD corrected for BW is reported in mm/g3

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 13: Pup anogenital distance

Group: Mid dose Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Anogenital Distance	5.20	2.90	2.50	2.60	3.20	3.00	2.50	3.00	.	.	.	.	.	.	.	.
	AGD corrected for BW	2.23	1.28	1.08	1.15	1.38	1.29	1.08	1.31	.	.	.	.	.	.	.	.
51	Anogenital Distance	6.50	5.90	6.00	6.10	3.80	4.00	4.00	3.80	6.00	3.60	3.90	3.90	.	.	.	.
	AGD corrected for BW	2.99	2.66	2.73	2.76	1.74	1.88	1.82	1.74	2.65	1.67	1.82	1.78	.	.	.	.
53	Anogenital Distance	6.30	6.00	6.40	6.10	3.40	3.60	3.80	.	.	.	.	.	.	.	.	.
	AGD corrected for BW	2.68	2.55	2.77	2.63	1.45	1.56	1.62	.	.	.	.	.	.	.	.	.
55	Anogenital Distance	5.30	5.50	5.20	5.20	5.50	3.00	3.10	3.30	5.20	5.20	5.50	6.00	.	.	.	.
	AGD corrected for BW	2.54	2.47	2.37	2.40	2.56	1.42	1.39	1.56	2.47	2.43	2.55	2.84	.	.	.	.
57	Anogenital Distance	6.80	6.20	6.70	3.90	3.60	3.60	3.80	4.10	5.00	3.60	3.90	.	.	.	.	.
	AGD corrected for BW	2.91	2.58	2.81	1.67	1.54	1.51	1.62	1.74	2.19	1.58	1.70	.	.	.	.	.
61	Anogenital Distance	6.50	6.00	6.40	5.90	4.10	3.80	3.20	3.70	6.30	6.40	6.00	.	.	.	.	.
	AGD corrected for BW	2.86	2.67	2.97	2.63	1.86	1.74	1.48	1.70	3.00	2.88	2.68	.	.	.	.	.
63	Anogenital Distance	6.20	6.50	6.00	6.20	3.60	3.60	4.00	3.40	6.30	3.80	4.00	.	.	.	.	.
	AGD corrected for BW	2.76	2.98	2.78	2.72	1.61	1.59	1.81	1.57	2.76	1.74	1.80	.	.	.	.	.
65	Anogenital Distance	6.50	7.10	7.10	6.50	4.00	4.20	4.20	4.10	7.00	.	.	.	.	.	.	.
	AGD corrected for BW	2.78	3.09	3.04	2.77	1.75	1.85	1.84	1.79	3.07	.	.	.	.	.	.	.
69	Anogenital Distance	6.00	6.00	6.60	6.40	3.50	3.70	3.40	4.00	6.20	3.90	3.60	4.00	.	.	.	.
	AGD corrected for BW	2.62	2.93	2.89	2.98	1.54	1.65	1.58	1.77	2.81	1.72	1.65	1.81	.	.	.	.
71	Anogenital Distance	7.20	7.10	6.50	4.00	4.00	4.10	.	.	.	.	.	.	.	.	.	.
	AGD corrected for BW	2.91	2.88	2.64	1.64	1.62	1.68	.	.	.	.	.	.	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
Anogenital Distance is reported in mm; AGD corrected for BW is reported in mm/g3

02/Feb/2018 12:26:05

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 13: Pup anogenital distance

