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US Environmental Protection Agency
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and toxics
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001
Phone: 202-564-8940



TSCA Section 8(e) Document Control Number: 8EHQ-10-17890

Subject Chemical: 3,3,3-trifluoroprop-1-ene (CAS No. 677-21-4)
Alternative Name: Refrigerant 1243zf (R-1243zf)

Dear Sir or Madam:

On April 15, 2010 Mexichem Fluor Inc. submitted a notice under Section 8(e) of the Toxic Substances Control Act (TSCA) regarding preliminary findings from a 28-day inhalation study in the rat employing 0, 500, 1500, and 15,000 ppm levels of R-1243zf. Mexichem Fluor Inc. indicated that the full results of the 28-day study would be submitted to the TSCA 8(e) Coordinator. The final report is enclosed.

Mexichem Fluor Inc. hereby withdraws its requests for confidentiality regarding all information previously submitted regarding R-1243zf.

Sincerely,

Joel R. Hall
Security, Safety, Health & Environmental Manager
Mexichem Fluor Inc.



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CONTAINS NO CBI

TNO Quality of Life

TNO Report

V8668 | Final |

A sub-acute (28-day) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene (HFO 1243zf) in rats

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Sponsor	Ineos Fluor Limited
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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 TNO Quality of Life were carried out in compliance with the current OECD Principles of Good Laboratory Practice¹. 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 test material identity and properties was not performed in this study.

Study director

Dr. H. Muijser
(Study Director)



10-12-2010

Name

Signature

Date (dd-mm-yyyy)

Approval by management *b/a*

Dr. M.A. Bos



10-12-2010

Name

Signature

Date (dd-mm-yyyy)

M. JST STEENWINKEL

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

Quality Assurance Statement

Report title: A sub-acute (28-day) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene (HFO 1243zf) in rats
Report Number: V8668
Report date: 3 December, 2010

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	15 September 2009	15 September 2009
Authorised study plan amendment 1	Yes	22 September 2009	22 September 2009
Animal receipt	No	12 August 2009	12 August 2009
Animal allocation	No	7 September 2009	7 September 2009
Analytical inhalation techniques	Yes	22 September 2009	22 September 2009
Inhalatory exposure	Yes	22 September 2009	22 September 2009
Body weight	No	5 October 2009	5 October 2009
Clinical signs	No	5 October 2009	5 October 2009
Food consumption	No	5 October 2009	5 October 2009
Urine collection	Yes	20 October 2009	20 October 2009
Necropsy	Yes	20 October 2009	20 October 2009
Terminal blood collection	Yes	20 October 2009	20 October 2009
Haematology	No	15 December 2009	15 December 2009
Clinical chemistry	No	14 December 2009	14 December 2009
Urinalysis	Yes	22 October 2009	22 October 2009
Histology	No	16 December 2009	16 December 2009
Pathology	No	29 September 2009	29 September 2009
F-analysis	Yes	23 November 2009	23 November 2009
Draft report (excl. F-analysis) and study file	Yes	1 March 2010	5 March 2010
Draft report (F-analysis) and study file	Yes	5 March 2010	5 March 2010
Final report	Yes	3 December 2010	3 December 2010

* 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.



P.B. Davis B.A.
Quality Assurance auditor

Date: 10 December 2010

Contents

Statement of GLP Compliance	2
Quality Assurance Statement.....	3
Summary	5
1 General.....	8
1.1 Study sponsor and monitor	8
1.2 Test facility	8
1.3 Responsible personnel	8
1.4 Time schedule.....	8
2 Introduction.....	9
2.1 Objective.....	9
2.2 Applicable guidelines	9
2.3 Animal welfare	9
3 Study plan and deviations	10
3.1 Study plan.....	10
3.2 Deviations	10
4 Materials and Methods.....	11
4.1 Test material	11
4.2 Test system	11
4.3 Experimental conditions	12
4.4 Experimental procedures	13
4.5 Observations, analyses and measurements	14
4.6 Statistical analysis of the results	19
5 Results.....	20
6 Discussion and Conclusion	24
7 Documentation and retention of records	26
8 References.....	27
Figures	28
Tables	32
Annexes	66
Appendices.....	80

Summary

The inhalation toxicity of **3,3,3-Trifluoroprop-1-ene** was studied in a sub-acute (28-day) study in Wistar rats. Groups of 10 male and 10 female rats were exposed nose-only to target concentrations of 0 (group 1, control), 500 ppm (group 2), 1,500 ppm (group 3), 5,000 ppm (group 4) or 15,000 ppm (group 5) **3,3,3-Trifluoroprop-1-ene** for 6 hours a day, 5 days a week during a 4-week period, with a total number of 20 exposure days. To study the recovery of effects, two groups of also 10 rats/sex were similarly exposed to 0 and 15,000 ppm. After exposure these animals were kept for a recovery period of 17 days and sacrificed thereafter. To examine the toxicity of the test material, data on clinical observations, body weight gain, food consumption, haematology and clinical chemistry were used. In addition, animals were examined macroscopically at necropsy, organs were weighed, and a selection of organs and tissues (including the complete respiratory tract and nasal passages) was examined microscopically.

The mean actual concentrations (\pm standard deviation) of **3,3,3-Trifluoroprop-1-ene** in the test atmospheres, based on total carbon analysis, were 501 (\pm 3), 1,498 (\pm 11), 4,983 (\pm 25) and 15,013 (\pm 99) ppm for groups 1, 2, 3, 4 and 5 respectively. The total amount of test material used for all groups was 31.8 kg. The amount used for all groups, as calculated from the actual concentration, the duration of the exposure and the flow, was 30.8 kg. This implies a generation efficiency of 103 %.

Daily observation of the animals did not reveal treatment-related clinical abnormalities. One male animal of group 4 was found dead in the morning after urine collection. The probable cause of death was atrial congestion.

Treatment-related differences in body weight gain and food consumption were not seen during the exposure period, however, terminal body weight (after fasting during the night) was significantly decreased in male animals of group 5 and in female animals of groups 2, 4 and 5.

Red blood cells and packed cell volume were slightly, but significantly increased in male and female animals of all exposed groups. Haemoglobin content was also increased, reaching significance in male animals of all exposed groups and in female animals of groups 3 and 5. Prothrombin time was significantly increased in all exposed female groups. These effects were no longer seen at the end of the recovery period.

Lymphocyte count was significantly decreased in male and female animals of groups 4 and 5. Neutrophil count was significantly increased in all exposed male groups and basophil count was significantly decreased in the male animals of group 5. White blood cell count was significantly decreased in the female animals of groups 4 and 5. At the end of the recovery period, these effects were no longer seen, however, the number of eosinophils was significantly increased in male animals of group 5.

Both males and females showed increased ALP (significant for groups 4 and 5), ASAT (significant for all exposed groups), ALAT (significant for all female exposed groups and for males of groups 3, 4 and 5), glucose (significant for all exposed groups) and urea (significant for all exposed female groups and for the male animals of group 5). Males showed increased calcium concentrations (significant for groups 2, 4 and 5). Females showed decreased phospholipid concentrations (significant for groups 3-5),

and changes in electrolyte balance by an increase of the chloride concentration (significant for group 3), an increase in the potassium concentration (significant for all exposed groups), and an increased inorganic phosphorus concentration (significant for group 3).

At the end of the recovery period, only a few significant differences were present. Glucose and total protein were still increased in male animals of group 5 and the albumin-globulin ratio was decreased. Finally, in contrast to the increase at the end of the exposure period, ASAT was decreased in female animals of group 5 at the end of the recovery period.

Urinary volume was decreased in the exposed groups and this reached significance in male groups 3 and 4 and female group 3. As a consequence, urinary creatinine was significantly increased in these groups. Significant differences in urinary volume were not seen at the end of the recovery period. The content of fluoride in urine normalized to creatinine, was clearly and significantly increased in all exposed groups at the end of the exposure period, although a strong relationship with the exposure concentration was absent. At the end of the recovery period, the urinary fluoride concentration was still slightly, but significantly, increased in the exposed animals (group 5).

Relative liver weights were slightly increased with a shallow exposure-effect relationship in all exposed groups. Significance was reached in male animals of groups 2, 4 and 5 and in female animals of groups 3, 4 and 5. Relative heart weights were significantly increased in female animals of groups 2 and 3.

Macroscopic examination at necropsy revealed a high incidence of hydrothorax in the males exposed to 1500 ppm HFO 1243zf. Hydrothorax was also observed in some males exposed to 5000 ppm, a single male exposed to 500 ppm, a single male exposed to 15000 ppm, a single female exposed to 500 ppm and a single female exposed to 1500 ppm. The lesion was only minimal, because the amount of (clear) fluid in the thorax was limited. Another unusual finding was a red or dark area, sometimes elevated, in the wall of the (right) ventricle of the heart. This gross change occurred in a single male exposed to 1500 ppm and in a few females exposed to 500, 1500 and 15000 ppm respectively.

Microscopic examination at the end of the treatment period revealed myocardial vacuolation and focal and multifocal mononuclear cell infiltrate, ascribed to a direct toxic effect on the myocardial fibres and to effects on the blood vasculature, respectively. The former was prominent in the groups exposed to the higher concentrations, while the latter did not show a clear concentration-response. In addition, inflammatory cells were found attached to the endocardium. Hepatocellular microvesicular vacuolation was seen in the liver of the male animals of group 5.

At the end of the recovery period, no exposure-related histopathological changes were observed in the hearts. Changes in the liver were not investigated.

Conclusion

Exposure by inhalation of rats to 3,3,3-Trifluoroprop-1-ene (HFO 1243zf) for 28 days to concentrations ranging from 500 to 15,000 ppm induced adverse effects at all concentrations. The principle target tissue was the myocardium. As a consequence, a no-observed-adverse-effect-level (NOAEL) was not found at the lowest concentration used (500 ppm).

The changes in haematology, clinical chemistry, liver weight and histopathology in the heart were largely reversible after a recovery period of 17 days. Reversibility of the changes in the liver was not investigated.

1 General

1.1 Study sponsor and monitor

Sponsor: Ineos Fluor Limited
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1.2 Test facility

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1.3 Responsible personnel

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Management: Dr. M.A. Bos¹
Scientific contributor: Dr C.F. Kuper¹ (Pathology)
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³ Analytical Research Department

1.4 Time schedule

Arrival of the animals	: 9 September 2009
First exposure of the animals (day 0)	: 22-25 September 2009
Sacrifice of the animals of the main groups	: 20 – 23 October 2009
Sacrifice of the animals of the recovery groups	: 9 November 2009

2 Introduction

2.1 Objective

At the request of Ineos Fluor Limited, a sub-acute (28-day) inhalation toxicity study with 3,3,3-Trifluoroprop-1-ene (HFO 1243zf) was carried out in rats. A 17-day recovery period was included.

2.2 Applicable guidelines

The study was drafted based on the following guidelines:

- OECD Guideline for the Testing of Chemicals 412, sub-acute inhalation toxicity study, adopted 12 May 1981.

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 86/609/EEC) and Dutch legislation (The Experiments on Animals Act, 1997). This includes approval of the study by TNO's ethical review committee (DEC-number 2832).

3 Study plan and deviations

3.1 Study plan

The study was conducted according to study plan P8668, entitled 'Study plan for a sub-acute (28-day) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats' and amendment 01 thereof. The study plan and the amendment 01 were approved by the study director on 4 and 22 September 2009, respectively.

3.2 Deviations

The temperature in the animal room exceeded the maximum of 24°C, on 6 October 2009 when the temperature was 24.6 °C for 10 minutes. The relative humidity exceeded the maximum of 70% on 14 September 2009 and 19 October 2009 when the relative humidity was maximum 82.3% and 99.4% respectively for approximately 30 minutes.

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

4 Materials and Methods

4.1 Test material

The test material was supplied by the sponsor in a cylinder. This cylinder was labeled 'Cylindernr.:315000; INEOS FLUOR LTD; UN 3161, class 2.1; Liquefied gas flammable N.O.S.; 3,3,3-Trifluoropropene; N.W. 49.6 kg; B.W. 82.0 kg'. The cylinder was received in good condition on 11 September 2009 and was stored in a fume hood at ambient temperature. The TNO dispense number was 0900F1.

3,3,3-Trifluoroprop-1-ene is a liquefied gas with the following characteristics (as supplied by the sponsor):

Name	: 3,3,3-Trifluoroprop-1-ene
Other name	: HFO 1243zf
Molecular formula	: $\text{CF}_3\text{CH}=\text{CH}_2$
Molecular weight	: 96
CAS reg no.	: 000677-21-4
Batch number	: 20090810-1
Purity	: 99.995%
Total quantity	: 49.6 kg
Boiling point	: - 25.3 °C
Volatile	: yes
Storage conditions	: ambient temperature (15-25°C)
Expiry date	: 10 August 2012

Any analysis for the identity, quality and purity of the test material, with supporting documentation was the responsibility of the sponsor (see Annex 2).

4.2 Test system

4.2.1 *Animal characterization*

Rats were chosen as a test system, because this animal species is normally used in toxicity studies of this type. Young adult male and female Wistar outbred (CrI:[WI]WU BR) were obtained from a colony maintained under SPF conditions by Charles River, Deutschland, Sulzfeld, Germany.

On 9 September 2009, 75 male and 75 female animals arrived at an age of 6 weeks. They were taken in their unopened shipping containers to animal room 5.2.20, were checked for overt signs of ill health and anomalies, and were kept in quarantine. After approval of the lot (negative titers to micro-organisms tested), quarantine was raised on 11 September 2009 and the animals were moved to animal room 6.0.04, a similar animal room. On 14 September 2009 the animals were moved to a similar animal room, 6.0.08. The rats were uniquely identified by ear tattoo.

On 21 September 2009, 70 male animals and 70 female animals were weighed and assigned to the study groups proportionally to body weight by computer randomization. The body weights at initiation of treatment (day 0) were within $\pm 20\%$

of the mean weight and the average was 254.7 g for males and 176.5 g for females. The duration of the acclimatization period in the animal room was 13 days.

4.2.2 *Identification*

The study was identified with study number 8668. After allocation to the study, each group of rats was coded with a number and color. The individual rats were identified by unique animal identification numbers which were tattooed in their ears (see Annex 3). Each cage was provided with a card showing the study number, color code, group number, cage number and animal identification numbers.

4.3 **Experimental conditions**

4.3.1 *Animal maintenance*

The animals were housed under conventional conditions in macrolon cages with bedding of wood shavings (Lignocel, type 3/4, Rettenmaier, Rosenberg, Germany) and shreds of paper as environmental enrichment (Enviro-dri, Lillico, Betchworth, England). The number of air changes was about 10 per hour. The animals were housed five males or five females to a cage. During exposure the animals had no access to feed or water and were housed individually in the holders.

The temperature in the animal room was generally within the range of 20-24°C, except on 6 October 2009 (temperature was 24.6°C for 10 minutes). The relative humidity was in the 40-70% range, except during short periods associated with wet cleaning activities, and on 14 September 2009 and 19 October 2009 when the relative humidity reached a maximum of 82.3% and 99.4% respectively for approximately 30 minutes. A 12-hour light and 12-hour dark cycle was maintained.

4.3.2 *Feed and drinking water*

Feed and drinking water were provided *ad libitum*, except during exposure. All rats were fed a commercially available rodent diet (Rat & Mouse No. 3 Breeding Diet RM3) from SDS (Special Diet Services, Witham, England). Each batch of diet is analyzed by SDS for nutrients and contaminants. The certificate of analysis pertaining to the batches used (Batch nos. 7264 and 7327) can be found in Annex 4.1. The feed was provided as a powder in stainless steel cans, covered by a perforated stainless steel plate that served to prevent spillage.

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 microbial examination of the drinking water as conducted by the supplier are made available to TNO Quality of Life. In addition, the supplier periodically (twice per year) analyses water samples taken on the premises of TNO in Zeist for a limited number of variables. The results of the analyses of samples obtained on 21 May 2009 are given in Annex 4.2.

4.4 Experimental procedures

4.4.1 Administration of the test material

The test material was administered to the animals by inhalation, because this is the most likely route of human exposure. The control group was exposed to clean air, but otherwise treated in the same manner as the exposed groups.

4.4.2 Number and size of test groups and exposure levels

The study comprised five main test groups of 10 male and 10 female rats each, viz. one control group and four groups exposed to different concentrations of the test material. The study was started on 22 September 2009 with the first exposure of 5 male animals/group (see also Annex 3). The first exposure of the other male animals was on 23 September 2009. Likewise, exposure of the female animals was started on 24 September 2009 with 5 female animals/group and on the next day with the remaining female animals. All animals were exposed during a 28-day period for 6 hours/day, 5 days/week (i.e. 20 exposure days). A staggered start was applied to allow a balanced order of sacrifices. Additionally, a recovery control group and a recovery high concentration group of 10 male and 10 female animals each were exposed similarly and kept for a recovery period of 17 days before sacrifice. Exposure of the latter animals was started on 25 September 2009, together with the last main female group.

The various groups are presented in the tables below:

Group No.	Group description	Colour code	Target concentration in air (ppm)	Number of animals/group (main study)	Number of animals/group (recovery study)
1	Control	White	0	10 ♂ and 10 ♀	10 ♂ and 10 ♀
2	Low	Blue	500	10 ♂ and 10 ♀	
3	Lower mid	Green	1,500	10 ♂ and 10 ♀	
4	Higher mid	Red	5,000	10 ♂ and 10 ♀	
5	High	Yellow	15,000	10 ♂ and 10 ♀	10 ♂ and 10 ♀

4.4.3 Exposure equipment

The animals were exposed to the test atmosphere in nose-only exposure units consisting of a cylindrical column, surrounded by a transparent hood. The test atmosphere was introduced at the bottom of the central column, and was exhausted at the top of a ca. 70 L exposure unit, except for one group (group 5), for which the test atmosphere was introduced at the top and exhausted at the bottom of a ca. 50 L exposure unit. Each column included two or three rodent tube sections of 20 ports each for animal exposure. Several empty ports were used for test atmosphere sampling and measurement of temperature and relative humidity. The animals were secured in plastic animal holders (Battelle), positioned radially through the outer cylinder around the central column. The remaining ports were closed. Only the nose of the rats protruded into the interior of the column. The animals were placed in the exposure unit after stabilization of the test atmosphere.

In our experience, the animal's body does not exactly fit in the animal holder which always results in some leakage from high to low pressure side. By securing a positive pressure in the central column and a slightly negative pressure in the outer cylinder, which encloses the entire animal holder, air leaks from nose to thorax rather than from thorax to nose, and dilution of the test atmosphere is avoided.