Group: High dose   Day: 4 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Anogenital Distance	6.30	6.00	6.20	7.00	6.90	5.90	3.60	3.80	6.90	.	.	.	.	.	.	.
	AGD corrected for BW	2.66	2.52	2.65	2.95	2.97	2.52	1.53	1.64	2.87	.	.	.	.	.	.	.
77	Anogenital Distance	4.50	4.10	3.90	4.40	4.80	2.60	2.40	2.40	.	.	.	.	.	.	.	.
	AGD corrected for BW	2.13	1.90	1.84	2.09	2.23	1.27	1.15	1.14	.	.	.	.	.	.	.	.
79	Anogenital Distance	6.80	6.80	3.60	3.40	3.80	3.80	3.60	3.60	3.90	3.60	3.60	.	.	.	.	.
	AGD corrected for BW	3.09	3.10	1.67	1.52	1.78	1.77	1.66	1.63	1.78	1.67	1.69	.	.	.	.	.
81	Anogenital Distance	6.30	6.00	6.00	6.00	3.90	4.00	3.90	4.00	6.20	6.40	3.80	.	.	.	.	.
	AGD corrected for BW	2.91	2.74	2.75	2.70	1.83	1.87	1.78	1.82	2.82	2.89	1.74	.	.	.	.	.
83	Anogenital Distance	6.00	6.10	6.30	6.30	3.60	3.80	3.70	3.40	5.50	.	.	.	.	.	.	.
	AGD corrected for BW	2.73	2.91	2.89	2.91	1.66	1.81	1.78	1.59	2.51	.	.	.	.	.	.	.
85	Anogenital Distance	5.70	6.40	3.90	3.90	4.00	3.70	3.70	3.90	3.80	.	.	.	.	.	.	.
	AGD corrected for BW	2.59	2.90	1.80	1.79	1.86	1.71	1.73	1.82	1.76	.	.	.	.	.	.	.
89	Anogenital Distance	5.10	5.20	5.00	5.50	3.30	3.30	3.30	3.30	5.40	5.60	5.60	5.40	3.50	.	.	.
	AGD corrected for BW	2.52	2.47	2.54	2.63	1.57	1.59	1.58	1.60	2.54	2.67	2.72	2.59	1.68	.	.	.
91	Anogenital Distance	6.40	6.70	6.30	6.30	6.40	3.50	3.40	3.50	5.40	6.20	.	.	.	.	.	.
	AGD corrected for BW	2.80	2.89	2.72	2.74	2.86	1.54	1.47	1.56	2.36	2.69	.	.	.	.	.	.
93	Anogenital Distance	6.60	6.70	3.70	4.00	.	.	.	.	.	.	.	.	.	.	.	.
	AGD corrected for BW	2.87	2.76	1.56	1.67	.	.	.	.	.	.	.	.	.	.	.	.
95	Anogenital Distance	5.70	5.50	6.10	6.60	3.50	3.70	3.80	3.60	3.80	3.70	3.70	3.80	.	.	.	.
	AGD corrected for BW	2.65	2.66	2.93	3.17	1.64	1.74	1.78	1.68	1.81	1.71	1.76	1.79	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead
Anogenital Distance is reported in mm; AGD corrected for BW is reported in mm/g3

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 14: Pup nipple retention (males)

Group: Control Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	Number of Nipples	M	0	0	M	K	A	A	A	0	0	C	C	C	.	.	.
3	Number of Nipples	0	0	0	0	K	A	A	A	C	C	.	.	.	.	.	.
5	Number of Nipples	0	2	0	0	K	A	A	A	C	C	C	C	.	.	.	.
7	Number of Nipples	0	0	1	0	K	A	A	A	C	C	C	C	C	C	.	.
9	Number of Nipples	0	0	0	0	K	A	A	A	C	C	.	.	.	.	.	.
11	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
13	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.
15	Number of Nipples	0	0	M	0	K	A	A	A	A	C	.	.	.	.	.	.
17	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.
19	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
21	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
23	Number of Nipples	0	0	0	1	K	A	A	A	C	C	C	C	C	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

02/Feb/2018 12:26:05

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 14: Pup nipple retention (males)

Group: Low dose Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
25	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	C	C	C	C
27	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.
29	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.
31	Number of Nipples	0	0	0	0	0	K	A	A	C	C	C	C	C	.	.	.
33	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
35	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	C	.	.	.
37	Number of Nipples	0	0	0	0	K	A	A	A	C	C	.	.	.	.	.	.
39	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
41	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
43	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
45	Number of Nipples	0	0	0	0	0	K	A	A	C	C	C	C	C	.	.	.
47	Number of Nipples	0	1	0	0	K	A	A	A	C	C	C	C	.	.	.	.

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Sanitized

02/Feb/2018 12:26:05

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 14: Pup nipple retention (males)

Group: Mid dose Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
49	Number of Nipples	0	K	A	A	A	A	A	A	.	.	.	.	.	.	.	.
51	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.
53	Number of Nipples	0	0	0	0	K	A	A	.	.	.	.	.	.	.	.	.
55	Number of Nipples	0	0	0	0	0	K	A	A	C	C	C	C	.	.	.	.
57	Number of Nipples	0	0	0	K	A	A	A	A	C	C	C	.	.	.	.	.
61	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
63	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
65	Number of Nipples	0	0	0	0	K	A	A	A	C	.	.	.	.	.	.	.
69	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.
71	Number of Nipples	0	0	0	K	A	A	.	.	.	.	.	.	.	.	.	.

[redacted]

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Sanitized

02/Feb/2018 12:26:05

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 14: Pup nipple retention (males)

Group: High dose   Day: 13 Relative to Littering (Litter: A)

Dam	Measurement	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
75	Number of Nipples	0	0	0	0	0	0	K	A	C	.	.	.	.	.	.	.
77	Number of Nipples	0	0	0	0	0	K	A	A	.	.	.	.	.	.	.	.
79	Number of Nipples	0	0	K	A	A	A	A	A	C	C	C	.	.	.	.	.
81	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	.	.	.	.	.
83	Number of Nipples	0	0	1	0	K	A	A	A	C	.	.	.	.	.	.	.
85	Number of Nipples	0	0	K	A	A	A	A	A	C	.	.	.	.	.	.	.
89	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	C	.	.	.
91	Number of Nipples	0	0	0	0	0	K	A	A	C	C	.	.	.	.	.	.
93	Number of Nipples	0	0	K	A	.	.	.	.	.	.	.	.	.	.	.	.
95	Number of Nipples	0	0	0	0	K	A	A	A	C	C	C	C	.	.	.	.

[redacted]

Litter: A = First litter
Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

02/Feb/2018 13:46:53

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 15: Pup organ weight

Day(s): 13 Relative to Littering (Litter: A)

0 ppm Dam	Pup Sex	Pup	Pup Terminal Bodywt (g)	Pup Thyroid Wt (g)	Pup Thyroid rel.wgt (g/kg body wgt)
1	Male	1-2	30.5	0.0047	0.154
	Female	1-5	29.5	0.0042	0.142
3	Male	3-1	30.6	0.0028	0.092
	Female	3-5	29.1	0.0048	0.165
5	Male	5-1	25.8	0.0018	0.070
	Female	5-5	24.4	0.0047	0.193
7	Male	7-1	27.1	0.0041	0.151
	Female	7-5	25.0	0.0028	0.112
9	Male	9-1	32.3	0.0054	0.167
	Female	9-5	30.0	0.0053	0.177
11	Male	11-1	31.1	0.0037	0.119
	Female	11-5	32.8	0.0044	0.134
13	Male	13-1	30.2	0.0032	0.106
	Female	13-5	28.3	0.0022	0.078
15	Male	15-1	26.8	0.0044	0.164
	Female	15-5	25.9	0.0036	0.139
17	Male	17-1	29.7	0.0030	0.101
	Female	17-5	29.0	0.0039	0.134
19	Male	19-1	29.0	0.0045	0.155
	Female	19-5	26.9	0.0044	0.164
21	Male	21-1	28.2	0.0057	0.202
	Female	21-5	26.4	0.0043	0.163
23	Male	23-1	24.9	0.0035	0.141
	Female	23-5	24.1	0.0047	0.195

Litter: A = First litter

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 15: Pup organ weight

Day(s): 13 Relative to Littering (Litter: A)