Animals were rotated each week with respect to the position in the column, viz. they were moved 5 places each time. The units were illuminated externally by normal laboratory TL-lighting. The air entering the unit was controlled at $22 \pm 2^\circ\text{C}$ and the relative humidity was maintained between 30 and 70%, if possible. Temperature and relative humidity were recorded continuously during exposure.

4.4.4 *Generation of the test atmosphere*

The inhalation equipment was designed to expose the rats to a continuous supply of fresh test atmosphere. To generate the test atmosphere, a mass flow controlled flow (Bronkhorst Hi Tec, Ruurlo, The Netherlands) of evaporated test material was mixed with a mass flow controlled stream of humidified air (Bronkhorst Hi Tec, Ruurlo, The Netherlands). Oxygen was added for group 5 to maintain oxygen content between 20 and 21% (Bronkhorst Hi Tec, Ruurlo, The Netherlands). The exposure unit for the control animals was supplied with a stream of humidified compressed air only.

Mean test atmosphere flows were 47, 25, 25, 25 and 45 L/min for groups 1, 2, 3, 4 and 5, respectively. These flows were checked each morning at the start of the generation, and subsequently at regular intervals during exposure (approximately bi-hourly, i.e. three times a day). The period between the start of the generation and the start of the exposure was about 30 minutes.

4.5 Observations, analyses and measurements

4.5.1 *Actual concentration*

The actual concentration of the test material in the test atmosphere was monitored with a total carbon analyser (for groups 2 and 3: Ratfish RS55T, Munich, Germany; for group 4: Sick Instruments Benelux, Hedel, The Netherlands; and for group 5: Dräger, Lubeck, Germany). The responses of the analysers were recorded on a PC every minute using a CAN transmitter (G.Lufft Mess- und Regeltechnik GmbH, 70719 Fellbach, Germany).

Test atmosphere samples were taken continuously from the exposure unit at the animals' breathing zone and were passed to the total carbon analyser through a sample line. The mean response was calculated by averaging values read every minute.

Prior to the various exposures, the total carbon analysers were calibrated for a particular target concentration by sampling from three concentrations in a range including the target concentration in duplicate. The concentrations were prepared by injecting a known amount of **3,3,3-trifluoroprop-1-ene** into a sample bag containing a mixture of air and oxygen. These calibrations were checked weekly by measuring the concentration from a sample bag close to the target concentration. If the measured concentration from the sample bags deviated more than 5% from the calculated concentration during the study, the total carbon analyzer was calibrated again.

Group 2

On 15 September 2009, sample bags with a concentration of 400, 500, 604, 400, 500 and 604 ppm respectively were used for the low concentration (group 2). The response Y of the analyzer (in % full scale) was linearly related to the concentration X of the test material (in ppm) with a coefficient of determination of 0.9974:

$$Y = 1.168E-1 * X + 2.079E+1$$

On 5 October 2009 the difference between measured and calculated concentration for the low concentration (group 2) was more than 5% (6.2% and 5.8% in duplicate measurements, respectively). Therefore, sample bags with a concentration of 408, 512, 616, 408, 512 and 616 ppm respectively were used for recalibration. The response Y of the analyzer (in % full scale) was linearly related to the concentration X of the test material (in ppm) with a coefficient of determination of 0.9993:

$$Y = 1.407E-1 * X + 3.267$$

Group 3

On 15 September 2009, sample bags with a concentration of 1196, 1500, 1792, 1196, 1500 and 1792 ppm respectively were used for the lower mid concentration (group 3). The response Y of the analyzer (in % full scale) was linearly related to the concentration X of the test material (in ppm) with a coefficient of determination of 0.9994:

$$Y = 1.414E-2 * X + 9.086E-1$$

Group 4

On 15 September 2009, sample bags with a concentration of 3999, 4999, 5997, 3999, 4999 and 5997 ppm respectively were used for the higher mid concentration (group 4). The response Y of the analyzer (in % full scale) was linearly related to the concentration X of the test material (in ppm) with a coefficient of determination of 0.9990:

$$Y = 8.841E-3 * X + 4.613E-2$$

Group 5

On 15 September 2009, sample bags with a concentration of 12020, 14999, 17939, 12020, 14999 and 17939 ppm respectively were used for the high concentration (group 5). The response Y of the analyzer (in % full scale) was linearly related to the concentration X of the test material (in ppm) with a coefficient of determination of 0.9990:

$$Y = 2.289E-3 * X + 3.244E+1$$

On 5 October 2009 the difference between measured and calculated concentration for the high concentration (group 5) was more than 5% (8.3% and 6.3 % in duplicate measurements, respectively). Therefore, sample bags with a concentration of 12057, 14991, 17774, 12057, 14991 and 17774 ppm respectively were used for recalibration. The response Y of the analyzer (in % full scale) was linearly related to the

concentration X of the test material (in ppm) with a coefficient of determination of 0.9995:

$$Y = 2.690E-3 * X + 2.361E+1$$

Since the difference between calculated and measured concentration at the next occasion was again relatively high (4%), the total carbon analyser was replaced on 15 October 2009 by another (Ratfisch RS55, Munich, Germany). This total carbon analyser was calibrated on 14 October 2009, using sample bags with a concentration of 12036, 14985, 17921, 12036, 14985 and 17921 ppm respectively. The response Y of the analyzer (in % full scale) was linearly related to the concentration X of the test material (in ppm) with a coefficient of determination of 0.9996:

$$Y = 4.023E-3 * X + 9.828E-1$$

4.5.2 *Nominal concentration*

The test material usage was determined by dividing the total amount of test material used for all groups (by weighing) by the total volumes of air, oxygen and **3,3,3-trifluoroprop-1-ene** passed through the exposure units.

4.5.3 *Measurement of temperature and relative humidity*

Temperature and relative humidity were continuously monitored and recorded on a PC every minute using a CAN transmitter (G.Luft Mess- und Regeltechnik GmbH, 70719 Fellbach, Germany).

4.5.4 *Clinical observations*

All animals were observed daily in the morning hours by cage-side observations and, if necessary, handled to detect signs of toxicity. A group-wise observation was made halfway through each exposure day. On working days, all cages were checked again in the afternoon, especially for dead or moribund animals. In weekends and on public holidays only one check per day was carried out. All abnormalities, signs of ill health, reaction to treatment and mortality were recorded.

4.5.5 *Body weights*

The body weight of each animal was recorded prior to exposure (day-4, -3, -2 or -1) on 21 September 2009, on the day of first exposure of each subgroup (prior to exposure) and weekly thereafter (prior to exposure). All animals were weighed on the day before overnight fasting and on their scheduled sacrifice date in order to calculate the correct organ to body weight ratios.

4.5.6 *Food consumption*

Food consumption was measured per cage by weighing the feeders. The results were expressed in g per animal per day. The consumption was measured over three 7-day periods, starting on the first day of exposure and followed by a 6-day period for animals of the main groups. For the animals of the recovery groups food consumption was measured likewise over three 7-day periods and one 6-day period followed by two 7-day periods and one 2-day period.

4.5.7 *Haematology*

Haematology was conducted at necropsy the day after the last exposure on all surviving animals of the main groups. Blood samples were taken from the abdominal aorta of

overnight fasted rats at necropsy whilst under pentobarbital anaesthesia. Likewise, haematology was conducted at necropsy at the end of the recovery period on all animals of the recovery groups.

K₂-EDTA was used as anticoagulant. In each sample the following determinations were carried out according to the methods listed in Annex 5:

- haemoglobin
- packed cell volume
- red blood cell count
- reticulocytes
- total white blood cell count
- differential white blood cell count
- prothrombin time
- thrombocyte count

The following parameters were calculated:

- mean corpuscular volume (MCV)
- mean corpuscular haemoglobin (MCH)
- mean corpuscular haemoglobin concentration (MCHC)

Many parameters of the list above were significantly different in animals of the main exposed groups. Therefore, these parameters were also determined in animals of the recovery groups.

4.5.8 *Clinical chemistry*

Clinical chemistry was conducted on all surviving rats at the same time blood samples for haematology were collected (see section 4.5.7). The blood was collected in heparinized plastic tubes and plasma was prepared by centrifugation. The following measurements were made in the plasma according to the methods listed in Annex 6:

- alkaline phosphatase activity (ALP)
- aspartate aminotransferase activity (ASAT)
- alanine aminotransferase activity (ALAT)
- gamma glutamyl transferase activity (GGT)
- total protein
- albumin
- ratio albumin to globulin
- urea
- creatinine
- fasting glucose
- bilirubin total
- cholesterol
- triglycerides
- phospholipids
- calcium (Ca)
- sodium (Na)
- potassium (K)
- chloride (Cl)
- inorganic phosphate

Many parameters of the list above were significantly different in animals of the main exposed groups. Therefore, these parameters were also determined in animals of the recovery groups.

4.5.9 *Fluoride measurements in urine*

On the day before necropsy, all animals of the main groups were deprived of food for 16h (water was available). Urine was collected during these 16 hours and was used for fluoride concentration measurement. Prior to overnight collection of urine samples, the metabolism cages were washed with a solution of nitric acid in deionised water (1:20 v/v dilution), rinsed with deionised water and air dried. The urine separators were treated similarly.

Creatinine content was measured to standardize fluoride concentrations in urine. Thereafter, urine samples were stored (<-18°C) and used for determination of fluoride concentration by a gas chromatographic method (Fresen et al., 1968). Fluoride was bound by an exchange reaction with chloride in trimethylchloro-silane (TMCS) in toluene at low pH (4 N sulfuric acid). The concentration of trimethylfluorosilane was measured by GC-FID (gas chromatographic analysis with a flame ionisation detector).

4.5.10 Pathology

Gross examination

Surviving animals of the main study were killed the day after the last exposure in such a sequence that the average time of killing was approximately the same for each group. Animals of the recovery groups were killed in a similar way at the end of the 17-day observation period.

Animals were killed by exsanguination from the abdominal aorta under pentobarbital anaesthesia and then subjected to a complete macroscopic examination.

The following organs of all surviving animals were weighed (paired organs together) as soon as possible after dissection to avoid drying.

- brain
- adrenals
- heart
- kidneys
- liver
- spleen
- testes
- lungs with trachea and larynx

For histopathological examination, samples of the following tissues and organs of all animals were preserved in a neutral aqueous phosphate-buffered 4 per cent solution of formaldehyde (10% solution of formalin). The lungs (after weighing) were infused with the fixative under ca. 15 cm water pressure to insure fixation.

- brain
- adrenals
- heart
- kidneys
- liver
- spleen
- testes
- complete respiratory tract including nasal passages
- all relevant gross lesions

Slide preparation

Tissues to be examined were embedded in paraffin wax, sectioned at 5 µm and stained with haematoxylin and eosin.

Histopathological examination

All preserved tissues of all animals of the control group and those exposed to 15000 ppm HFO 1243zf in the main study were examined histopathologically (by light microscopy). The nose was examined at 6 levels (Woutersen et al., 1994; Annex 7), the

larynx at 3 levels, the trachea at 3 levels (including the bifurcation), and each lung lobe at 1 level. In addition, the heart, liver and all relevant gross lesions observed in rats of the intermediate concentration groups were examined microscopically. The heart was also examined in the animals of the recovery groups. Although treatment-related changes were observed in the liver in animals exposed to 15000 ppm HFO 1243zf, the examination of this organ was not extended to the animals of the recovery groups.

4.6 Statistical analysis of the results

The statistical analysis of data was carried out using Provantis 6.5 (except the fluoride concentrations in urine, these were carried out using SAS version 8.2 directly) and are described below.

- Body weight data, food consumption data, clinical pathology data measured on continuous or semi-continuous scales, and organ weights: data was analysed using one-way analysis of variance (Anova), after checking for homogeneity of variance (Bartlett test) and normality of data distribution (Shapiro-Wilks test). If variances were not homogeneous or data not normally distributed, the data were stepwise log or rank transformed prior to the Anova. If the Anova yielded a significant effect ($p < 0.05$), intergroup comparisons with the control group were made by Dunnett's multiple comparison test.
- Incidences of histopathological changes: Fisher's exact probability test. It was originally envisaged to evaluate histopathological abnormalities in the heart also with resampling statistics. Resampling methods are useful if the assumed null distribution of the test statistic does not appear satisfactory. However, the Fisher's exact test does provide a generally accepted null distribution. Hence, there is no clear use for an additional test based on resampling.

Arithmetic means and standard errors of the means or standard deviations are given in the reports of continuous and semi-continuous data. Tests were performed as two-sided tests with results taken as significant where the probability of the results is $p < 0.05$ (*) or $p < 0.01$ (**). Because numerous variables are subjected to statistical analysis, the overall false positive rate (Type I errors) is greater than suggested by a probability level of 0.05. Therefore, the final interpretation of results is based not only on statistical analysis but also on other considerations such as dose-response relationships and whether the results are significant in the light of other biological and pathological findings.

5 Results

5.1.1 *Actual concentration*

Mean and actual concentrations are shown in Table 1.1. The mean concentrations (\pm standard deviation) as measured on-line during each exposure, were 501 (\pm 3), 1498 (\pm 11), 4983 (\pm 25) and 15013 (\pm 99) ppm for groups 2, 3, 4 and 5, respectively. These were close to their target concentrations.

5.1.2 *Nominal concentration*

The nominal concentration was calculated from the total amount of test material used (by weighing) and the air flow (Table 1.2). The total amount of test material used for all groups was 31.8 kg. The amount used for all groups, as calculated from the actual concentration, the duration of the exposure and the flow, was 30.8 kg. This implies a generation efficiency of 103 %.

5.1.3 *Temperature and relative humidity during exposure*

Mean temperature (\pm standard deviation) during exposure was 23.0 (\pm 0.3), 22.6 (\pm 0.3), 22.7 (\pm 0.3), 22.6 (\pm 0.4) and 22.7 (\pm 0.3) °C for groups 2, 3, 4 and 5, respectively (Table 1.3). The temperature in the exposure chamber was consistently between 20 and 24 °C, except for one occasion on 16 October 2009 when the temperature maximum was 24.2 °C for 14 minutes in group 1 only.

Mean relative humidity (\pm standard deviation) during exposure was 38 (\pm 2), 37 (\pm 2), 39 (\pm 2), 38 (\pm 2) and 39 (\pm 1) % for groups 2, 3, 4 and 5, respectively (Table 1.4). The relative humidity in the exposure chamber was consistently between 30 and 70%.

5.1.4 *Clinical observations (Table 2; Appendix 1)*

One animal (no. 86, group 4) was found dead in the morning after urine collection before sacrifice. In one female animal (no. 111, recovery group 5) a sparsely haired area was seen on day 28. The latter finding was not considered to be related to the exposure.

5.1.5 *Body weights (Figure 2; Table 3; Appendix 2)*

Body weight of the female animals of group 2 was significantly decreased on day 21. This was considered an isolated finding not related to the exposure, since other significant differences were not seen during the exposure period. However, terminal body weight (after fasting during the night) was significantly decreased in male animals of group 5 and in female animals of groups 2, 4 and 5 (see Tables 9 and 10).

5.1.6 *Food consumption (Table 4; Appendix 3)*

Food consumption was similar among the groups.

5.1.7 *Haematology (Tables 5 and 6; Appendices 4 and 5)*

The concentration of red blood cells and packed cell volume were slightly, but significantly increased in male and female animals of all exposed groups (Table 5.1). Haemoglobin content was also increased and the increase reached significance in male animals of all exposed groups and in female animals of groups 3 and 5. Prothrombin time was significantly increased in all exposed female groups. These effects were no longer seen at the end of the recovery period (Table 5.2).

Total white blood cell count was decreased in group 4 and 5, which was significant for the female animals. This was due to a significant decrease in the number of lymphocytes in male and female animals of groups 4 and 5. The number of neutrophils was significantly increased in all exposed male groups and the number of basophils was significantly decreased in the male animals of group 5. At the end of the recovery period these effects were no longer seen, however the number of eosinophils was significantly increased in male animals of group 5. The relative numbers of the different white blood cells were as expected from the absolute numbers.

5.1.8 *Clinical chemistry (Table 7; Appendix 6)*

Both males and females showed increased ALP (significant for groups 4 and 5), ASAT (significant for all exposed groups), ALAT (significant for all female exposed groups and for males of groups 3, 4 and 5), glucose (significant for all exposed groups) and urea (significant for all exposed female groups and in the male animals of group 5). Males additionally showed increased calcium concentrations (significant for groups 2, 4 and 5). Females additionally showed decreased phospholipid concentrations (significant for groups 3-5), and changes in electrolyte balance by an increase of the chloride concentration (significant for group 3), an increase in the potassium concentration (significant for all exposed groups), and an increased inorganic phosphorus concentration (significant for group 3).

Triglycerides were increased in male animals of group 2 and decreased in female animals of groups 2 and 3. Because of the absence of a concentration-effect relationship these effects were not considered to be related to the exposure. Similarly, the decreased albumin-globulin ratio in male animals of group 2 was not considered to be related to the exposure.

At the end of the recovery period, only a few significant differences were present. Glucose and total protein were still increased in male animals of group 5. In contrast to the increase at the end of the main study, ASAT was decreased in female animals of group 5 at the end of the recovery study.

5.1.9 *Urinalysis (Table 8; Appendix 7)*

Although highly variable, urinary volume appeared to be decreased in the exposed groups and this reached significance in male groups 3 and 4 and female group 3. As a consequence, urinary creatinine was significantly increased in these groups. Significant differences in urinary volume were not seen at the end of the recovery period. The relative concentration of fluoride in urine (relative to the concentration of creatinine in urine) was significantly increased at the end of the exposure period in all exposed groups. The relation with the concentration was, however, rather weak. At the end of the recovery period, the fluoride concentration was still slightly, but significantly, increased.

5.1.10 *Organ weights (Tables 9 and 10; Appendices 8 and 9)*

Relative liver weight was slightly increased with a shallow exposure-effect relationship in all exposed groups. Significance was reached in male animals of groups 2, 4 and 5 and in female animals of groups 3, 4 and 5. Relative heart weights were significantly increased in female animals of groups 2 and 3.

Absolute lung weight and absolute spleen weight were significantly decreased in male animals of group 5, however this was considered to be due to decreased body weight, because relative weight of these organs had not changed. Absolute, but not relative spleen weight was also significantly increased in female animals of groups 2 and 5. This

was also considered to be due to decreased body weights. Relative brain weights were significantly increased in female animals of groups 2, 4 and 5. This was also considered to be due to decreased body weights.