250 ppm Dam	Pup Sex	Pup	Pup Terminal Bodywt (g)	Pup Thyroid Wt (g)	Pup Thyroid rel.wgt (g/kg body wgt)
25	Male	25-1	26.3	0.0028	0.106
	Female	25-5	22.7	0.0034	0.150
27	Male	27-1	26.8	0.0027	0.101
	Female	27-5	24.5	0.0045	0.184
29	Male	29-1	28.2	0.0048	0.170
	Female	29-5	24.7	0.0031	0.126
31	Male	31-1	26.9	0.0030	0.112
	Female	31-6	26.3	0.0031	0.118
33	Male	33-1	29.8	0.0036	0.121
	Female	33-5	29.3	0.0045	0.154
35	Male	35-1	26.2	0.0016	0.061
	Female	35-5	26.1	0.0040	0.153
37	Male	37-1	26.2	0.0020	0.076
	Female	37-5	27.9	0.0029	0.104
39	Male	39-1	28.8	0.0033	0.115
	Female	39-5	29.1	0.0027	0.093
41	Male	41-1	30.5	0.0033	0.108
	Female	41-5	28.2	0.0035	0.124
43	Male	43-1	28.7	0.0057	0.199
	Female	43-5	28.7	0.0062	0.216
45	Male	45-1	30.0	0.0026	0.087
	Female	45-6	30.3	0.0029	0.096
47	Male	47-1	30.2	0.0046	0.152
	Female	47-5	29.7	0.0031	0.104

Litter: A = First litter

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 15: Pup organ weight

Day(s): 13 Relative to Littering (Litter: A)

750 ppm Dam	Pup Sex	Pup	Pup Terminal Bodywt (g)	Pup Thyroid Wt (g)	Pup Thyroid rel.wgt (g/kg body wgt)
49	Male	49-1	26.3	0.0047	0.179
	Female	49-2	24.2	0.0026	0.107
51	Male	51-1	26.3	0.0040	0.152
	Female	51-5	25.8	0.0022	0.085
53	Male	53-1	28.2	0.0029	0.103
	Female	53-5	27.6	0.0025	0.091
55	Male	55-1	24.3	0.0048	0.198
	Female	55-6	24.2	0.0072	0.298
57	Male	57-1	30.9	0.0062	0.201
	Female	57-4	33.4	0.0061	0.183
61	Male	61-1	29.0	0.0068	0.234
	Female	61-5	28.2	0.0042	0.149
63	Male	63-1	26.4	0.0036	0.136
	Female	63-5	26.1	0.0032	0.123
65	Male	65-1	27.8	0.0025	0.090
	Female	65-5	26.2	0.0033	0.126
69	Male	69-1	30.3	0.0038	0.125
	Female	69-5	30.5	0.0038	0.125
71	Male	71-1	34.5	0.0027	0.078
	Female	71-4	32.9	0.0048	0.146

Litter: A = First litter

[redacted]

02/Feb/2018 13:46:53

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 15: Pup organ weight

Day(s): 13 Relative to Littering (Litter: A)

1500 ppm Dam	Pup Sex	Pup	Pup Terminal Bodywt (g)	Pup Thyroid Wt (g)	Pup Thyroid rel.wgt (g/kg body wgt)
75	Male	75-1	28.9	0.0034	0.118
	Female	75-7	28.2	0.0071	0.252
77	Male	77-1	21.8	0.0028	0.128
	Female	77-6	21.0	0.0032	0.152
79	Male	79-1	27.6	0.0039	0.141
	Female	79-3	26.5	0.0030	0.113
81	Male	81-1	25.0	0.0037	0.148
	Female	81-5	24.5	0.0043	0.176
83	Male	83-1	23.9	0.0028	0.117
	Female	83-5	22.7	0.0031	0.137
85	Male	85-1	23.8	0.0048	0.202
	Female	85-3	23.5	0.0036	0.153
89	Male	89-1	21.8	0.0046	0.211
	Female	89-5	24.2	0.0048	0.198
91	Male	91-1	27.2	0.0047	0.173
	Female	91-6	28.0	0.0043	0.154
93	Male	93-1	30.7	0.0048	0.156
	Female	93-3	31.5	0.0022	0.070
95	Male	95-1	25.5	0.0037	0.145
	Female	95-5	25.1	0.0023	0.092

Litter: A = First litter

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

0 ppm	Death Code	Pup Day of Death	Findings
Dam: 1			
1-1	M	4	
1-2	K	13	.....Pup Necropsy, No abnormalities detected
1-3	A		
1-4	M	4	
1-5	K	13	.....Pup Necropsy, No abnormalities detected
1-6	A		
1-7	A		
1-8	A		
1-9	A		
1-10	A		
1-11	C	4	
1-12	C	4	
1-13	C	4	
Dam: 3			
3-1	K	13	.....Pup Necropsy, No abnormalities detected
3-2	A		
3-3	A		
3-4	A		
3-5	K	13	.....Pup Necropsy, No abnormalities detected
3-6	A		
3-7	A		
3-8	A		
3-9	C	4	
3-10	C	4	
Dam: 5			
5-1	K	13	.....Pup Necropsy, General Skin, Total, Sparsely haired area(s)
5-2	A		
5-3	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

Sanitized

13/Sep/2018 13:40:19

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

[redacted]

0 ppm	Death Code	Pup Day of Death	Findings
Dam: 5	(Continued...)		
5-4	A		
5-5	K	13	.....Pup Necropsy, General Skin, Total, Sparsely haired area(s)
5-6	A		
5-7	A		
5-8	A		
5-9	C	4	
5-10	C	4	
5-11	C	4	
5-12	C	4	
Dam: 7			
7-1	K	13	.....Pup Necropsy, No abnormalities detected
7-2	A		
7-3	A		
7-4	A		
7-5	K	13	.....Pup Necropsy, No abnormalities detected
7-6	A		
7-7	A		
7-8	A		
7-9	C	4	
7-10	C	4	
7-11	C	4	
7-12	C	4	
7-13	C	4	
7-14	C	4	
Dam: 9			
9-1	K	13	.....Pup Necropsy, No abnormalities detected
9-2	A		
9-3	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Appendix 16: Pup macroscopic observations, necropsy

0 ppm	Death Code	Pup Day of Death	Findings
Dam: 9	(Continued...)		
9-4	A		
9-5	K	13	.....Pup Necropsy, No abnormalities detected
9-6	A		
9-7	A		
9-8	A		
9-9	C	4	
9-10	C	4	
Dam: 11			
11-1	K	13	.....Pup Necropsy, No abnormalities detected
11-2	A		
11-3	A		
11-4	A		
11-5	K	13	.....Pup Necropsy, No abnormalities detected
11-6	A		
11-7	A		
11-8	A		
11-9	C	4	
11-10	C	4	
11-11	C	4	
Dam: 13			
13-1	K	13	.....Pup Necropsy, No abnormalities detected
13-2	A		
13-3	A		
13-4	A		
13-5	K	13	.....Pup Necropsy, No abnormalities detected
13-6	A		
13-7	A		
13-8	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

0 ppm	Death Code	Pup Day of Death	Findings
Dam: 13	(Continued...)		
13-9	C	4	
13-10	C	4	
13-11	C	4	
13-12	C	4	
Dam: 15			
15-1	K	13	.....Pup Necropsy, No abnormalities detected
15-2	A		
15-3	M	4	
15-4	A		
15-5	K	13	.....Pup Necropsy, No abnormalities detected
15-6	A		
15-7	A		
15-8	A		
15-9	A		
15-10	C	4	
Dam: 17			
17-1	K	13	.....Pup Necropsy, No abnormalities detected
17-2	A		
17-3	A		
17-4	A		
17-5	K	13	.....Pup Necropsy, No abnormalities detected
17-6	A		
17-7	A		
17-8	A		
17-9	C	4	
17-10	C	4	
17-11	C	4	
17-12	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

0 ppm	Death Code	Pup Day of Death	Findings
Dam: 19			
19-1	K	13	.....Pup Necropsy, No abnormalities detected
19-2	A		
19-3	A		
19-4	A		
19-5	K	13	.....Pup Necropsy, No abnormalities detected
19-6	A		
19-7	A		
19-8	A		
19-9	C	4	
19-10	C	4	
19-11	C	4	
Dam: 21			
21-1	K	13	.....Pup Necropsy, No abnormalities detected
21-2	A		
21-3	A		
21-4	A		
21-5	K	13	.....Pup Necropsy, No abnormalities detected
21-6	A		
21-7	A		
21-8	A		
21-9	C	4	
21-10	C	4	
21-11	C	4	
Dam: 23			
23-1	K	13	.....Pup Necropsy, No abnormalities detected
23-2	A		
23-3	A		
23-4	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