5.1.11 Pathology (Tables 11 and 12; Appendix 10)

Macroscopy

At the end of the treatment period (Table 11.1; Appendix 10.1)

Macroscopic examination at necropsy revealed a high incidence of hydrothorax in the males exposed to either 1500 or 5000 ppm HFO 1243zf, in a single male exposed to 500 ppm, a single male exposed to 15000 ppm, a single female exposed to 500 ppm and a single female exposed to 1500 ppm. The lesion was only minimal, because the amount of (clear) fluid in the thorax was limited. Another unusual finding was a red or dark area, sometimes elevated, in the wall of the (right) ventricle of the heart. This gross change occurred in a single male exposed to 1500 ppm and a few females exposed to 500, 1500 or 5000 ppm, respectively. In the male animal found dead (no. 86, group 4) the atria of the heart were bilaterally enlarged.

The other gross changes were considered to be incidental findings, including the malformed hydrocephale brain in a female of group 4, or to be common, background findings, unrelated to the exposure to the test compound.

At the end of the recovery period (Table 11.2; Appendix 10.2)

Macroscopic examination at necropsy did not reveal distinct treatment-related gross changes. Hydrothorax was observed in one control male and two females exposed to 15000 ppm HFO 1243zf. Other gross changes in the animals exposed to 15000 ppm were flabby walls in the right ventricular of the hearts in two males, and petechiae in the lung in one female, but these changes occurred only incidentally. Unilateral red patches were observed in the thymus at comparable incidences in rats exposed to 15000 ppm and controls.

Microscopy

At the end of the treatment period (Table 12.1; Appendix 10.1)

Microscopic examination revealed treatment-related effects in the heart. These effects consisted mainly of myocardial vacuolation and multifocal mononuclear cell infiltrate. The vacuolation is considered to be related to a direct toxic effect on the myocardial fibres, whereas multifocal mononuclear cell infiltration is considered to be indirectly caused by effects on the blood vasculature. In some animals, either the direct or indirect effect was predominant, in other animals it appeared to be a mixture of both the indirect and direct effects. The myocardial vacuolation (direct effect) was especially prominent at the higher concentrations (males: 15000 ppm; females: 5000 and 15000 ppm). The incidences of the multifocal mononuclear cell infiltrates (indirect effect) did not show a distinct linear concentration-response relationship: it was prominent in males exposed to 1500 ppm, and in females exposed to either 500, 1500 and 15000 ppm HFO 1243zf. In addition, inflammatory cells were found attached to the endocardium in several exposed animals. Although the incidences of this finding did not differ statistically significantly from those of the control groups, it is considered a toxicologically relevant finding because of its unusual character (no background pathology).

The microscopically observed signs of congestion corresponded to the macroscopically observed red/dark ventricular areas.

With the exception of hepatocellular microvesicular vacuolation, all other histopathological changes were considered background pathology and/or they occurred

in only one or two animals. The livers of almost all males exposed to either 5000 or 15000 ppm HFO 1243zf contained microvesicular vacuolation, whereas this lesion was not seen in any of the livers from the control male rats. Six out of 10 control females demonstrated this change, but the degree was slightly more pronounced in the treated females than in the controls. The vacuolation may offer an explanation for the difference in liver weight between males of group 1 (controls) and group 4 (5000 ppm). The incidence of mononuclear cell aggregates was statistically significantly decreased in females of group 5. This was considered to reflect the normal variability in incidences of this background finding.

The cause of death of the animal found dead on day 28 (animal no. 86) was probably related to congestion of the atria of the heart (macroscopically observed as enlarged atria).

At the end of recovery period (Table 12.2; Appendix 10.2)

Microscopic examination of the hearts of control rats and those exposed to 15000 ppm HFO 1243zf at the end of the recovery period did not reveal treatment-related histopathological changes. The incidences of (multifocal) mononuclear cell infiltrates were distributed about equally between the controls and exposed groups. Other lesions were not observed.

6 Discussion and Conclusion

The sub-acute (28-day) inhalation toxicity of **3,3,3-Trifluoroprop-1-ene** (HFO 1243zf) was investigated in rats. Five groups, of 10 animals per sex each, were exposed to 500, 1,500, 5,000 or 15,000 ppm test material or to clean air (control group). Animals were exposed by nose-only inhalation exposure for 6 hours/day on 5 days/week in a 28 day period, resulting in 20 exposure days. Animals were sacrificed on the day after the last exposure day. Additionally, two groups of 10 animals per sex were exposed to 15,000 ppm or to clean air, but kept for a recovery period of 17 days before sacrifice. To examine the toxicity of the test material, data on clinical signs, body weight, food consumption, haematology and clinical chemistry was collected. In addition, a full necropsy was performed, organs were weighed and a selection of organs including the respiratory tract was examined microscopically.

The mean concentrations (\pm standard deviation) were 501 (\pm 3), 1,498 (\pm 11), 4,983 (\pm 25) and 15,013 (\pm 99) ppm for groups 2, 3, 4 and 5, respectively. These were close to their target concentrations. The total amount of test material used for all groups was 30.8 kg. The calculated amount used for all groups was 31.8 kg. This implies a generation efficiency of 103%.

The present study showed treatment-related effects on the heart in male and female animals of all exposed groups. Cardiotoxicity is considered generally to be due to either a direct myocardial effect of the compound or to an indirect effect, namely by vasoactive properties of a compound. Direct cardiotoxicity generally leads to widespread/diffuse vacuolation (degeneration) of the myocardial fibres, together with a minimal (interstitial) inflammatory cell infiltrate. The inflammatory cell component may be underestimated, because it is difficult to appreciate properly. In contrast, indirect toxicity is typically associated with multifocal inflammatory cell infiltrates, with hypereosinophilic or infrequent vacuolated myocytes. Whereas multifocal inflammatory cell infiltrates also occur spontaneously, in relation to aging, direct damage (widespread/diffuse vacuolation) does not. In the present study with **3,3,3-Trifluoroprop-1-ene**, both types of toxicity apparently played a role: multifocal lesions (multifocal mononuclear cell infiltrates with eosinophilic myocytes) were observed, but also widespread/diffuse vacuolation of myocytes (possibly associated with an increased incidence of focal mononuclear cell infiltrate). The direct cardiotoxicity was especially prominent in rats exposed to either 5000 (female rats) or 15000 ppm (male and female rats), whereas the concentration-response relationship of the indirect toxicity was less clear. The indirect cardiotoxicity may be related to the macroscopically observed (minimal) hydrothorax, because of its link with vasoactivity. However, hydrothorax was also observed in one control male of the recovery group, thus its biological and toxicological significance should be put in perspective. At the end of the recovery period, no exposure-related histopathological changes were observed. Because cardiotoxicity was present in all treatment groups including group 2 (500 ppm), the current study does not provide a NOAEL for **3,3,3-Trifluoroprop-1-ene**.

Besides the effects on the heart, other variables were affected in all treatment groups. These included:

- Signs of haemoconcentration (increased concentration, increased haemoglobin and increased packed cell volume) in males and females of all treatment groups.
- Effects on differential white blood cell counts in males of all treatment groups.

- Effects on clinical chemistry variables (ASAT, ALAT, glucose in both sexes; and urea and potassium in females) in all treatment groups.
- Increased relative liver weight in males and/or females of all treatment groups, associated with histopathological alterations in the animals that were examined microscopically (high-concentration group only).

Conclusion

Exposure by inhalation of rats to **3,3,3-Trifluoroprop-1-ene (HFO 1243zf)** for 28 days to concentrations ranging from 500 to 15,000 ppm induced adverse effects at all concentrations. The principle target tissue was the myocardium. As a consequence, a no-observed-adverse-effect-level (NOAEL) was not found at the lowest concentration used (500 ppm).

The changes in haematology, clinical chemistry, liver weight and histopathology in the heart were largely reversible after a recovery period of 17 days. Reversibility of the changes in the liver was not investigated.

7 Documentation and retention of records

The following documents and materials will be retained for 5 years:

- Master copies of the approved study plan and any amendments thereof
- Raw data or true copies of these
- Correspondence
- All other information related to the study
- Tissue specimens and paraffin blocks

At the end of the retention period, the sponsor will be asked whether these documents and materials should be discarded, retained for an additional period, or transferred to the archives of the sponsor.

The master copy of the final report will be retained for at least 15 years.

Unless otherwise agreed, remaining test material will be retained for at least a month and then discarded. Samples of blood and urine and the carcass containing any remaining tissues were discarded after the analysis. Microscopic slides for histopathology will be retained for 15 years and then removed from the archives.

Documents and materials will be retained in the archives of TNO Quality of Life, located in Zeist. The archiving period starts on the cover date of this report.

8 References

Woutersen RA, Garderen-Hoetmer, A van, Slootweg PJ, Feron VJ (1994) *Upper respiratory tract carcinogenesis in experimental animals and in humans*. In: Carcinogenesis, Waalkes MP and Ward JM (eds), Target Organ Toxicology Series, Raven Press, New York, 215-263

Figures

Fig 2.1 – Mean body weight in males

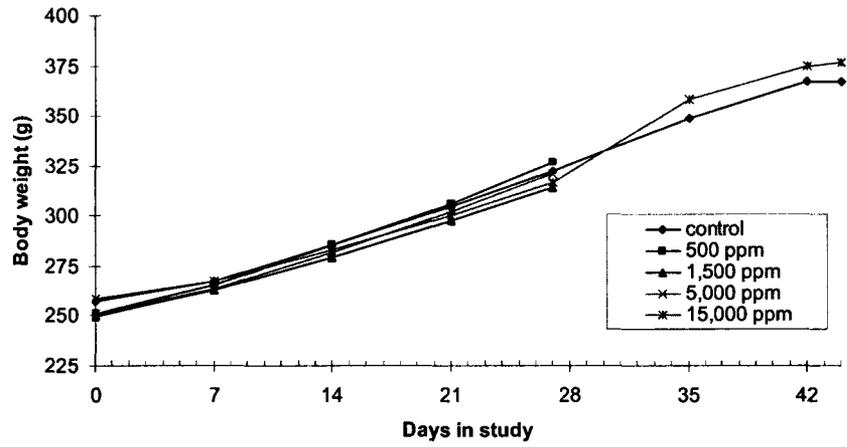
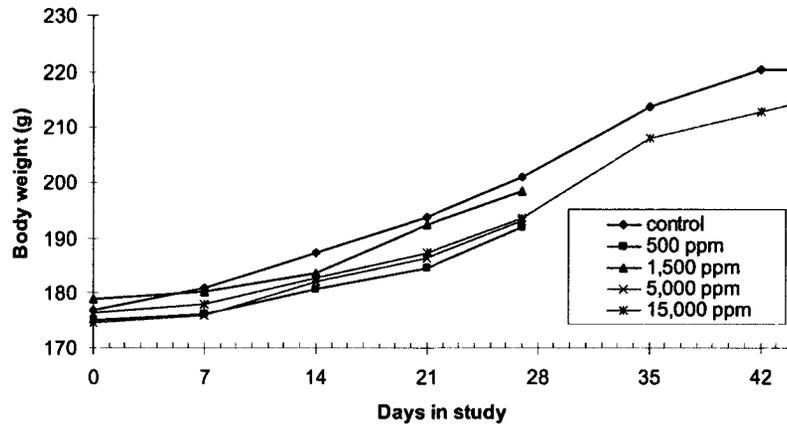


Fig 2.2 – Mean body weight in females



Tables

Table 1.1 Actual concentration of the test material in the exposure chamber during exposure

Date (dd-mm-yyyy)	Group 2 - 500 ppm			Group 3 - 1500 ppm			Group 4 - 5000 ppm			Group 5 - 15000 ppm		
	Average (ppm)	sd	n	Average (ppm)	sd	n	Average (ppm)	sd	n	Average (ppm)	sd	n
22-9-2009	501	4	360	1494	5	360	4983	20	360	14988	77	360
23-9-2009	499	3	360	1503	4	360	4976	23	360	14963	59	360
24-9-2009	503	3	360	1515	16	360	4974	28	360	14887	79	360
25-9-2009	500	4	360	1492	5	360	4952	29	360	14933	96	360
28-9-2009	505	6	360	1503	13	360	4973	21	360	15103	55	360
29-9-2009	503	4	360	1481	6	360	4971	29	360	15084	54	360
30-9-2009	501	2	360	1488	8	360	4999	44	360	14858	109	360
1-10-2009	499	3	360	1491	5	360	4973	43	360	15063	79	360
2-10-2009	496	5	360	1491	7	360	5062	27	360	15005	81	360
5-10-2009	506	4	360	1502	5	360	4958	18	360	15140	67	360
6-10-2009	496	3	360	1487	5	360	4918	24	360	15221	70	360
7-10-2009	502	2	360	1489	4	360	4973	36	360	15052	55	360
8-10-2009	503	1	360	1490	6	360	4971	21	360	14940	85	360
9-10-2009	496	2	360	1487	5	360	5036	23	360	14976	51	360
12-10-2009	504	3	360	1490	5	359	5004	20	359	14937	41	359
13-10-2009	501 ¹	6	354	1520 ¹	4	354	5005 ¹	13	354	15127 ¹	85	354
14-10-2009	503	2	360	1512	6	360	4978	13	360	15087	88	360
15-10-2009	504	3	360	1513	4	360	4993	34	360	15050	184	360
16-10-2009	501	2	360	1507	5	360	4967	15	360	15088	104	360
19-10-2009	502	2	360	1509	4	360	5026	19	360	15034	111	360
20-10-2009	501	2	360	1502	4	360	4994	47	360	14822	68	360
21-10-2009	499	3	360	1502	4	360	4994	23	360	14921	86	360
22-10-2009	499	2	360	1498	4	360	5014	19	360	14955	54	360
Average (ppm)	501			1498			4987			15010		
sd	2.8			10.7			30.0			98.4		
n	23			23			23			23		
target	500			1500			5000			15000		
deviation	0.2%			-0.1%			-0.3%			0.1%		

¹ data acquisition failure from 12:50 - 12:57

Table 1.2 Nominal concentration as calculated from the consumption of test material and the air flow during exposure

Date (dd-mm-yyyy)	vessel weight (kg)		Generation (hh:mm)		Calculated use (g)					Total use (kg)	Measured ¹ use (kg)	Daily efficiency (%)
	start	stop	start	stop	group 2	group 3	group 4	group 5				
22-9-2009	76.0	75.0	8:50	15:05	18.6	55.6	185.4	1003.2		1.263	1.00	126
23-9-2009	75.0	73.5	7:35	14:00	19.1	57.4	190.0	1028.2		1.295	1.50	86
24-9-2009	73.5	73.0	7:31	13:51	19.0	57.1	187.5	1009.7		1.273	0.50	255
25-9-2009	71.5	70.0	7:30	14:07	19.7	58.7	195.0	1058.2		1.332	1.50	89
28-9-2009	70.00	68.50	7:37	14:07	19.5	58.1	192.4	1051.3		1.321	1.50	88
29-9-2009	68.25	66.70	7:48	14:09	19.2	56.3	189.1	1039.5		1.304	1.55	84
30-9-2009	66.65	65.10	7:39	14:03	19.2	57.0	191.7	1032.0		1.300	1.55	84
1-10-2009	65.10	63.40	7:29	14:10	20.0	59.6	199.1	1092.5		1.371	1.70	81
2-10-2009	63.45	61.95	8:23	14:40	18.7	56.1	190.6	1023.2		1.289	1.50	86
5-10-2009	61.90	60.50	7:35	14:15	20.3	59.9	198.1	1095.4		1.374	1.40	98
6-10-2009	60.05	58.55	7:31	14:22	20.4	61.3	202.9	1136.2		1.421	1.50	95
7-10-2009	58.25	56.90	7:43	14:19	20.0	59.1	197.7	1083.9		1.361	1.35	101
8-10-2009	56.85	55.50	7:54	14:27	19.9	58.7	196.1	1067.6		1.342	1.35	99
9-10-2009	55.50	54.15	8:00	14:22	19.1	57.0	193.1	1040.3		1.310	1.35	97
12-10-2009	54.15	52.80	7:40	14:21	20.4	59.9	201.4	1089.2		1.371	1.35	102
13-10-2009	52.45	51.15	7:44	14:15	19.5	59.0	194.9	1059.0		1.332	1.30	102
14-10-2009	50.95	49.45	7:36	14:16	20.0	60.1	198.3	1076.6		1.355	1.50	90
15-10-2009	49.15	47.80	7:50	14:24	19.7	59.2	195.9	1059.1		1.334	1.35	99
16-10-2009	47.80	46.35	7:30	14:20	20.4	61.4	202.8	1104.9		1.390	1.45	96
19-10-2009	46.35	44.95	7:34	14:14	20.0	60.0	200.2	1074.1		1.354	1.40	97
20-10-2009	44.80	43.50	7:47	14:13	19.4	58.1	192.8	1041.8		1.312	1.30	101
21-10-2009	43.50	42.00	7:35	14:30	20.8	62.4	207.3	1127.5		1.418	1.50	95
22-10-2009	42.00	40.60	7:36	14:11	19.8	59.3	198.0	1075.6		1.353	1.40	97
Average efficiency												102
Overall total										30.773	31.800	
Overall efficiency												103

¹ Until 28 September 2009 a balance with a resolution of 0.5 kg was used, therefore daily differences could only be 0.5, 1.0 or 1.5 kg and calculated efficiencies varied widely. Thereafter a balance with a resolution of 0.05 kg was used. In addition, on 2 October a leak was discovered on the reduction valve and sealed. Thereafter efficiency was more consistently close to 100%.

Table 1.3 Daily mean, minimum and maximum temperatures in the test atmosphere during exposure

Date (dd-mm-yyyy)	Group 1 - control			Group 2 - 500 ppm			Group 3 - 1500 ppm			Group 4 - 5000 ppm			Group 5 - 15000 ppm		
	Average (°C)	Min (°C)	Max (°C)	Average (°C)	Min (°C)	Max (°C)	Average (°C)	Min (°C)	Max (°C)	Average (°C)	Min (°C)	Max (°C)	Average (°C)	Min (°C)	Max (°C)
22-9-2009	22.8	22.0	23.2	22.7	22.0	23.1	22.6	21.9	23.2	22.7	21.9	23.2	22.5	21.7	22.9
23-9-2009	22.9	21.5	23.3	22.8	21.6	23.2	22.8	21.6	23.3	23.0	21.5	23.4	22.5	21.4	22.8
24-9-2009	23.0	21.4	23.4	22.9	21.5	23.3	22.9	21.5	23.3	23.2	21.5	23.5	22.7	21.4	23.0
25-9-2009	22.4	21.5	23.2	23.0	21.5	23.3	23.2	21.4	23.6	23.0	21.3	23.7	23.1	21.3	23.5
28-9-2009	23.3	20.9	23.7	22.6	20.8	23.0	22.7	20.8	23.2	23.0	20.7	23.5	22.7	20.6	23.2
29-9-2009	23.2	21.3	23.6	22.6	21.3	22.9	22.6	21.2	22.9	22.6	21.2	22.9	22.8	20.9	23.1
30-9-2009	23.1	21.4	23.4	22.6	21.4	22.9	22.5	21.4	22.9	22.5	21.3	22.8	22.7	20.9	23.1
1-10-2009	23.2	21.4	23.5	22.5	21.3	22.9	22.5	21.3	22.8	22.5	21.3	22.8	22.7	21.0	23.1
2-10-2009	23.4	21.3	23.8	22.6	21.4	23.0	22.6	21.3	22.9	22.6	21.2	23.0	22.6	20.8	23.0
5-10-2009	22.7	20.7	23.1	22.1	20.7	22.5	22.0	20.6	22.3	21.9	20.4	22.3	22.3	20.3	22.7
6-10-2009	22.9	21.0	23.2	22.4	21.1	22.7	22.5	21.0	22.7	22.5	20.9	22.8	22.3	20.6	22.7
7-10-2009	23.3	21.5	23.7	22.6	21.5	23.0	22.8	21.4	23.2	22.9	21.4	23.2	22.7	21.0	23.0
8-10-2009	23.0	21.5	23.3	22.6	21.5	22.7	22.6	21.4	22.9	22.7	21.3	22.9	22.5	21.0	23.0
9-10-2009	23.2	21.4	23.6	22.7	21.3	23.2	22.8	21.1	23.3	22.8	21.1	23.5	22.7	20.9	23.2
12-10-2009	22.7	20.7	23.1	22.1	20.7	22.5	22.2	20.6	22.6	22.2	20.4	22.7	22.3	20.4	22.8
13-10-2009	23.0	21.3	23.2	22.4	21.3	22.7	22.4	21.2	22.7	22.3	21.1	22.7	22.5	20.8	23.0
14-10-2009	23.0	21.4	23.2	22.4	21.5	22.7	22.3	21.3	22.8	22.2	21.1	22.6	22.5	21.0	22.9
15-10-2009	22.8	21.1	23.4	22.3	21.2	22.9	22.3	21.1	23.1	22.0	20.8	22.8	22.2	20.6	22.9
16-10-2009	22.1	21.4	24.2	23.1	22.3	23.7	23.4	22.2	23.8	23.3	22.1	23.7	23.3	21.8	23.7
19-10-2009	22.9	21.4	23.8	22.7	21.4	23.1	22.7	21.3	23.1	22.5	21.1	22.9	22.8	21.0	23.1
20-10-2009	23.2	21.8	23.6	23.0	21.9	23.4	23.1	21.6	23.5	22.9	21.4	23.6	22.8	21.1	23.3
21-10-2009	23.2	21.9	23.6	22.9	22.1	23.3	22.9	21.8	23.3	22.8	21.8	23.3	23.1	21.4	23.5
22-10-2009	23.1	22.2	23.4	22.9	22.2	23.1	22.8	22.1	23.1	22.6	22.0	22.9	23.2	21.5	23.5
Average (°C)	23.0	21.4	23.5	22.6	21.5	23.0	22.7	21.4	23.1	22.6	21.3	23.1	22.7	21.0	23.1
sd	0.30			0.28			0.33			0.36			0.28		
n	23			23			23			23			23		
Minimum (°C)		20.7			20.7			20.6			20.4			20.3	
Maximum (°C)			24.2			23.7		23.8				23.7			23.7

Table 1.4 Daily mean, minimum and maximum relative humidity in the test atmosphere during exposure

Date (dd-mm-yyyy)	Group 1 - control			Group 2 - 500 ppm			Group 3 - 1500 ppm			Group 4 - 5000 ppm			Group 5 - 15000 ppm		
	Average (%)	Min (%)	Max (%)	Average (%)	Min (%)	Max (%)	Average (%)	Min (%)	Max (%)	Average (%)	Min (%)	Max (%)	Average (%)	Min (%)	Max (%)
22-9-2009	34.1	32.0	38.0	33.7	31.0	38.0	35.2	33.5	38.5	33.2	30.5	39.0	35.5	33.5	38.5
23-9-2009	34.4	32.0	41.0	36.4	31.0	44.0	37.5	34.5	45.5	36.4	33.0	44.5	36.6	35.0	42.0
24-9-2009	34.8	32.0	46.0	37.6	32.5	49.5	38.6	35.5	48.5	36.9	32.5	49.0	36.9	34.5	44.0
25-9-2009	39.0	35.0	53.0	37.2	32.5	47.0	39.8	34.5	51.0	38.8	34.5	47.0	38.8	35.5	51.5
28-9-2009	38.7	35.0	59.0	38.9	32.5	49.5	40.8	36.5	50.5	38.8	34.5	50.0	39.7	36.5	52.5
29-9-2009	37.9	35.0	56.5	37.6	33.5	48.0	38.5	35.5	48.5	39.8	36.5	47.0	38.9	36.5	50.5
30-9-2009	40.2	36.5	57.5	37.8	32.5	47.0	39.3	36.5	50.5	39.1	35.5	51.0	39.2	36.5	48.5
1-10-2009	38.6	35.5	56.5	37.4	33.5	45.5	39.3	36.5	47.0	38.8	35.5	48.5	39.3	36.5	49.5
2-10-2009	38.5	35.0	55.5	37.4	34.0	48.0	38.9	36.5	50.0	38.9	35.5	48.5	39.4	36.5	50.5
5-10-2009	38.8	36.0	54.0	38.4	34.5	47.0	40.6	37.5	48.5	40.3	37.0	49.0	40.3	37.5	50.5
6-10-2009	38.7	36.0	58.0	39.0	33.5	51.5	41.6	37.5	50.0	39.3	35.5	52.0	40.5	38.0	50.5
7-10-2009	37.4	33.5	53.0	37.8	32.5	47.0	39.8	35.5	47.0	38.9	34.0	49.5	39.0	36.5	50.5
8-10-2009	38.8	35.5	57.5	38.8	33.5	47.0	40.7	37.5	48.5	38.9	35.5	49.0	39.5	37.5	51.5
9-10-2009	43.0	36.0	65.0	39.1	32.5	49.5	40.8	37.5	50.5	37.7	32.5	50.0	39.1	36.5	52.0
12-10-2009	40.4	36.5	58.0	40.5	34.5	49.5	42.5	38.5	53.0	40.3	35.5	53.0	40.5	37.5	50.5
13-10-2009	38.6	35.5	54.0	38.7	35.0	48.0	40.5	37.5	49.0	39.9	37.0	47.0	40.8	38.0	50.5
14-10-2009	38.2	35.5	53.0	38.6	33.5	45.5	41.1	38.5	48.5	39.7	34.5	47.0	40.3	36.5	49.5
15-10-2009	39.6	36.5	54.0	38.8	34.5	47.0	40.6	37.5	48.5	40.6	37.5	47.0	41.1	38.0	51.5
16-10-2009	40.5	33.5	56.0	36.7	33.5	45.0	36.9	34.0	47.0	36.7	34.0	44.5	38.2	36.5	46.0
19-10-2009	38.6	35.0	55.0	38.0	33.5	46.0	39.6	36.5	47.0	39.7	36.5	46.0	39.9	37.5	48.5
20-10-2009	37.2	35.0	56.0	35.7	32.5	48.0	38.9	35.5	47.0	37.2	34.5	48.5	39.1	37.0	49.5
21-10-2009	37.3	32.5	54.0	35.0	32.5	39.0	35.8	33.5	41.5	34.9	31.0	41.0	37.5	35.5	48.5
22-10-2009	36.5	32.5	52.0	33.0	30.5	38.0	35.2	33.0	39.0	33.0	30.5	39.0	36.8	35.0	45.0
Average (%)	38.3	34.7	54.0	37.5	33.0	46.3	39.2	36.1	47.6	38.2	34.5	47.3	39.0	36.5	48.8
sd	2.03			1.78			1.99			2.13			1.47		
n	23			23			23			23			23		
Minimum (%)		32.0			30.5			33.0			30.5			33.5	
Maximum (%)			65.0			51.5			53.0			53.0			52.5

Table 2 Summary of clinical observations

	Day numbers relative to Start Date				
	Group 1 control	Group 2 500 ppm	Group 3 1 500 ppm	Group 4 5 000 ppm	Group 5 15 000 ppm
MALES					
DEAD Found dead	.	.	.	1	.
Number of Observations	.	.	.	1	.
Number of Animals	.	.	.	28	.
Day
DEAD Killed scheduled	20	10	10	9	20
Number of Observations	20	10	10	9	20
Number of Animals	28	28	28	28	28
Days from - to	45	28	28	28	45
FEMALES					
DEAD Killed scheduled	20	10	10	10	20
Number of Observations	20	10	10	10	20
Number of Animals	28	28	28	28	28
Days from - to	45	28	28	28	45
SKIN Sparsely haired area(s)	1
Number of Observations	1
Number of Animals	28
Days from - to	28

Table 3 Mean body weights (g)

Group Sex	Day numbers relative to Start Date											
	-4 ¹	-2 ¹	-1 ¹	0	7	14	21	27	35	42	44	
1m	Mean S.D. N	236.00 9.48 10	231.40 4.85 5	236.62 11.71 5	257.16 12.03 20	267.14 10.78 20	285.55 12.72 20	304.69 16.14 20	322.43 17.20 20	349.14 15.61 10	366.90 18.36 10	367.33 17.83 10
2m	Mean S.D. N	236.10 9.94 5	236.10 9.94 5	236.42 8.12 5	251.12 9.95 10	265.45 9.46 10	285.54 11.54 10	305.92 13.27 10	326.58 12.19 10	349.14 15.61 10	366.90 18.36 10	367.33 17.83 10
3m	Mean S.D. N	234.60 7.17 5	234.60 7.17 5	238.70 7.57 5	249.92 8.56 10	262.62 14.68 10	279.35 20.42 10	297.50 25.64 10	314.22 27.75 10	349.14 15.61 10	366.90 18.36 10	367.33 17.83 10
4m	Mean S.D. N	237.36 10.97 5	237.36 10.97 5	238.02 7.90 5	251.13 10.79 10	263.67 12.00 10	281.55 12.71 10	302.29 14.05 10	320.91 14.38 10	349.14 15.61 10	366.90 18.36 10	367.33 17.83 10
5m	Mean S.D. N	236.23 8.56 10	236.54 6.35 5	234.80 12.58 5	258.29 13.36 20	267.49 13.96 20	283.38 16.69 20	299.90 18.52 20	316.66 20.44 20	358.04 14.07 10	374.94 15.34 10	376.73 17.78 10

¹ Body weights were recorded prior to exposure (day-4, day-2 and day-1 which were on the same calendar day), on the day of exposure (day 0, i.e. 22 September 2009 for the first five male animals of each group, 23 September for the second five male animals of each group and 25 September for the male animals of the recovery groups), and weekly thereafter.

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 3 Mean body weights (g)

Group Sex	Day numbers relative to Start Date										
	-4	-3	0	7	14	21	27	35	42	44	
1f	Mean S.D. N	164.48 8.61 15	163.00 6.19 5	176.91 8.62 20	180.94 10.12 20	187.30 10.87 20	193.90 11.39 20	200.86 13.03 20	213.66 13.85 10	220.41 13.31 10	220.47 13.60 10
2f	Mean S.D. N	160.08 6.35 5	164.76 8.86 5	175.15 9.20 10	176.26 9.13 10	180.77 8.51 10	184.75* 9.57 10	192.06 11.48 10	.	.	.
3f	Mean S.D. N	164.84 6.53 5	164.24 7.85 5	178.98 7.88 10	180.20 5.55 10	183.81 5.25 10	192.44 5.35 10	198.51 4.84 10	.	.	.
4f	Mean S.D. N	163.84 4.20 5	161.16 9.34 5	174.58 7.62 10	176.06 8.16 10	182.18 6.72 10	186.52 6.24 10	193.11 6.58 10	.	.	.
5f	Mean S.D. N	164.39 7.97 15	161.96 8.17 5	176.42 8.97 20	178.08 8.55 20	182.75 9.36 20	187.45 9.10 20	193.49 10.69 20	207.92 8.22 10	212.82 7.90 10	214.21 9.28 10

* Body weights were recorded prior to exposure (day-4 and day-3 which were on the same calendar day), on the day of exposure (day 0, i.e. 24 September 2009 for the first five female animals of each group and 25 September for the second five female animals of each group and the female animals of the recovery groups), and weekly thereafter.

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 4 Mean food consumption (g/rat/day)

Group Sex	Day numbers relative to Start Date									
	0 7	7 14	14 21	21 27	28 35	35 42	42 44	42 44	42 44	42 44
1m	Mean 18.05	18.30	19.55	20.55	21.30	21.00	21.70	21.00	21.00	21.70
	S.D. 0.29	0.84	0.83	0.79	0.42	0.42	1.13	0.42	0.42	1.13
	N 4	4	4	4	2	2	2	2	2	2
2m	Mean 18.90	19.00	20.10	20.80
	S.D. 0.28	0.28	0.57	0.28
	N 2	2	2	2	0	0	0	0	0	0
3m	Mean 18.30	18.00	18.85	19.40
	S.D. 0.42	0.42	0.07	0.28
	N 2	2	2	2	0	0	0	0	0	0
4m	Mean 18.35	18.75	19.80	20.75
	S.D. 0.92	0.64	0.57	0.35
	N 2	2	2	2	0	0	0	0	0	0
5m	Mean 18.35	18.03	18.83	19.68	22.10	21.80	22.90	21.80	21.80	22.90
	S.D. 0.64	0.67	0.93	0.92	1.56	1.27	1.84	1.27	1.27	1.84
	N 4	4	4	4	2	2	2	2	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Food consumption was measured per cage (5 animals/cage) over successive periods of 7 days (6 or 2 days in the week prior to necropsy) and expressed as g/rat/day

Table 4 Mean food consumption (g/rat/day)

Group From: Sex To:	Day numbers relative to Start Date											
	0	7	14	14	21	21	28	28	35	35	42	42
1f	Mean	12.63	12.80	13.05	13.38	13.38	14.50	14.50	13.95	13.95	14.15	14.15
	S.D.	0.43	0.42	0.13	0.28	0.28	0.42	0.42	0.21	0.21	0.07	0.07
	N	4	4	4	4	4	2	2	2	2	2	2
2f	Mean	12.05	12.15	12.40	12.75	12.75
	S.D.	0.07	0.07	0.42	0.35	0.35
	N	2	2	2	2	2	0	0	0	0	0	0
3f	Mean	12.30	12.55	13.55	13.25	13.25
	S.D.	0.14	0.35	1.06	0.21	0.21
	N	2	2	2	2	2	0	0	0	0	0	0
4f	Mean	12.25	12.50	12.60	13.05	13.05
	S.D.	0.64	0.57	0.00	0.21	0.21
	N	2	2	2	2	2	0	0	0	0	0	0
5f	Mean	11.95	12.18	12.38	12.75	13.85	13.85	13.55	13.55	13.80	13.80	13.80
	S.D.	0.39	0.54	0.53	0.53	0.07	0.07	0.21	0.21	0.14	0.14	0.14
	N	4	4	4	4	2	2	2	2	2	2	2

Statistical Analysis (Dunnett's): * = p < 0.05; ** = p < 0.01

Food consumption was measured per cage (5 animals/cage) over successive periods of 7 days (6 or 2 days in the week prior to necropsy) and expressed as g/rat/day

Table 5.1 Mean haematology results: red blood cell and coagulation parameters (Main groups)

Group Sex	RBC 10E12/L	Hb mmol/L	PCV L/L	MCV fL	MCH fmol	MCHC mmol/L	Reticulo cytes %	Thrombo cytes 10E9/L	Prothrom Time s
1m	Mean S.D. N	9.34 0.28 10	0.4464 0.0121 10	52.97 1.47 10	1.107 0.028 10	20.92 0.34 10	1.314 0.203 10	938.8 62.6 10	43.54 9.67 10
2m	Mean S.D. N	9.93** 0.28 10	0.4743** 0.0132 10	52.94 1.67 10	1.107 0.039 10	20.94 0.26 10	1.250 0.313 10	918.4 83.1 10	40.02 4.52 10
3m	Mean S.D. N	9.056** 0.352 10	0.4719** 0.0186 10	52.13 1.28 10	1.091 0.032 10	20.93 0.47 10	1.088 0.332 10	901.7 84.2 10	40.40 5.03 10
4m	Mean S.D. N	9.088** 0.397 9	0.4802** 0.0215 9	52.88 1.58 9	1.107 0.028 9	20.89 0.35 9	1.160 0.262 9	906.4 78.9 9	38.86 4.39 9
5m	Mean S.D. N	9.464** 0.328 10	0.4960** 0.0179 10	52.42 1.04 10	1.089 0.026 10	20.75 0.44 10	1.023 0.272 10	864.6 74.2 10	40.89 5.52 10
1f	Mean S.D. N	8.407 0.397 10	0.4408 0.0165 10	52.46 0.97 10	1.093 0.029 10	20.86 0.29 10	1.105 0.333 10	927.8 85.2 10	31.33 2.03 10
2f	Mean S.D. N	8.987** 0.198 10	0.4602* 0.0177 10	51.20 1.13 10	1.058 0.026 10	20.62 0.29 10	0.882 0.275 10	914.5 85.1 10	35.89** 2.70 10
3f	Mean S.D. N	8.968** 0.286 10	0.4648** 0.0120 10	51.85 1.31 10	1.070 0.032 10	20.65 0.39 10	1.009 0.272 10	984.9 108.4 10	36.23** 2.15 10
4f	Mean S.D. N	8.877** 0.244 10	0.4612* 0.0179 10	51.96 1.30 10	1.079 0.029 10	20.77 0.29 10	1.035 0.259 10	923.3 91.7 10	38.11** 2.80 10
5f	Mean S.D. N	8.959** 0.230 10	0.4680** 0.0087 10	52.26 1.29 10	1.083 0.032 10	20.70 0.28 10	0.947 0.240 10	945.9 54.8 10	39.16** 3.88 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 5.2 Mean haematology results: red blood cell and coagulation parameters (Recovery groups)