Appendix 16: Pup macroscopic observations, necropsy

0 ppm	Death Code	Pup Day of Death	Findings
Dam: 23	(Continued...)		
23-5	K	13	.....Pup Necropsy, No abnormalities detected
23-6	A		
23-7	A		
23-8	A		
23-9	C	4	
23-10	C	4	
23-11	C	4	
23-12	C	4	
23-13	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

250 ppm	Death Code	Pup Day of Death	Findings
Dam: 25			
25-1	K	13	.....Pup Necropsy, No abnormalities detected
25-2	A		
25-3	A		
25-4	A		
25-5	K	13	.....Pup Necropsy, No abnormalities detected
25-6	A		
25-7	A		
25-8	A		
25-9	C	4	
25-10	C	4	
25-11	C	4	
25-12	C	4	
25-13	C	4	
25-14	C	4	
25-15	C	4	
25-16	C	4	
Dam: 27			
27-1	K	13	.....Pup Necropsy, No abnormalities detected
27-2	A		
27-3	A		
27-4	A		
27-5	K	13	.....Pup Necropsy, No abnormalities detected
27-6	A		
27-7	A		
27-8	A		
27-9	C	4	
27-10	C	4	
27-11	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

250 ppm	Death Code	Pup Day of Death	Findings
Dam: 27	(Continued...)		
27-12	C	4	
Dam: 29			
29-1	K	13	.....Pup Necropsy, No abnormalities detected
29-2	A		
29-3	A		
29-4	A		
29-5	K	13	.....Pup Necropsy, No abnormalities detected
29-6	A		
29-7	A		
29-8	A		
29-9	C	4	
29-10	C	4	
29-11	C	4	
29-12	C	4	
Dam: 31			
31-1	K	13	.....Pup Necropsy, No abnormalities detected
31-2	A		
31-3	A		
31-4	A		
31-5	A		
31-6	K	13	.....Pup Necropsy, No abnormalities detected
31-7	A		
31-8	A		
31-9	C	4	
31-10	C	4	
31-11	C	4	
31-12	C	4	
31-13	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

Sanitized

13/Sep/2018 13:40:19

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

250 ppm	Death Code	Pup Day of Death	Findings
Dam: 33			
33-1	K	13	.....Pup Necropsy, No abnormalities detected
33-2	A		
33-3	A		
33-4	A		
33-5	K	13	.....Pup Necropsy, No abnormalities detected
33-6	A		
33-7	A		
33-8	A		
33-9	C	4	
33-10	C	4	
33-11	C	4	
Dam: 35			
35-1	K	13	.....Pup Necropsy, No abnormalities detected
35-2	A		
35-3	A		
35-4	A		
35-5	K	13	.....Pup Necropsy, No abnormalities detected
35-6	A		
35-7	A		
35-8	A		
35-9	C	4	
35-10	C	4	
35-11	C	4	
35-12	C	4	
35-13	C	4	
Dam: 37			
37-1	K	13	.....Pup Necropsy, No abnormalities detected
37-2	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

Appendix 16: Pup macroscopic observations, necropsy

[redacted]

250 ppm	Death Code	Pup Day of Death	Findings
Dam: 37	(Continued...)		
37-3	A		
37-4	A		
37-5	K	13	.....Pup Necropsy, No abnormalities detected
37-6	A		
37-7	A		
37-8	A		
37-9	C	4	
37-10	C	4	
Dam: 39			
39-1	K	13	.....Pup Necropsy, Liver Liver, Discolored - [brown]
39-2	A		
39-3	A		
39-4	A		
39-5	K	13	.....Pup Necropsy, No abnormalities detected
39-6	A		
39-7	A		
39-8	A		
39-9	C	4	
39-10	C	4	
39-11	C	4	
Dam: 41			
41-1	K	13	.....Pup Necropsy, No abnormalities detected
41-2	A		
41-3	A		
41-4	A		
41-5	K	13	.....Pup Necropsy, No abnormalities detected
41-6	A		
41-7	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