Group Sex	RBC 10E12/L	Hb mmol/L	PCV L/L	MCV fL	MCH fmol	MCHC mmol/L	Reticulo cytes %	Thrombo cytes 10E9/L	Prothrom Time s
1m	Mean S.D. N	9.18 0.22 10	0.4387 0.0115 10	50.51 1.46 10	1.057 0.037 10	20.94 0.38 10	1.967 0.189 10	1034.4 36.2 10	41.81 5.88 10
5m	Mean S.D. N	9.14 0.25 10	0.4395 0.0129 10	50.15 1.08 10	1.042 0.024 10	20.79 0.26 10	1.864 0.250 10	1044.6 82.3 10	42.58 5.55 10
1f	Mean S.D. N	8.411 0.198 10	0.4328 0.0102 10	51.45 1.08 10	1.083 0.025 10	21.02 0.31 10	1.577 0.287 10	935.7 76.1 10	28.24 1.32 10
5f	Mean S.D. N	8.461 0.185 10	0.4325 0.0132 10	51.10 1.12 10	1.072 0.027 10	20.95 0.31 10	1.610 0.316 10	965.1 53.9 10	28.18 1.84 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 6.1 Mean haematology results: total and differential white blood cell counts (absolute and relative numbers) (Main groups)

Group Sex	Mean	S.D.	N	WBC 10E9/L	Lympho Absolute 10E9/L	Neutro Absolute 10E9/L	Eosino Absolute 10E9/L	Baso Absolute 10E9/L	Mono Absolute 10E9/L
1m	6.77	1.03	10	6.05	0.50	0.063	0.037	0.111	
				0.94	0.09	0.016	0.013	0.028	
2m	5.67	1.64	10	4.72	0.75*	0.038	0.022	0.157	
				1.55	0.26	0.021	0.011	0.058	
3m	5.96	1.76	10	4.61	1.10**	0.047	0.033	0.153	
				1.62	0.34	0.026	0.018	0.055	
4m	5.47	1.53	9	4.40*	0.83**	0.036	0.027	0.164	
				1.45	0.17	0.026	0.015	0.071	
5m	5.14	0.99	10	4.08**	0.80*	0.038	0.020*	0.178	
				0.86	0.31	0.021	0.011	0.055	
1f	5.15	0.86	10	4.71	0.31	0.046	0.022	0.065	
				0.89	0.11	0.025	0.006	0.022	
2f	3.98	1.74	10	3.52	0.30	0.041	0.017	0.086	
				1.58	0.19	0.019	0.012	0.044	
3f	4.21	1.19	10	3.79	0.28	0.033	0.017	0.068	
				1.16	0.11	0.026	0.008	0.029	
4f	3.46**	1.79	10	2.92**	0.39	0.035	0.017	0.100	
				1.62	0.41	0.020	0.013	0.057	
5f	3.65*	0.83	10	3.08*	0.41	0.036	0.016	0.102	
				0.83	0.26	0.014	0.008	0.038	

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 6.1 Mean haematology results: total and differential white blood cell counts (absolute and relative numbers) (Main groups)

Group Sex		Lympho cytes %	Neutro phils %	Eosino phils %	Baso phils %	Mono cytes %
1m	Mean	89.45	7.43	0.93	0.54	1.65
	S.D.	1.16	0.97	0.19	0.14	0.35
	N	10	10	10	10	10
2m	Mean	82.52**	13.67**	0.65	0.36*	2.79**
	S.D.	5.10	4.73	0.33	0.10	0.92
	N	10	10	10	10	10
3m	Mean	76.51**	19.67**	0.74	0.52	2.58*
	S.D.	6.87	7.37	0.36	0.18	0.69
	N	10	10	10	10	10
4m	Mean	79.56**	16.38**	0.58	0.47	3.02**
	S.D.	5.46	5.70	0.33	0.10	1.00
	N	9	9	9	9	9
5m	Mean	79.52**	15.85**	0.71	0.40	3.51**
	S.D.	4.40	4.91	0.34	0.14	1.17
	N	10	10	10	10	10
1f	Mean	91.33	6.08	0.89	0.42	1.28
	S.D.	2.89	2.66	0.39	0.06	0.35
	N	10	10	10	10	10
2f	Mean	88.49	7.92	1.06	0.39	2.15*
	S.D.	3.33	3.07	0.30	0.17	0.76
	N	10	10	10	10	10
3f	Mean	89.88	7.24	0.81	0.39	1.66
	S.D.	4.12	3.19	0.59	0.12	0.89
	N	10	10	10	10	10
4f	Mean	84.63**	11.04*	1.05	0.44	2.90**
	S.D.	7.48	7.10	0.49	0.16	1.22
	N	10	10	10	10	10
5f	Mean	84.01**	11.63*	1.08	0.40	2.86**
	S.D.	7.06	6.56	0.47	0.13	0.95
	N	10	10	10	10	10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 6.2 Mean haematology results: total and differential white blood cell counts (absolute and relative numbers)
 (Recovery groups)

Group Sex	WBC		Lympho		Neutro		Eosino		Baso		Mono	
	10E9/L	Absolute 10E9/L	10E9/L	Absolute 10E9/L	10E9/L	Absolute 10E9/L	10E9/L	Absolute 10E9/L	10E9/L	Absolute 10E9/L	10E9/L	Absolute 10E9/L
1m	Mean S.D. N	7.20 1.20 10	6.21 1.13 10	0.79 0.33 10	0.067 0.013 10	0.026 0.007 10	0.127 0.039 10					
5m	Mean S.D. N	7.21 0.92 10	6.33 0.93 10	0.63 0.16 10	0.079* 0.012 10	0.025 0.008 10	0.139 0.053 10					
1f	Mean S.D. N	5.02 0.88 10	4.33 0.71 10	0.56 0.22 10	0.046 0.016 10	0.013 0.007 10	0.068 0.034 10					
5f	Mean S.D. N	5.34 1.21 10	4.75 1.06 10	0.46 0.16 10	0.044 0.021 10	0.014 0.007 10	0.072 0.027 10					

Statistics: One-way Analysis of Variance/ Dunnett's test; * p < 0.05; ** p < 0.01

Table 6.2 Mean haematology results: total and differential white blood cell counts (absolute and relative numbers)
 (Recovery groups)

Group Sex	Lympho cytes %	Neutro phils %	Eosino phils %	Baso phils %	Mono cytes %
1m	Mean 86.11	10.85	0.93	0.36	1.74
	S.D. 4.68	4.18	0.21	0.07	0.38
	N 10	10	10	10	10
5m	Mean 87.75	8.92	1.11*	0.34	1.90
	S.D. 2.55	2.49	0.10	0.07	0.55
	N 10	10	10	10	10
1f	Mean 86.41	11.13	0.91	0.25	1.31
	S.D. 3.30	2.89	0.25	0.08	0.55
	N 10	10	10	10	10
5f	Mean 89.26*	8.37*	0.79	0.25	1.34
	S.D. 2.03	1.98	0.31	0.07	0.38
	N 10	10	10	10	10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 7.1 Mean clinical chemistry results (Main groups)

Group Sex	ALP U/L	ASAT U/L	ALAT U/L	GGT U/L	Bilirub Total umol/L	Total Protein g/L	Albumin g/L	Albumin/ Globulin	Glucose Plasma mmol/L
1m	Mean 126.0 S.D. 26.2 N 10	Mean 63.0 S.D. 6.3 N 10	Mean 28.0 S.D. 5.1 N 10	Mean 0.57 S.D. 0.55 N 10	Mean 1.94 S.D. 0.11 N 10	Mean 56.3 S.D. 1.3 N 10	Mean 29.3 S.D. 0.8 N 10	Mean 1.085 S.D. 0.026 N 10	Mean 5.694 S.D. 0.716 N 10
2m	Mean 129.8 S.D. 10.1 N 10	Mean 156.7** S.D. 44.8 N 10	Mean 35.5 S.D. 6.5 N 10	Mean 0.31 S.D. 0.55 N 10	Mean 1.93 S.D. 0.23 N 10	Mean 57.8 S.D. 1.5 N 10	Mean 29.3 S.D. 0.7 N 10	Mean 1.029** S.D. 0.034 N 10	Mean 7.765* S.D. 1.547 N 10
3m	Mean 134.7 S.D. 15.0 N 10	Mean 226.7** S.D. 44.4 N 10	Mean 43.1** S.D. 9.2 N 10	Mean 0.50 S.D. 0.61 N 10	Mean 2.24 S.D. 0.42 N 10	Mean 57.3 S.D. 1.8 N 10	Mean 29.6 S.D. 0.7 N 10	Mean 1.071 S.D. 0.052 N 10	Mean 7.887* S.D. 2.046 N 10
4m	Mean 162.1** S.D. 21.0 N 9	Mean 222.2** S.D. 48.1 N 9	Mean 43.7** S.D. 10.4 N 9	Mean 0.21 S.D. 0.26 N 9	Mean 2.01 S.D. 0.21 N 9	Mean 58.3 S.D. 2.3 N 9	Mean 30.2 S.D. 1.4 N 9	Mean 1.076 S.D. 0.037 N 9	Mean 9.096** S.D. 1.741 N 9
5m	Mean 153.7* S.D. 23.6 N 10	Mean 229.5** S.D. 49.8 N 10	Mean 51.5** S.D. 7.3 N 10	Mean 0.48 S.D. 0.56 N 10	Mean 2.19* S.D. 0.19 N 10	Mean 58.9* S.D. 2.2 N 10	Mean 30.7* S.D. 1.4 N 10	Mean 1.090 S.D. 0.039 N 10	Mean 8.560** S.D. 1.608 N 10
1f	Mean 87.0 S.D. 13.1 N 10	Mean 65.6 S.D. 6.9 N 10	Mean 24.6 S.D. 3.7 N 10	Mean 0.38 S.D. 0.53 N 10	Mean 2.03 S.D. 0.29 N 10	Mean 55.6 S.D. 2.2 N 10	Mean 30.8 S.D. 1.0 N 10	Mean 1.243 S.D. 0.037 N 10	Mean 5.604 S.D. 0.791 N 10
2f	Mean 102.6 S.D. 23.5 N 10	Mean 136.6** S.D. 34.0 N 10	Mean 34.3** S.D. 5.2 N 10	Mean 0.47 S.D. 0.56 N 10	Mean 1.89 S.D. 0.27 N 10	Mean 56.1 S.D. 1.4 N 10	Mean 31.5 S.D. 0.8 N 10	Mean 1.282 S.D. 0.063 N 10	Mean 7.411** S.D. 1.515 N 10
3f	Mean 105.6 S.D. 18.9 N 10	Mean 160.9** S.D. 61.4 N 10	Mean 33.8** S.D. 7.2 N 10	Mean 0.40 S.D. 0.52 N 10	Mean 1.84 S.D. 0.12 N 10	Mean 54.8 S.D. 1.9 N 10	Mean 30.4 S.D. 1.1 N 10	Mean 1.246 S.D. 0.044 N 10	Mean 7.592** S.D. 1.399 N 10
4f	Mean 110.6* S.D. 26.7 N 10	Mean 190.1** S.D. 55.2 N 10	Mean 42.3** S.D. 9.8 N 10	Mean 0.44 S.D. 0.61 N 10	Mean 1.86 S.D. 0.24 N 10	Mean 55.8 S.D. 2.2 N 10	Mean 31.1 S.D. 1.4 N 10	Mean 1.262 S.D. 0.074 N 10	Mean 8.259** S.D. 1.394 N 10
5f	Mean 112.8* S.D. 12.1 N 10	Mean 269.6** S.D. 85.7 N 10	Mean 53.3** S.D. 15.7 N 10	Mean 0.45 S.D. 0.48 N 10	Mean 2.00 S.D. 0.23 N 10	Mean 56.2 S.D. 2.5 N 10	Mean 31.2 S.D. 1.1 N 10	Mean 1.250 S.D. 0.056 N 10	Mean 8.163** S.D. 0.846 N 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 7.1 Mean clinical chemistry results (Main groups)

Group Sex	Mean	S.D.	N	Cholest erol mmol/L	Phospho lipids mmol/L	Triglyc erides mmol/L	Creatin ine umol/L	Urea mmol/L	PO4 mmol/L	Ca mmol/L	Cl mmol/L	K mmol/L	Na mmol/L
1m	1.668	0.222	10	1.348	0.155	0.406	29.3	7.34	2.327	2.571	105.1	4.08	144.0
				0.110	0.110	0.110	3.2	0.70	0.118	0.046	1.0	0.20	0.9
				10	10	10	10	10	10	10	10	10	10
2m	1.831	0.156	10	1.529	0.125	0.673*	27.3	7.66	2.346	2.638*	103.8	4.20	143.8
				0.344	0.344	0.344	4.2	0.49	0.176	0.054	1.5	0.35	1.5
				10	10	10	10	10	10	10	10	10	10
3m	1.610	0.213	10	1.380	0.133	0.543	27.5	7.99	2.460	2.613	104.8	4.32	144.5
				0.149	0.143	0.143	2.5	1.06	0.134	0.047	1.1	0.40	1.4
				10	10	10	10	10	10	10	10	10	10
4m	1.682	0.348	9	1.421	0.222	0.569	26.2	8.57	2.402	2.648**	104.7	4.07	143.7
				0.181	0.181	0.181	3.3	1.61	0.199	0.055	1.5	0.37	1.2
				9	9	9	9	9	9	9	9	9	9
5m	1.479	0.227	10	1.323	0.149	0.484	27.9	9.24**	2.521	2.638*	104.9	4.26	144.1
				0.173	0.173	0.173	2.2	1.71	0.236	0.043	1.6	0.29	1.4
				10	10	10	10	10	10	10	10	10	10
1f	1.750	0.363	10	1.574	0.245	0.351	36.1	7.22	2.043	2.548	107.7	4.06	143.6
				0.092	0.092	0.092	3.8	1.07	0.258	0.052	1.6	0.38	1.8
				10	10	10	10	10	10	10	10	10	10
2f	1.454	0.415	10	1.336	0.298	0.276*	38.4	10.26**	2.207	2.559	107.8	4.83**	143.6
				0.049	0.049	0.049	7.4	1.57	0.244	0.065	1.3	0.35	1.3
				10	10	10	10	10	10	10	10	10	10
3f	1.403	0.387	10	1.272*	0.261	0.262**	37.0	10.98**	2.367*	2.549	109.1*	4.95**	144.0
				0.065	0.065	0.065	8.4	1.87	0.157	0.049	0.9	0.37	1.2
				10	10	10	10	10	10	10	10	10	10
4f	1.359	0.254	10	1.274*	0.190	0.301	37.7	12.30**	2.212	2.532	109.0	4.83**	143.5
				0.054	0.054	0.054	4.5	2.15	0.287	0.052	1.1	0.50	0.8
				10	10	10	10	10	10	10	10	10	10
5f	1.361	0.309	10	1.244*	0.217	0.296	37.7	11.91**	2.289	2.532	108.8	4.73**	143.2
				0.043	0.043	0.043	4.2	1.91	0.206	0.053	0.8	0.26	1.8
				10	10	10	10	10	10	10	10	10	10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 7.2 Mean clinical chemistry results (Recovery groups)

Group Sex	ALP U/L	ASAT U/L	ALAT U/L	GGT U/L	Bilirub Total umol/L	Total Protein g/L	Albumin g/L	Albumin/ Globulin	Glucose Plasma mmol/L
1m	Mean S.D. N	60.2 4.9 10	29.6 4.9 10	0.94 0.72 10	1.93 0.13 10	57.5 1.0 10	30.0 0.8 10	1.092 0.058 10	7.009 0.707 10
5m	Mean S.D. N	111.3 11.7 10	58.4 5.7 10	31.4 5.8 10	0.86 0.61 10	59.1** 1.4 10	30.2 0.6 10	1.044* 0.035 10	7.798* 0.796 10
1f	Mean S.D. N	80.4 10.2 10	62.2 5.7 10	23.3 3.4 10	1.13 0.80 10	58.1 1.9 10	31.8 1.0 10	1.210 0.029 10	6.023 0.804 10
5f	Mean S.D. N	76.0 15.0 10	53.7** 2.6 10	22.1 3.5 10	2.44 0.31 10	58.5 1.4 10	32.2 0.9 10	1.225 0.041 10	6.295 1.012 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 7.2 Mean clinical chemistry results (Recovery groups)

Group Sex	Cholest erol mmol/L	Phospho lipids mmol/L	Triglyc erides mmol/L	Creatin ine umol/L	Urea mmol/L	PO4 mmol/L	Ca mmol/L	Cl mmol/L	K mmol/L	Na mmol/L	
1m	Mean S.D. N	1.377 0.098 10	0.563 0.095 10	32.7 5.1 10	6.96 1.31 10	1.934 0.093 10	2.470 0.043 10	104.1 1.6 10	4.12 0.35 10	143.0 1.1 10	
5m	Mean S.D. N	1.672 0.196 10	1.432 0.139 10	33.2 3.9 10	6.88 0.67 10	1.922 0.133 10	2.500 0.044 10	105.0 0.9 10	4.07 0.22 10	142.5 1.3 10	
1f	Mean S.D. N	1.823 0.188 10	1.707 0.155 10	0.317 0.043 10	37.6 5.1 10	7.29 0.85 10	1.959 0.087 10	2.552 0.047 10	107.7 0.9 10	3.90 0.21 10	144.0 0.8 10
5f	Mean S.D. N	1.783 0.203 10	1.700 0.188 10	0.332 0.056 10	36.7 7.3 10	7.27 1.66 10	1.956 0.162 10	2.551 0.046 10	107.2 1.4 10	3.86 0.26 10	143.4 1.3 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 8.1 Mean volume and creatinine content of the urine (16-hour samples) collected on day 27-28 (Main groups)

Group Sex	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/mmol
1m	Mean S.D. N	4980.9 2015.5 10	0.98 0.46 10	0.21 0.07 10
2m	Mean S.D. N	5589.3 1351.7 10	6.68 1.37 10	1.22** 0.21 10
3m	Mean S.D. N	8202.3** 2991.2 10	11.36 4.15 10	1.39** 0.12 10
4m	Mean S.D. N	6725.7* 1326.8 10	11.06 3.00 10	1.63** 0.20 10
5m	Mean S.D. N	5632.9 1366.9 10	10.34 3.94 10	1.87** 0.57 10
1f	Mean S.D. N	3897.3 2674.1 10	0.93 0.54 10	0.27 0.10 10
2f	Mean S.D. N	5383.0 1998.7 10	4.43 1.65 10	0.85** 0.25 10
3f	Mean S.D. N	7696.6** 1683.5 10	6.30 1.18 10	0.83** 0.15 10
4f	Mean S.D. N	6303.5 1983.4 10	6.15 1.23 10	1.01** 0.16 10
5f	Mean S.D. N	5970.8 1777.6 10	7.15 1.66 10	1.22** 0.20 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 8.2 Mean volume and creatinine content of the urine (16-hour samples) collected on day 44-45 (Recovery groups)

Group Sex	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Urinary Fluoride/creat mg/mmol
1m	Mean S.D. N	16.41 06.20 9	5191.3 2128.3 9	1.02 0.52 10
5m	Mean S.D. N	18.18 8.81 10	5159.0 1969.4 10	1.64 1.37 10
1f	Mean S.D. N	11.57 6.22 10	5570.0 3182.7 10	1.20 0.61 10
5f	Mean S.D. N	16.11 8.85 10	4330.3 2680.0 10	1.29 0.88 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 9.1 Mean terminal body weights and absolute organ weights (Main groups)

Group Sex	Terminal body wgt		Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen		Testes		
	g		g		g		g		g		g		g		g		g		
1m	Mean	296.47	1.853	1.291	1.061	0.0480	1.975	8.365	0.6232	3.182									
	S.D.	16.29	0.039	0.059	0.068	0.0050	0.141	0.618	0.0514	0.203									
	N	10	10	10	10	10	10	10	10	10	10								
2m	Mean	293.63	1.803	1.275	1.098	0.0487	1.989	8.785	0.6270	3.007									
	S.D.	12.55	0.058	0.062	0.084	0.0057	0.116	0.585	0.0570	0.355									
	N	10	10	10	10	10	10	10	10	10									
3m	Mean	282.07	1.824	1.273	1.102	0.0487	1.944	8.234	0.5926	3.001									
	S.D.	25.08	0.066	0.120	0.146	0.0056	0.143	0.933	0.0925	0.672									
	N	10	10	10	10	10	10	10	10	10									
4m	Mean	286.17	1.826	1.302	1.079	0.0497	1.939	8.961	0.6092	3.180									
	S.D.	15.56	0.046	0.139	0.120	0.0068	0.134	0.695	0.0778	0.279									
	N	9	9	9	9	9	9	9	9	9									
5m	Mean	272.33*	1.819	1.174**	1.096	0.0511	1.893	8.378	0.5234**	2.830									
	S.D.	19.72	0.031	0.043	0.098	0.0034	0.084	0.618	0.0597	0.613									
	N	10	10	10	10	10	10	10	10	10									
1f	Mean	181.19	1.664	0.941	0.698	0.0565	1.316	4.991	0.4378										
	S.D.	11.06	0.053	0.062	0.051	0.0058	0.116	0.446	0.0520										
	N	10	10	10	10	10	10	10	10										
2f	Mean	169.56*	1.667	0.914	0.712	0.0557	1.252	5.050	0.3619**										
	S.D.	8.52	0.028	0.059	0.041	0.0060	0.070	0.517	0.0502										
	N	10	10	10	10	10	10	10	10										
3f	Mean	175.13	1.688	0.940	0.741	0.0564	1.306	5.265	0.3985										
	S.D.	5.13	0.049	0.055	0.057	0.0055	0.116	0.311	0.0244										
	N	10	10	10	10	10	10	10	10										
4f	Mean	171.21*	1.737	0.911	0.682	0.0553	1.328	5.273	0.3882										
	S.D.	6.48	0.201	0.050	0.060	0.0058	0.177	0.329	0.0550										
	N	10	10	10	10	10	10	10	10										
5f	Mean	169.56*	1.663	0.899	0.686	0.0550	1.244	5.379	0.3684**										
	S.D.	10.82	0.046	0.031	0.059	0.0059	0.075	0.484	0.0453										
	N	10	10	10	10	10	10	10	10										

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 9.2 Mean terminal body weights and absolute organ weights (Recovery groups)

Group Sex	Terminal body wgt		Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen		Testes		
	g		g		g		g		g		g		g		g		g		
1m	Mean	344.64	1.887	1.332	1.132	0.0460	2.141	9.770	0.6928	3.083									
	S.D.	18.78	0.053	0.087	0.047	0.0064	0.089	0.606	0.0398	0.351									
	N	10	10	10	10	10	10	10	10	10	10								
5m	Mean	356.36	1.868	1.328	1.168	0.0445	2.175	10.186	0.7062	2.968									
	S.D.	16.27	0.032	0.057	0.087	0.0026	0.165	0.876	0.0890	0.589									
	N	10	10	10	10	10	10	10	10	10	10								
1f	Mean	205.11	1.711	0.998	0.755	0.0545	1.352	5.470	0.4987										
	S.D.	13.80	0.047	0.053	0.065	0.0044	0.069	0.337	0.0346										
	N	10	10	10	10	10	10	10	10	10									
5f	Mean	198.86	1.717	0.965	0.728	0.0538	1.331	5.455	0.4834										
	S.D.	7.68	0.041	0.032	0.046	0.0060	0.093	0.574	0.0499										
	N	10	10	10	10	10	10	10	10	10									

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 10.1 Mean terminal body weights and relative organ weights (Main groups)

Group Sex	Terminal body wgt		Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen		Testes		
	g	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg
1m	Mean S.D. N	296.47 16.29 10	6.269 0.389 10	4.360 0.185 10	3.582 0.183 10	0.1621 0.0164 10	6.662 0.330 10	28.22 1.38 10	2.101 0.117 10	10.775 1.087 10									
2m	Mean S.D. N	293.63 12.55 10	6.148 0.269 10	4.349 0.287 10	3.740 0.254 10	0.1661 0.0212 10	6.774 0.245 10	29.89* 1.22 10	2.138 0.214 10	10.274 1.418 10									
3m	Mean S.D. N	282.07 25.08 10	6.511 0.631 10	4.529 0.427 10	3.902 0.314 10	0.1736 0.0227 10	6.907 0.285 10	29.14 1.30 10	2.094 0.199 10	10.545 2.085 10									
4m	Mean S.D. N	286.17 15.56 9	6.391 0.260 9	4.559 0.521 9	3.762 0.253 9	0.1738 0.0237 9	6.772 0.153 9	31.30** 1.58 9	2.131 0.259 9	11.127 0.953 9									
5m	Mean S.D. N	272.33* 19.72 10	6.717 0.574 10	4.328 0.268 10	4.049 0.537 10	0.1887 0.0206 10	6.939 0.430 10	30.78** 1.03 10	1.919 0.136 10	10.318 2.000 10									
1f	Mean S.D. N	181.19 11.06 10	9.205 0.477 10	5.204 0.369 10	3.858 0.275 10	0.3126 0.0349 10	7.264 0.495 10	27.56 2.13 10	2.412 0.203 10										
2f	Mean S.D. N	169.56* 8.52 10	9.852* 0.461 10	5.391 0.258 10	4.205* 0.273 10	0.3292 0.0399 10	7.386 0.224 10	29.73 1.91 10	2.133 0.258 10										
3f	Mean S.D. N	175.13 5.13 10	9.643 0.295 10	5.368 0.323 10	4.230* 0.268 10	0.3221 0.0289 10	7.454 0.582 10	30.06* 1.63 10	2.278 0.157 10										
4f	Mean S.D. N	171.21* 6.48 10	10.143** 1.043 10	5.325 0.281 10	3.984 0.306 10	0.3231 0.0329 10	7.772 1.114 10	30.84** 2.20 10	2.266 0.303 10										
5f	Mean S.D. N	169.56* 10.82 10	9.831* 0.439 10	5.314 0.256 10	4.055 0.387 10	0.3249 0.0343 10	7.341 0.230 10	31.72** 2.36 10	2.169 0.166 10										

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Table 10.2 Mean terminal body weights and relative organ weights (Recovery groups)

Group Sex	Terminal body wgt g	Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen		Testes	
		rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt	rel. wgt g/kg	body wgt
1m	Mean S.D. N	5.494 0.386 10	344.64 18.78 10	3.868 0.210 10	3.290 0.161 10	0.1335 0.0162 10	6.224 0.316 10	28.36 1.09 10	2.014 0.119 10	8.951 0.951 10	26.72 1.64 10	2.439 0.226 10	8.340 1.646 10	1.978 0.189 10	2.431 0.233 10	2.431 0.233 10	8.340 1.646 10
5m	Mean S.D. N	5.252 0.270 10	356.36 16.27 10	3.729 0.131 10	3.281 0.264 10	0.1251 0.0094 10	6.097 0.276 10	28.54 1.40 10	1.978 0.189 10	8.340 1.646 10	26.72 1.64 10	2.439 0.226 10	8.340 1.646 10	1.978 0.189 10	2.431 0.233 10	2.431 0.233 10	8.340 1.646 10
1f	Mean S.D. N	8.369 0.489 10	205.11 13.80 10	4.876 0.277 10	3.681 0.223 10	0.2664 0.0235 10	6.602 0.278 10	26.72 1.64 10	2.439 0.226 10	8.340 1.646 10	26.72 1.64 10	2.439 0.226 10	8.340 1.646 10	1.978 0.189 10	2.431 0.233 10	2.431 0.233 10	8.340 1.646 10
5f	Mean S.D. N	8.644 0.339 10	198.86 7.68 10	4.858 0.237 10	3.661 0.193 10	0.2706 0.0299 10	6.690 0.338 10	27.41 2.21 10	2.431 0.233 10	8.340 1.646 10	27.41 2.21 10	2.431 0.233 10	8.340 1.646 10	1.978 0.189 10	2.431 0.233 10	2.431 0.233 10	8.340 1.646 10

Statistics: One-way Analysis of Variance/ Dunnett's test: * p < 0.05; ** p < 0.01

Page: 2
 Date: 15-DEC 09

Sub-acute (4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
 TNO Quality of Life
 Study: -8668-
 Table 11.1 - Summary of macroscopic observations at the end of the treatment period

CHANGES	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)																			
		Males					Females														
		Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm	Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm										
LUNGS																					
Petechia(e) medial lobe		1																			
SKIN/SUBCUTIS																					
Sparsely haired																					1
TESTES																					
Cryptorchidism								1													
Swell				1					1												
THORACIC CAVITY																					
Hydrothorax			1	6	4	1								1							
THYMUS																					
(Uni-lateral) red patches														2	5	2	2	3			
Uni-lateral red appearance																					1
THYROID																					
Uni-latera. white nodule								1													

Study : 8668s1 Report Complete.

Page: 1
 Date: 21-DEC-09

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
 TNO Quality of Life
 Study: -8668-
 Table 11.2 - Summary of macroscopic observations at the end of the recovery period

CHANGES	INCIDENCE OF LESIONS (NUMERIC)												
	TREATMENT	Males					Females						
		Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm	Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm		
HEART													
Right ventricular flabby					2								
LUNGS													
Petechia(e) left lung													1
THORACIC CAVITY													
Hydrothorax						1							2
THYMUS													
Uni-lateral red patches						1				1			1

Study : 8668s2 Report Complete.

Page: 1
 Date: 26-JAN-10

Sub-acute (4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
 TNO Quality of Life
 Study: 8668-
 Table 12.1 - Summary of microscopic changes at the end of the treatment period

CHANGES	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)																		
		Males					Females													
		Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm	Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm									
ADRENALS		(10)			(1)	(10)														
Focal cortical mononuclear cell infiltrate		0			0	0					0									1
Uni-lateral focal hyperaemia		0			0	1					0									0
BRAIN		(10)			(1)	(10)					(1)									(10)
Focal gliosis		0			0	0					0									0
Hydrocephalus		0			0	0					0									0
Focal pineal gland mononuclear cell infiltrate		0			0	0					0									0
Pineal gland cyst(s)		0			0	0					0									0
EPIDIDYMIDES											(1)									0
Focal interstitial mononuclear cell infiltrate						1					1									0
Decreased number of spermatozoa											1									0
HEART		(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
(Focal) endocardial inflammatory cell infiltrate		0	3	3	2	2	2	2	2	2	0	1	1	2	2	2	2	2	2	2
very slight		0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
slight		0	0	3	4	2	4	2	2	2	0	1	1	2	2	2	2	2	2	2
Score Expanded Totals		0	3	3	4	2	4	2	2	2	0	1	1	2	2	2	2	2	2	2

Statistics: 2-sided Fisher's exact test between the controls & each of the treatment groups. *P<0.05, **P<0.01, ***P<0.001
 Figures in brackets represent the number of animals from which this tissue was examined microscopically
 Report Continued...

Page: 2
 Date: 26-JAN-10

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
 TNO Quality of Life
 Study: -8668-
 Table 12.1 - Summary of microscopic changes at the end of the treatment period

CHANGES	TREATMENT	INCIDENCE OF LESIONS (NUMERIC)											
		Males					Females						
		Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm	Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm		
HEART	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Slight myocardial vacuolation	0	4	4	4	8***	0	5*	5*	8***	8***	0	0	0
Focal mononuclear cell infiltrate	1	6	2	5	2	2	0	2	4	0	0	0	0
very slight	0	0	0	2	2	2	1	0	2	0	0	0	0
Slight	1	6	2	7*	4	2	1	2	6	0	0	0	0
Score Expanded Totals													
Multifocal mononuclear cell infiltrate	0	1	4	2	1	0	7	7	2	3	0	0	0
very slight	0	2	4	1	3	0	1	1	1	4	0	0	0
Slight	0	3	8***	3	4	0	8***	8***	3	7**	0	0	0
Score Expanded Totals													
Atrial congestion	0	0	0	1	0	0	0	0	0	0	0	0	0
(Focal) congestion	0	0	1	0	0	0	1	0	1	0	0	0	0
KIDNEYS	(10)	(2)	(1)	(1)	(10)	(10)	(10)	(1)	(2)	(10)	(10)	(10)	(10)
Basophilic tubules	7	1	0	1	5	5	5	1	0	4	0	0	0
Pyelitis	0	0	0	0	0	0	0	0	1	0	0	0	0
Focal mononuclear cell infiltrate	0	0	0	0	1	0	0	0	0	1	0	0	1
Mineralisation	1	0	0	0	0	0	0	0	0	0	0	0	2
Focal transitional cell hyperplasia	6	1	1	0	4	1	1	0	1	0	1	0	0
(Uni-lateral) pelvic dilatation	2	2	1	0	1	1	1	1	1	1	1	1	2

Statistics: 2-sided Fisher's exact test between the controls & each of the treatment groups. *P<0.05, **P<0.01, ***P<0.001
 Figures in brackets represent the number of animals from which this tissue was examined microscopically
 Study : 8668s1
 Report Continued ...

Page: 3
 Date: 26-JAN-10

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
 TNO Quality of Life
 Study: 8668-
 Table 12.1 - Summary of microscopic changes at the end of the treatment period

CHANGES	INCIDENCE OF LESIONS (NUMERIC)										
	TREATMENT	Males					Females				
		Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm	Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm
LARYNX	(10)			(1)	(10)					(10)	
Focd. inflammatory-cell infiltration	1			0	2					0	
LIVER	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	
Hepatocellular micro-vesicular vacuolation	0	0	0	0	4	6	0	0	0	5	
very slight	0	2	4	5	5	0	5	5	6	5	
slight	0	2	4	5*	9***	6	5	5	6	10	
Score Expanded Totals											
Mononuclear cell aggregates/necrotic hepatocytes	3	6	3	6	4	4	5	4	3	0	
very slight	6	3	5	3	6	3	0	0	1	1	
slight	9	9	8	9	10	7	5	4	4	1*	
Score Expanded Totals											
LUNGS	(10)			(1)	(10)	(10)				(10)	
Alveolar microhaemorrhage(s)	1			0	0	0				0	
Focal perivascular oedema	0			1	0	0				0	
NASAL CAVITY	(10)			(10)		(10)				(10)	
No abnormality detected	10			10		10				10	
SKIN/SUBCUTIS										(1)	
No abnormality detected										1	

Statistics: 2-sided Fisher's exact test between the controls & each of the treatment groups. *P<0.05, **P<0.01, ***P<0.001
 Figures in brackets represent the number of animals from which this tissue was examined microscopically
 Study : 8668s1
 Report Continued....

Page: 4
Date: 26-JAN-10

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Study: -8668-
Table 12.1 - Summary of microscopic changes at the end of the treatment period

CHANGES	INCIDENCE OF LESIONS (NUMERIC)										
	TREATMENT	Males					Females				
		Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm	Contr.	500 ppm	1,500 ppm	5,000 ppm	15,000 ppm
SPLEEN	(10)			(1)	(10)					(10)	
No abnormality detected	10			1	10	10				10	
TESTES	(10)		(1)	(1)	(10)						
Interstitial cell proliferation	0	1	0	0	1						
Seminiferous tubular mineralisation	0	1	0	0	1						
Seminiferous tubular atrophy	0	1	0	0	2						
THYMUS						(2)	(5)	(2)	(2)	(3)	
Microhaemorrhage(s)						2	5	2	2	3	
THYROID				(1)							
No abnormality detected				1							
TRACHEA/BRONCHI	(10)			(1)	(10)	(10)				(10)	
Focal mononuclear cell infiltrate	0			0	1	1				0	

Statistics: 2-sided Fisher's exact test between the controls & each of the treatment groups. *p<0.05, **p<0.01, ***p<0.001
Figures in brackets represent the number of animals from which this tissue was examined microscopically
Study: 8668s1 Report Complete.

Page: 1
 Date: 20-JAN-10

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
 TWO Quality of Life
 Study: -8668-
 Table 12.2 - Summary of microscopic changes at the end of the recovery period

CHANGES	INCIDENCE OF LESIONS (NUMBER)				
	TREATMENT	Males		Females	
		Contr. 15,000 ppm	(10)	Contr. 15,000 ppm	(10)
HEART	(10)	(10)	(10)	(10)	
Focal mononuclear cell infiltrate					
very slight		3	4	4	
slight		2	1	0	
Score Expanded Totals		5	5	4	
Multifocal mononuclear cell infiltrate					
very slight		1	0	0	
slight		0	1	0	
Score Expanded Totals		1	1	0	

Statistics: 2-sided Fisher's exact test between the controls & each of the treatment groups. *P<0.05, **P<0.01, ***P<0.001
 Figures in brackets represent the number of animals from which this tissue was examined microscopically
 Study : 86682 Report Complete.