250 ppm	Death Code	Pup Day of Death	Findings
Dam: 41	(Continued...)		
41-8	A		
41-9	C	4	
41-10	C	4	
41-11	C	4	
Dam: 43			
43-1	K	13	.....Pup Necropsy, No abnormalities detected
43-2	A		
43-3	A		
43-4	A		
43-5	K	13	.....Pup Necropsy, No abnormalities detected
43-6	A		
43-7	A		
43-8	A		
43-9	C	4	
43-10	C	4	
43-11	C	4	
Dam: 45			
45-1	K	13	.....Pup Necropsy, No abnormalities detected
45-2	A		
45-3	A		
45-4	A		
45-5	A		
45-6	K	13	.....Pup Necropsy, No abnormalities detected
45-7	A		
45-8	A		
45-9	C	4	
45-10	C	4	
45-11	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

Appendix 16: Pup macroscopic observations, necropsy

250 ppm	Death Code	Pup Day of Death	Findings
Dam: 45 (Continued...)			
45-12	C	4	
45-13	C	4	
Dam: 47			
47-1	K	13	.....Pup Necropsy, No abnormalities detected
47-2	A		
47-3	A		
47-4	A		
47-5	K	13	.....Pup Necropsy, No abnormalities detected
47-6	A		
47-7	A		
47-8	A		
47-9	C	4	
47-10	C	4	
47-11	C	4	
47-12	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

750 ppm	Death Code	Pup Day of Death	Findings
Dam: 49			
49-1	K	13	.....Pup Necropsy, No abnormalities detected
49-2	K	13	.....Pup Necropsy, No abnormalities detected
49-3	A		
49-4	A		
49-5	A		
49-6	A		
49-7	A		
49-8	A		
Dam: 51			
51-1	K	13	.....Pup Necropsy, No abnormalities detected
51-2	A		
51-3	A		
51-4	A		
51-5	K	13	.....Pup Necropsy, No abnormalities detected
51-6	A		
51-7	A		
51-8	A		
51-9	C	4	
51-10	C	4	
51-11	C	4	
51-12	C	4	
Dam: 53			
53-1	K	13	.....Pup Necropsy, No abnormalities detected
53-2	A		
53-3	A		
53-4	A		
53-5	K	13	.....Pup Necropsy, No abnormalities detected
53-6	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

750 ppm	Death Code	Pup Day of Death	Findings
Dam: 53	(Continued...)		
53-7	A		
Dam: 55			
55-1	K	13	.....Pup Necropsy, No abnormalities detected
55-2	A		
55-3	A		
55-4	A		
55-5	A		
55-6	K	13	.....Pup Necropsy, No abnormalities detected
55-7	A		
55-8	A		
55-9	C	4	
55-10	C	4	
55-11	C	4	
55-12	C	4	
Dam: 57			
57-1	K	13	.....Pup Necropsy, No abnormalities detected
57-2	A		
57-3	A		
57-4	K	13	.....Pup Necropsy, No abnormalities detected
57-5	A		
57-6	A		
57-7	A		
57-8	A		
57-9	C	4	
57-10	C	4	
57-11	C	4	
Dam: 61			
61-1	K	13	.....Pup Necropsy, No abnormalities detected

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

750 ppm	Death Code	Pup Day of Death	Findings
Dam: 61	(Continued...)		
61-2	A		
61-3	A		
61-4	A		
61-5	K	13	.....Pup Necropsy, No abnormalities detected
61-6	A		
61-7	A		
61-8	A		
61-9	C	4	
61-10	C	4	
61-11	C	4	
Dam: 63			
63-1	K	13	.....Pup Necropsy, No abnormalities detected
63-2	A		
63-3	A		
63-4	A		
63-5	K	13	.....Pup Necropsy, No abnormalities detected
63-6	A		
63-7	A		
63-8	A		
63-9	C	4	
63-10	C	4	
63-11	C	4	
Dam: 65			
65-1	K	13	.....Pup Necropsy, No abnormalities detected
65-2	A		
65-3	A		
65-4	A		
65-5	K	13	.....Pup Necropsy, No abnormalities detected