Annexes

Annex 1 - GLP compliance monitoring unit statement



voedsel en waren autoriteit

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 27-31 October 2008 at

TNO Quality of Life
Utrechtseweg 48, 3704 HE Zeist
P.O. Box 360, 3700 AJ 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, kinetics and metabolism, safety pharmacology, worker exposure and in-vitro studies.

Den Haag, 03 February 2009

A handwritten signature in black ink, appearing to read 'Th. Helder', is written over a faint circular stamp.

Dr Th. Helder

Manager GLP Compliance Monitoring Program

Food and Consumer Product Safety Authority (VWA)
Prinses Beatrixlaan 2, 2595 AL Den Haag
Postbus 19506, 2500 CM Den Haag, The Netherlands

Annex 2 - Certificate of analysis of the test material

INEOS Fluor

INEOS FLUOR R&T
 LABORATORY
 CERTIFICATE OF ANALYSIS

Name: 3,3,3-Trifluoroprop-1-ene

Synonyms: HFO1243zf

Sample Status: Authorized

LIMS Reference No:	105310	Cylinder Number	315000
Batch No:	20090810_1	Ineos R&T Reference	IF20090810
Date of Manufacture:	10-Aug-2009	Expiry Date	10-Aug-2012
Date/Time of Sampling :	10/08/2009 11:12:00	Date/Time Logged :	20/08/2009 11:14:52
Quality:	PASS	Specification Ref :	1243ZF_PRODUCT
			Issue No : 1

Analyte	Result	Units	Spec. Status	Analyst
125	N/D	ppm w/w		AWEIR
143a	N/D	ppm w/w		AWEIR
134a	N/D	ppm w/w		AWEIR
1225zc	N/D	ppm w/w		AWEIR
1234yf	28.6	ppm w/w		AWEIR
134	N/D	ppm w/w		AWEIR
1225yc-Z	2.0	ppm w/w		AWEIR
152a	0.5	ppm w/w		AWEIR
12	N/D	ppm w/w		AWEIR
263fb	7.4	ppm w/w		AWEIR
Methyl Chloride	N/D	ppm w/w		AWEIR
1122	N/D	ppm w/w		AWEIR
Vinyl Chloride	N/D	ppm w/w		AWEIR
31	N/D	ppm w/w		AWEIR
1233xf	N/D	ppm w/w		AWEIR
1233zd	N/D	ppm w/w		AWEIR
Unknown1	2.3	ppm w/w		AWEIR
Unknown2	5.6	ppm w/w		AWEIR
Unknown3	N/D	ppm w/w		AWEIR
Unknown4	N/D	ppm w/w		AWEIR
Unknown5	N/D	ppm w/w		AWEIR
Total Unknowns	8	ppm w/w		AWEIR
1243zf Purity	99.995	% wt		LIMS Calc.

Notes:

Reviewed By : AWEIR
 Date Reviewed : 20-Aug-2009 11:36

Date Report Printed : 01-Sep-2009

Annex 3 – Cross reference listing

Animal	Group	Cage	Sex	Replicate	Start exposure	main/recovery
-----	-----	----	---	-----	-----	-----
2	1	2	M	1	22-09-2009	main
4	1	2	M	1	22-09-2009	main
6	1	2	M	1	22-09-2009	main
8	1	2	M	1	22-09-2009	main
10	1	2	M	1	22-09-2009	main
12	1	4	M	2	23-09-2009	main
14	1	4	M	2	23-09-2009	main
16	1	4	M	2	23-09-2009	main
18	1	4	M	2	23-09-2009	main
20	1	4	M	2	23-09-2009	main
22	1	6	M	5	25-09-2009	recovery
24	1	6	M	5	25-09-2009	recovery
26	1	6	M	5	25-09-2009	recovery
28	1	6	M	5	25-09-2009	recovery
30	1	6	M	5	25-09-2009	recovery
32	1	8	M	5	25-09-2009	recovery
34	1	8	M	5	25-09-2009	recovery
36	1	8	M	5	25-09-2009	recovery
38	1	8	M	5	25-09-2009	recovery
40	1	8	M	5	25-09-2009	recovery
42	2	10	M	1	22-09-2009	main
44	2	10	M	1	22-09-2009	main
46	2	10	M	1	22-09-2009	main
48	2	10	M	1	22-09-2009	main
50	2	10	M	1	22-09-2009	main
52	2	12	M	2	23-09-2009	main
54	2	12	M	2	23-09-2009	main
56	2	12	M	2	23-09-2009	main
58	2	12	M	2	23-09-2009	main
60	2	12	M	2	23-09-2009	main
62	3	14	M	1	22-09-2009	main
64	3	14	M	1	22-09-2009	main
66	3	14	M	1	22-09-2009	main
68	3	14	M	1	22-09-2009	main
70	3	14	M	1	22-09-2009	main
72	3	16	M	2	23-09-2009	main
74	3	16	M	2	23-09-2009	main
76	3	16	M	2	23-09-2009	main
78	3	16	M	2	23-09-2009	main
80	3	16	M	2	23-09-2009	main
82	4	18	M	1	22-09-2009	main
84	4	18	M	1	22-09-2009	main
86	4	18	M	1	22-09-2009	main
88	4	18	M	1	22-09-2009	main

90	4	18	M	1	22-09-2009	main
92	4	20	M	2	23-09-2009	main
94	4	20	M	2	23-09-2009	main
96	4	20	M	2	23-09-2009	main
98	4	20	M	2	23-09-2009	main
100	4	20	M	2	23-09-2009	main
102	5	22	M	1	22-09-2009	main
104	5	22	M	1	22-09-2009	main
106	5	22	M	1	22-09-2009	main
108	5	22	M	1	22-09-2009	main
110	5	22	M	1	22-09-2009	main
112	5	24	M	2	25-09-2009	recovery
114	5	24	M	2	25-09-2009	recovery
116	5	24	M	2	25-09-2009	recovery
118	5	24	M	2	25-09-2009	recovery
120	5	24	M	2	25-09-2009	recovery
122	5	26	M	5	25-09-2009	recovery
124	5	26	M	5	25-09-2009	recovery
126	5	26	M	5	25-09-2009	recovery
128	5	26	M	5	25-09-2009	recovery
130	5	26	M	5	25-09-2009	recovery
132	5	28	M	5	25-09-2009	recovery
134	5	28	M	5	25-09-2009	recovery
136	5	28	M	5	25-09-2009	recovery
138	5	28	M	5	25-09-2009	recovery
140	5	28	M	5	25-09-2009	recovery

Annex 3 – Cross reference listing (continued)

Animal	Group	Cage	Sex	Replicate	Start exposure	main/recovery
1	1	1	F	3	24-09-2009	main
3	1	1	F	3	24-09-2009	main
5	1	1	F	3	24-09-2009	main
7	1	1	F	3	24-09-2009	main
9	1	1	F	3	24-09-2009	main
11	1	3	F	4	25-09-2009	main
13	1	3	F	4	25-09-2009	main
15	1	3	F	4	25-09-2009	main
17	1	3	F	4	25-09-2009	main
19	1	3	F	4	25-09-2009	main
21	1	5	F	5	25-09-2009	recovery
25	1	5	F	5	25-09-2009	recovery
25	1	5	F	5	25-09-2009	recovery
27	1	5	F	5	25-09-2009	recovery
29	1	5	F	5	25-09-2009	recovery
31	1	7	F	5	25-09-2009	recovery
33	1	7	F	5	25-09-2009	recovery
35	1	7	F	5	25-09-2009	recovery
37	1	7	F	5	25-09-2009	recovery
39	1	7	F	5	25-09-2009	recovery
41	2	9	F	3	24-09-2009	main
43	2	9	F	3	24-09-2009	main
45	2	9	F	3	24-09-2009	main
47	2	9	F	3	24-09-2009	main
49	2	9	F	3	24-09-2009	main
51	2	11	F	4	25-09-2009	main
53	2	11	F	4	25-09-2009	main
55	2	11	F	4	25-09-2009	main
57	2	11	F	4	25-09-2009	main
59	2	11	F	4	25-09-2009	main
61	3	13	F	3	24-09-2009	main
63	3	13	F	3	24-09-2009	main
65	3	13	F	3	24-09-2009	main
67	3	13	F	3	24-09-2009	main
69	3	13	F	3	24-09-2009	main
71	3	15	F	4	25-09-2009	main
73	3	15	F	4	25-09-2009	main
75	3	15	F	4	25-09-2009	main
77	3	15	F	4	25-09-2009	main
79	3	15	F	4	25-09-2009	main
81	4	17	F	3	24-09-2009	main
83	4	17	F	3	24-09-2009	main
85	4	17	F	3	24-09-2009	main
87	4	17	F	3	24-09-2009	main

89	4	17	F	3	24-09-2009	main
91	4	19	F	4	25-09-2009	main
93	4	19	F	4	25-09-2009	main
95	4	19	F	4	25-09-2009	main
97	4	19	F	4	25-09-2009	main
99	4	19	F	4	25-09-2009	main
101	5	21	F	3	24-09-2009	main
103	5	21	F	3	24-09-2009	main
105	5	21	F	3	24-09-2009	main
107	5	21	F	3	24-09-2009	main
109	5	21	F	3	24-09-2009	main
111	5	25	F	4	25-09-2009	recovery
113	5	25	F	4	25-09-2009	recovery
115	5	25	F	4	25-09-2009	recovery
117	5	25	F	4	25-09-2009	recovery
119	5	25	F	4	25-09-2009	recovery
121	5	25	F	5	25-09-2009	recovery
125	5	25	F	5	25-09-2009	recovery
125	5	25	F	5	25-09-2009	recovery
127	5	25	F	5	25-09-2009	recovery
129	5	25	F	5	25-09-2009	recovery
131	5	27	F	5	25-09-2009	recovery
133	5	27	F	5	25-09-2009	recovery
135	5	27	F	5	25-09-2009	recovery
137	5	27	F	5	25-09-2009	recovery
139	5	27	F	5	25-09-2009	recovery

Annex 4.1 – Certificate of analysis of the diet (RM3)



Special Quality Control Certificate of Analysis

PRODUCT : RM3 (E) SQC
BATCH NO : 7264
PREMIX BATCH NO: 15425

DATE OF MANUFACTURE: 10-JUN-09
DATE OF EXPIRY : 09-MAR-10

Nutrient	Found Analysis	Contaminant	Found Analysis	Limit of Detection
Moisture	9.0 †	Fluoride	17 mg/kg	1.0 mg/kg
Crude Fat	5.5 †	Nitrate as NaNO ₃	52 mg/kg	2.0 mg/kg
Crude Protein	23.7 †	Nitrite as NaNO ₂	Non Detected mg/kg	1.0 mg/kg
Crude Fibre	4.1 †	Lead	0.27 mg/kg	0.25 mg/kg
Ash	6.3 †	Arsenic	0.77 mg/kg	0.2 mg/kg
Calcium	0.87 †	Cadmium	0.07 mg/kg	0.05 mg/kg
Phosphorus	0.70 †	Mercury	Non Detected mg/kg	0.01 mg/kg
Sodium	0.25 †	Selenium	0.35 mg/kg	0.05 mg/kg
Chloride	0.44 †			
Potassium	0.94 †			
Magnesium	0.18 †	Total Aflatoxins	Non Detected mcg/kg	1 mcg/kg each of B1, B2, G1, G2
Iron	240 mg/kg			
Copper	14 mg/kg	Total P.C.B	Non Detected mcg/kg	10.0 mcg/kg
Manganese	65 mg/kg	Total D.D.T	Non Detected mcg/kg	10.0 mcg/kg
Zinc	52 mg/kg	Dieldrin	Non Detected mcg/kg	10.0 mcg/kg
		Lindane	Non Detected mcg/kg	10.0 mcg/kg
		Heptachlor	Non Detected mcg/kg	10.0 mcg/kg
		Malathion	Non Detected mcg/kg	20.0 mcg/kg
Vitamin A	12.6 iu/g	Total Viable Organisms x 1000	5.40 per grm	1000/g
Vitamin E	78 mg/kg			
Vitamin C	mg/kg	Mesophilic Spores x 100	Non Detected per grm	100/g
		Salmonellae Species	Non Detected per grm	Absent in 20 grm
		Enterobacteriaceae	Non Detected per grm	Absent in 20 grm
		Escherichia Coli	Non Detected per grm	Absent in 20 grm
		Fungal Units	70 per grm	Absent in 20 grm
		Antibiotic Activity	Non Detected	

Signed ... *mbus*
Dated ... 09/07/09

Annex 4.1 – Certificate of analysis of the diet (RM3) (continued)



Special Quality Control Certificate of Analysis

PRODUCT : RM3 (E) SQC FG
 BATCH NO 7327 DATE OF MANUFACTURE: 10-JUN 09
 PREMIX BATCH NO: 15425 DATE OF EXPIRY 09 MAR 10

Nutrient	Found Analysis	Contaminant	Found Analysis	Limit of Detection
Moisture	9.0 %	Fluoride	17 mg/kg	1.0 mg/kg
Crude Fat	5.5 %	Nitrate as NaNO ₃	52 mg/kg	2.0 mg/kg
Crude Protein	23.7 %	Nitrite as NaNO ₂	Non Detected	1.0 mg/kg
Crude Fibre	4.1 %	Lead	0.27 mg/kg	0.25 mg/kg
Ash	6.3 %	Arsenic	0.77 mg/kg	0.2 mg/kg
Calcium	0.87 %	Cadmium	0.07 mg/kg	0.05 mg/kg
Phosphorus	0.70 %	Mercury	Non Detected	0.01 mg/kg
Sodium	0.25 %	Selenium	0.35 mg/kg	0.05 mg/kg
Chloride	0.44 %			
Potassium	0.94 %			
Magnesium	0.18 %	Total Aflatoxins	Non Detected	1 mcg/kg each of B1, B2, G1, G2
Iron	269 mg/kg			
Copper	14 mg/kg	Total P.C.B	Non Detected	10.0 mcg/kg
Manganese	65 mg/kg	Total D.D.T	Non Detected	10.0 mcg/kg
Zinc	52 mg/kg	Dieldrin	Non Detected	10.0 mcg/kg
		Lindane	Non Detected	10.0 mcg/kg
		Heptachlor	Non Detected	10.0 mcg/kg
		Malathion	Non Detected	20.0 mcg/kg
Vitamin A	11.0 iu/g	Total Viable Organisms x 1000	1.70 per grm	1000/g
Vitamin E	76 mg/kg			
Vitamin C	mg/kg	Mesophilic Spores x 100	10.00 per grm	100/g
		Salmonellae Species	Non Detected	Absent in 20 grm
		Enterobacteriaceae	Non Detected	Absent in 20 grm
		Escherichia Coli	Non Detected	Absent in 20 grm
		Fungal Units	20 per grm	Absent in 20 grm
Signed .. <i>Denise Mycott</i>		Antibiotic Activity	Non Detected	
Dated .. 03.08.09				

Annex 4.2 – Parameters checked in drinking water

Results of periodical analyses in drinking water collected on the premises of TNO Quality of Life in Zeist, the Netherlands.

This is a translation of the Analysis Report of the local waterworks (Vitens), dated 21 May 2009.

The analyses were conducted in samples taken on 18 May 2009 (12:53 hr) in room number 05.1.11 at TNO Quality of Life, Utrechtseweg 48, Zeist.

Parameter	Unit	Measured
Turbidity	FTU	0.23
Oxygen	mg O ₂ /l	13.0 ²
pH		8.31
Temperature	°C	14.5
Non Purgeable Organic Carbon	mg C/l	<0.5
Iron	mg/l	0.016
Electrical conductivity	mS/m	24.4
Manganese	mg/l	<0.005
Ammonia	mg N/l	<0.02
Nitrite	mg N/l	<0.003
Nitrate	mg N/l	1.3
Cadmium	µg/l	<0.10
Copper	µg/l	15.9
Lead	µg/l	<0.5
Aeromonas bacteria (30°C)	#/100 ml	<1
Coli bacteria (37°C)	#/100 ml	<1
Escherichia coli	#/100 ml	<1
Plate count (22°C)	#/ml	2 ¹

¹ Indicative value (result <10/ml)

² Sample oversaturated with oxygen, no accurate determination possible

Conclusion:

The above parameters meet the requirements of the Dutch Water Supply Act.