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

750 ppm	Death Code	Pup Day of Death	Findings
Dam: 65	(Continued...)		
65-6	A		
65-7	A		
65-8	A		
65-9	C	4	
Dam: 69			
69-1	K	13	.....Pup Necropsy, No abnormalities detected
69-2	A		
69-3	A		
69-4	A		
69-5	K	13	.....Pup Necropsy, No abnormalities detected
69-6	A		
69-7	A		
69-8	A		
69-9	C	4	
69-10	C	4	
69-11	C	4	
69-12	C	4	
Dam: 71			
71-1	K	13	.....Pup Necropsy, No abnormalities detected
71-2	A		
71-3	A		
71-4	K	13	.....Pup Necropsy, No abnormalities detected
71-5	A		
71-6	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

1500 ppm	Death Code	Pup Day of Death	Findings
Dam: 75			
75-1	K	13	.....Pup Necropsy, No abnormalities detected
75-2	A		
75-3	A		
75-4	A		
75-5	A		
75-6	A		
75-7	K	13	.....Pup Necropsy, No abnormalities detected
75-8	A		
75-9	C	4	
Dam: 77			
77-1	K	13	.....Pup Necropsy, No abnormalities detected
77-2	A		
77-3	A		
77-4	A		
77-5	A		
77-6	K	13	.....Pup Necropsy, No abnormalities detected
77-7	A		
77-8	A		
Dam: 79			
79-1	K	13	.....Pup Necropsy, No abnormalities detected
79-2	A		
79-3	K	13	.....Pup Necropsy, No abnormalities detected
79-4	A		
79-5	A		
79-6	A		
79-7	A		
79-8	A		
79-9	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

1500 ppm	Death Code	Pup Day of Death	Findings
Dam: 79	(Continued...)		
79-10	C	4	
79-11	C	4	
Dam: 81			
81-1	K	13	.....Pup Necropsy, No abnormalities detected
81-2	A		
81-3	A		
81-4	A		
81-5	K	13	.....Pup Necropsy, No abnormalities detected
81-6	A		
81-7	A		
81-8	A		
81-9	C	4	
81-10	C	4	
81-11	C	4	
Dam: 83			
83-1	K	13	.....Pup Necropsy, No abnormalities detected
83-2	A		
83-3	A		
83-4	A		
83-5	K	13	.....Pup Necropsy, No abnormalities detected
83-6	A		
83-7	A		
83-8	A		
83-9	C	4	
Dam: 85			
85-1	K	13	.....Pup Necropsy, No abnormalities detected
85-2	A		
85-3	K	13	.....Pup Necropsy, No abnormalities detected

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted]

Appendix 16: Pup macroscopic observations, necropsy

1500 ppm	Death Code	Pup Day of Death	Findings
Dam: 85	(Continued...)		
85-4	A		
85-5	A		
85-6	A		
85-7	A		
85-8	A		
85-9	C	4	
Dam: 89			
89-1	K	13	.....Pup Necropsy, No abnormalities detected
89-2	A		
89-3	A		
89-4	A		
89-5	K	13	.....Pup Necropsy, No abnormalities detected
89-6	A		
89-7	A		
89-8	A		
89-9	C	4	
89-10	C	4	
89-11	C	4	
89-12	C	4	
89-13	C	4	
Dam: 91			
91-1	K	13	.....Pup Necropsy, No abnormalities detected
91-2	A		
91-3	A		
91-4	A		
91-5	A		
91-6	K	13	.....Pup Necropsy, No abnormalities detected
91-7	A		

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead

[redacted] - Inhalation reproduction and developmental toxicity screening test with [redacted] in rats

Appendix 16: Pup macroscopic observations, necropsy

1500 ppm	Death Code	Pup Day of Death	Findings
Dam: 91	(Continued...)		
91-8	A		
91-9	C	4	
91-10	C	4	
Dam: 93			
93-1	K	13	.....Pup Necropsy, No abnormalities detected
93-2	A		
93-3	K	13	.....Pup Necropsy, No abnormalities detected
93-4	A		
Dam: 95			
95-1	K	13	.....Pup Necropsy, No abnormalities detected
95-2	A		
95-3	A		
95-4	A		
95-5	K	13	.....Pup Necropsy, No abnormalities detected
95-6	A		
95-7	A		
95-8	A		
95-9	C	4	
95-10	C	4	
95-11	C	4	
95-12	C	4	

Pup status codes: A-Alive S-Stillborn C-Culled M-Missing K-Scheduled Sacrifice D-Dead