Annex 5 – Listing of haematology parameters and methods of analysis

Parameter	Method	Reference
Haemoglobin (Hb)	Advia 120 haematology analyser, Bayer HealthCare, Ireland	Manufacturer's manual
Packed cell volume (PCV)	Advia 120 haematology analyser, Bayer HealthCare, Ireland	Manufacturer's manual
Red blood cells (RBC)	Advia 120 haematology analyser, Bayer HealthCare, Ireland.	Manufacturer's manual
Reticulocytes	Advia 120 haematology analyser, Bayer HealthCare, Ireland	Manufacturer's manual 04/11/99 chapter 5
Total and differential white blood cells	Advia 120 haematology analyser, Bayer HealthCare, Ireland	Manufacturer's manual
Differential white blood cell counts (manual); conducted only if automatic differential count fails	Microscopic examination of stained blood smears according to Pappenheim. Absolute numbers are calculated from total white blood cells and percentage distribution of each cell type	Gorter, E. and W.C. de Graaff, Klinische Diagnostiek, 7th ed. H.E. Stenfert Kroese N.V. Leiden, 1955, the Netherlands, part I, p. 34
Thrombocytes	Advia 120 haematology analyser, Bayer HealthCare, Ireland	Manufacturer's manual
Prothrombin time (PT)	Normotest, method for EDTA blood. Nyegaard and Co. A/S Oslo, Norway	Manufacturer's manual Based on Owren, P.A. (1969) Pharmakoterapi 25
Mean corpuscular volume (MCV)	Calculated $MCV = \frac{\text{packed cell volume}}{\text{red blood cells}}$	
Mean corpuscular haemoglobin (MCH)	Calculated $MCH = \text{haemoglobin} / \text{red blood cells}$	
Mean corpuscular haemoglobin concentration (MCHC)	Calculated $MCHC = \text{haemoglobin} / \text{packed cell volume}$	

Annex 6 – Listing of clinical chemistry parameters and methods of analysis

Parameter	Method
Alkaline phosphatase (ALP) activity	Olympus AU-400 analyser ¹ , Olympus reagent according to I.F.C.C.
Alanine aminotransferase (ALAT)/ glutamic-pyruvic transaminase (GPT) activity	Olympus AU-400 analyser ¹ , Olympus reagent according to I.F.C.C. without PLP.
Aspartate aminotransferase (ASAT)/ glutamic-oxalacetic transaminase (GOT) activity	Olympus AU-400 analyser ¹ , Olympus reagent according to I.F.C.C. without PLP.
γ -Glutamyl transferase (GGT) activity	Olympus AU-400 analyser ¹ , Olympus reagent according to I.F.C.C.
Bilirubin (total)	Olympus AU-400 analyser ² , Randox reagent Diazotized sulphanilic acid
Total protein	Olympus AU-400 analyser ¹ , Olympus reagent Biuret
Albumin	Olympus AU-400 analyser ¹ , Olympus reagent Bromcresol green
Ratio albumin to globulin	Calculated, ratio = albumin / (total protein – albumin)
Glucose (plasma)	Olympus AU-400 analyser ¹ , Olympus reagent Hexokinase
Cholesterol (total)	Olympus AU-400 analyser ¹ , Olympus reagent CHOD-PAP
Phospholipids	Olympus AU-400 analyser ² , Wako reagent Enzymatic
Triglycerides	Olympus AU-400 analyser ¹ , Olympus reagent Enzymatic GPO-PAP
Creatinine	Olympus AU-400 analyser ² , Roche reagent Enzymatic PAP
Urea	Olympus AU-400 analyser ¹ , Olympus reagent Urease-UV

Annex 6 – Listing of clinical chemistry parameters and methods of analysis (continued)

Parameter	Method
Calcium (Ca)	Olympus AU-400 analyser ¹ , Olympus reagent Arsenazo III
Sodium (Na)	Olympus AU-400 analyser, Olympus reagent I.S.E.
Potassium (K)	Olympus AU-400 analyser ¹ , Olympus reagent I.S.E.
Chloride (Cl)	Olympus AU-400 analyser ¹ , Olympus reagent I.S.E.
Inorganic phosphate	Olympus AU-400 analyser ¹ , Olympus reagent Molybdate-UV

I.F.C.C. = International Federation of Clinical Chemistry

PLP = pyridoxalphosphate

PAP = phenol-4-aminophenazone

CHOD-PAP = cholesterol oxidase - phenol-4-aminophenazone

GPO-PAP = glycerolphosphate oxidase - phenol-4-aminophenazone

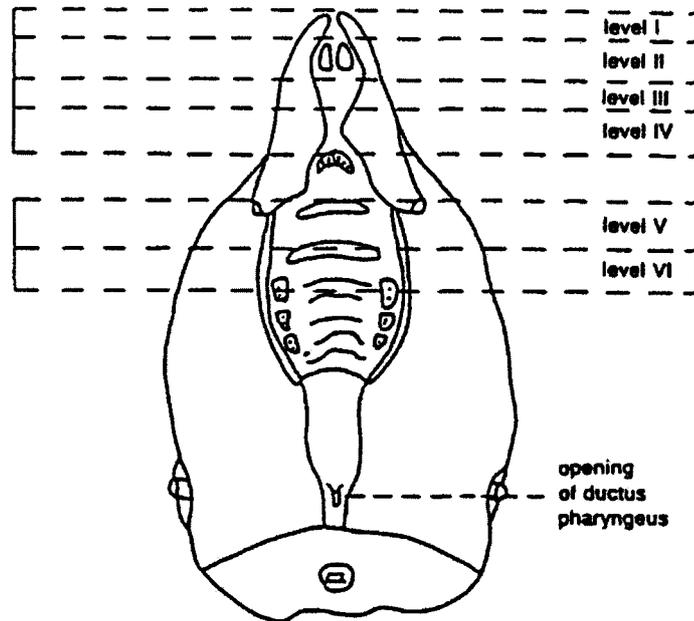
I.S.E. = Ion Selective Electrode

¹ Reference: Manufacturer's manual

² Reference: Manufacturer's manual, adapted for the Olympus AU-400 analyser

Annex 7 – Levels of cross-sections through the nasal cavity (Woutersen et al., 1994)

Ventral view of the rat hard palate region with the lower jaw removed, indicating the six standard cross-sections through the nose (I to VI; Woutersen et al., 1994).



Appendices

Appendix 1 Individual clinical observations

Day numbers during which observation was seen (relative to Start Date)

Group Sex	Animal Number	Clinical Sign	(28 - 28)
1m	2	DEAD Killed scheduled	(28 - 28)
	4	DEAD Killed scheduled	(28 - 28)
	6	DEAD Killed scheduled	(28 - 28)
	8	DEAD Killed scheduled	(28 - 28)
	10	DEAD Killed scheduled	(28 - 28)
	12	DEAD Killed scheduled	(28 - 28)
	14	DEAD Killed scheduled	(28 - 28)
	16	DEAD Killed scheduled	(28 - 28)
	18	DEAD Killed scheduled	(28 - 28)
	20	DEAD Killed scheduled	(28 - 28)
	22	DEAD Killed scheduled	(45 - 45)
	24	DEAD Killed scheduled	(45 - 45)
	26	DEAD Killed scheduled	(45 - 45)
	28	DEAD Killed scheduled	(45 - 45)
	30	DEAD Killed scheduled	(45 - 45)
	32	DEAD Killed scheduled	(45 - 45)
	34	DEAD Killed scheduled	(45 - 45)
	36	DEAD Killed scheduled	(45 - 45)
	38	DEAD Killed scheduled	(45 - 45)
	40	DEAD Killed scheduled	(45 - 45)
1f	1	DEAD Killed scheduled	(28 - 28)
	3	DEAD Killed scheduled	(28 - 28)
	5	DEAD Killed scheduled	(28 - 28)
	7	DEAD Killed scheduled	(28 - 28)
	9	DEAD Killed scheduled	(28 - 28)
	11	DEAD Killed scheduled	(28 - 28)
	13	DEAD Killed scheduled	(28 - 28)
	15	DEAD Killed scheduled	(28 - 28)
	17	DEAD Killed scheduled	(28 - 28)
	19	DEAD Killed scheduled	(28 - 28)
	21	DEAD Killed scheduled	(45 - 45)
	23	DEAD Killed scheduled	(45 - 45)
	25	DEAD Killed scheduled	(45 - 45)
	27	DEAD Killed scheduled	(45 - 45)
	29	DEAD Killed scheduled	(45 - 45)
	31	DEAD Killed scheduled	(45 - 45)
	33	DEAD Killed scheduled	(45 - 45)
	35	DEAD Killed scheduled	(45 - 45)
	37	DEAD Killed scheduled	(45 - 45)
	39	DEAD Killed scheduled	(45 - 45)

Appendix 1 Individual clinical observations

Day numbers during which observation was seen (relative to Start Date)

Group Sex	Animal Number	Clinical Sign	(28 - 28)
2m	42	DEAD Killed scheduled	(28 - 28)
	44	DEAD Killed scheduled	(28 - 28)
	46	DEAD Killed scheduled	(28 - 28)
	48	DEAD Killed scheduled	(28 - 28)
	50	DEAD Killed scheduled	(28 - 28)
	52	DEAD Killed scheduled	(28 - 28)
	54	DEAD Killed scheduled	(28 - 28)
	56	DEAD Killed scheduled	(28 - 28)
	58	DEAD Killed scheduled	(28 - 28)
60	DEAD Killed scheduled	(28 - 28)	
2f	41	DEAD Killed scheduled	(28 - 28)
	43	DEAD Killed scheduled	(28 - 28)
	45	DEAD Killed scheduled	(28 - 28)
	47	DEAD Killed scheduled	(28 - 28)
	49	DEAD Killed scheduled	(28 - 28)
	51	DEAD Killed scheduled	(28 - 28)
	53	DEAD Killed scheduled	(28 - 28)
	55	DEAD Killed scheduled	(28 - 28)
	57	DEAD Killed scheduled	(28 - 28)
59	DEAD Killed scheduled	(28 - 28)	
3m	62	DEAD Killed scheduled	(28 - 28)
	64	DEAD Killed scheduled	(28 - 28)
	66	DEAD Killed scheduled	(28 - 28)
	68	DEAD Killed scheduled	(28 - 28)
	70	DEAD Killed scheduled	(28 - 28)
	72	DEAD Killed scheduled	(28 - 28)
	74	DEAD Killed scheduled	(28 - 28)
	76	DEAD Killed scheduled	(28 - 28)
	78	DEAD Killed scheduled	(28 - 28)
80	DEAD Killed scheduled	(28 - 28)	

Appendix 1 Individual clinical observations

Day numbers during which observation was seen (relative to Start Date)

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
3f	61	DEAD Killed scheduled	(28 - 28)
	63	DEAD Killed scheduled	(28 - 28)
	65	DEAD Killed scheduled	(28 - 28)
	67	DEAD Killed scheduled	(28 - 28)
	69	DEAD Killed scheduled	(28 - 28)
	71	DEAD Killed scheduled	(28 - 28)
	73	DEAD Killed scheduled	(28 - 28)
	75	DEAD Killed scheduled	(28 - 28)
	77	DEAD Killed scheduled	(28 - 28)
4m	82	DEAD Killed scheduled	(28 - 28)
	84	DEAD Killed scheduled	(28 - 28)
	86	DEAD Found dead	(28 - 28)
	88	DEAD Killed scheduled	(28 - 28)
	90	DEAD Killed scheduled	(28 - 28)
	92	DEAD Killed scheduled	(28 - 28)
	94	DEAD Killed scheduled	(28 - 28)
	96	DEAD Killed scheduled	(28 - 28)
	98	DEAD Killed scheduled	(28 - 28)
	100	DEAD Killed scheduled	(28 - 28)
4f	81	DEAD Killed scheduled	(28 - 28)
	83	DEAD Killed scheduled	(28 - 28)
	85	DEAD Killed scheduled	(28 - 28)
	87	DEAD Killed scheduled	(28 - 28)
	89	DEAD Killed scheduled	(28 - 28)
	91	DEAD Killed scheduled	(28 - 28)
	93	DEAD Killed scheduled	(28 - 28)
	95	DEAD Killed scheduled	(28 - 28)
	97	DEAD Killed scheduled	(28 - 28)
99	DEAD Killed scheduled	(28 - 28)	

Appendix 1 Individual clinical observations

Day numbers during which observation was seen (relative to Start Date)

Group Sex	Animal Number	Clinical Sign	Day numbers during which observation was seen (relative to Start Date)
5m	102	DEAD Killed scheduled	(28 - 28)
	104	DEAD Killed scheduled	(28 - 28)
	106	DEAD Killed scheduled	(28 - 28)
	108	DEAD Killed scheduled	(28 - 28)
	110	DEAD Killed scheduled	(28 - 28)
	112	DEAD Killed scheduled	(28 - 28)
	114	DEAD Killed scheduled	(28 - 28)
	116	DEAD Killed scheduled	(28 - 28)
	118	DEAD Killed scheduled	(28 - 28)
	120	DEAD Killed scheduled	(28 - 28)
	122	DEAD Killed scheduled	(45 - 45)
	124	DEAD Killed scheduled	(45 - 45)
	126	DEAD Killed scheduled	(45 - 45)
	128	DEAD Killed scheduled	(45 - 45)
130	DEAD Killed scheduled	(45 - 45)	
132	DEAD Killed scheduled	(45 - 45)	
134	DEAD Killed scheduled	(45 - 45)	
136	DEAD Killed scheduled	(45 - 45)	
138	DEAD Killed scheduled	(45 - 45)	
140	DEAD Killed scheduled	(45 - 45)	
5f	101	DEAD Killed scheduled	(28 - 28)
	103	DEAD Killed scheduled	(28 - 28)
	105	DEAD Killed scheduled	(28 - 28)
	107	DEAD Killed scheduled	(28 - 28)
	109	DEAD Killed scheduled	(28 - 28)
	111	DEAD Killed scheduled	(28 - 28)
	113	SKIN Sparsely haired area(s)	(28 - 28)
	115	DEAD Killed scheduled	(28 - 28)
	117	DEAD Killed scheduled	(28 - 28)
	119	DEAD Killed scheduled	(28 - 28)
	121	DEAD Killed scheduled	(45 - 45)
	123	DEAD Killed scheduled	(45 - 45)
	125	DEAD Killed scheduled	(45 - 45)
	127	DEAD Killed scheduled	(45 - 45)
129	DEAD Killed scheduled	(45 - 45)	
131	DEAD Killed scheduled	(45 - 45)	
133	DEAD Killed scheduled	(45 - 45)	
135	DEAD Killed scheduled	(45 - 45)	
137	DEAD Killed scheduled	(45 - 45)	
139	DEAD Killed scheduled	(45 - 45)	

Appendix 2 Individual body weights (g)

Group	Animal Sex Number	Day numbers relative to Start Date											
		-2	-1	0	7	14	21	27					
3m	62	.	226.5	236.8	230.1	234.1	239.7	251.4					
	64	.	241.6	259.6	275.2	303.4	324.5	344.6					
	66	.	236.6	242.3	260.6	279.8	299.8	318.7					
	68	.	243.2	256.5	271.1	289.9	307.6	327.1					
	70	.	245.6	256.5	271.7	295.0	317.4	334.2					
	72	228.0	.	241.6	256.6	263.4	279.9	291.7					
	74	234.2	.	250.0	256.1	272.7	287.6	300.2					
	76	227.1	.	241.4	253.4	272.0	294.4	316.8					
	78	242.3	.	256.9	270.2	283.9	296.2	315.6					
	80	241.4	.	257.6	281.2	299.3	327.9	341.9					
	Mean	234.60	238.70	249.92	262.62	279.35	297.50	314.22					
	S.D.	7.17	7.57	8.56	14.68	20.42	25.64	27.75					
	N	5	5	10	10	10	10	10					
4m	82	.	231.3	239.7	248.3	262.8	283.1	303.8					
	84	.	250.6	262.4	268.3	290.6	310.5	330.8					
	86	.	240.8	250.8	269.5	289.6	308.0	330.2					
	88	.	234.5	239.7	251.0	268.4	287.2	309.8					
	90	.	232.9	241.8	257.5	276.6	296.3	313.2					
	92	230.1	.	247.0	255.3	270.6	287.6	305.2					
	94	242.7	.	261.8	274.5	293.0	321.8	340.6					
	96	253.2	.	270.6	286.2	299.5	317.5	331.9					
	98	225.3	.	243.7	255.6	272.6	295.5	306.9					
	100	235.5	.	253.8	270.5	291.8	315.4	336.7					
	Mean	237.36	238.02	251.13	263.67	281.55	302.29	320.91					
	S.D.	10.97	7.90	10.79	12.00	12.71	14.05	14.38					
	N	5	5	10	10	10	10	10					

Appendix 2 Individual body weights (g)

Group Sex	Animal Number	Day numbers relative to Start Date												
		-4	-2	-1	0	7	14	21	27	35	42	44		
5m	102			219.5	229.4	241.4	258.5	278.2	295.5					
	104			243.0	258.0	272.1	289.4	307.8	328.7					
	106			238.9	239.9	252.6	268.3	281.5	299.8					
	108			251.6	265.8	280.8	299.1	305.5	327.3					
	110			231.0	243.9	256.7	273.4	287.5	303.2					
	112		238.8		253.4	243.3	241.0	245.1	255.0					
	114		225.8		245.1	256.7	272.3	290.2	307.2					
	116		240.0		253.5	259.8	274.0	290.1	305.4					
	118		236.2		250.1	260.4	279.7	297.3	317.8					
	120		241.9		258.9	275.0	285.0	304.4	313.9					
	122		227.7		252.2	254.3	269.0	288.5	301.5	329.0	348.5	346.9		
	124		246.6		279.1	284.5	301.9	315.9	330.0	358.0	373.2	376.7		
	126		232.4		257.6	267.1	283.6	303.7	321.4	352.3	372.4	367.9		
	128		237.6		257.2	270.4	289.7	312.1	330.4	350.7	360.6	362.0		
	130		233.5		261.7	273.1	289.2	306.0	315.2	345.8	360.6	359.4		
	132		238.0		266.5	272.8	299.2	316.8	335.9	367.2	384.4	390.8		
	134		248.9		278.4	285.3	301.7	313.9	331.3	360.5	373.8	375.4		
	136		244.6		281.2	292.8	309.9	327.7	348.8	371.7	387.6	382.6		
	138		230.5		271.1	273.6	290.7	307.3	330.9	372.4	396.1	401.0		
	140		222.5		262.8	277.1	292.0	318.4	333.9	372.8	392.2	394.6		
Mean		236.23	236.54	234.80	258.29	267.49	283.38	299.90	316.66	358.04	374.94	376.73		
S.D.		8.56	6.35	12.58	13.36	13.96	16.69	18.52	20.44	14.07	15.34	17.78		
N		10	5	5	20	20	20	20	20	10	10	10		

Appendix 2 Individual body weights (g)

Group Sex	Animal Number	Day numbers relative to Start Date													
		-4	-3	0	7	14	21	27	35	42	44				
1f	1		159.5	168.7	175.9	187.7	202.6	212.4							
	3		162.3	177.7	176.3	181.9	191.5	197.9							
	5		168.1	175.1	194.7	200.9	211.9	217.7							
	7		170.1	177.5	185.1	189.6	195.5	197.3							
	9		155.0	168.0	167.7	173.9	182.0	179.6							
	11		155.7	166.6	171.3	174.3	183.4	188.6							
	13		176.7	190.1	190.0	195.4	204.1	213.7							
	15		170.0	178.8	181.6	191.6	189.1	190.9							
	17		165.3	181.8	193.1	200.2	207.7	207.1							
	19		162.7	174.4	175.2	180.2	187.3	196.6							
	21		160.3	173.4	175.1	179.4	186.8	192.5	204.9	213.0	215.6				
	23		155.3	167.6	167.6	169.8	177.5	184.9	196.8	201.2	200.9				
	25		153.4	165.7	169.8	175.6	173.3	178.9	197.1	206.5	205.8				
	27		177.5	188.8	195.0	202.5	208.2	214.1	234.6	243.1	243.1				
	29		163.2	177.9	189.4	193.3	197.2	220.9	226.4	233.6	230.4				
	31		166.2	181.3	186.0	193.9	195.2	205.0	219.3	220.3	222.5				
	33		152.0	170.4	174.7	183.5	192.5	199.7	206.4	212.4	211.8				
	35		160.2	170.2	168.0	173.7	181.0	191.3	203.0	216.0	213.6				
	37		176.6	194.6	183.6	193.1	201.0	210.3	217.9	223.7	223.3				
	39		172.1	189.5	198.7	205.4	210.2	217.7	230.2	234.3	237.7				
	Mean		164.48	163.00	176.91	180.94	187.30	193.90	200.86	213.66	220.41	220.47			
	S.D.		8.61	6.19	8.62	10.12	10.87	11.39	13.03	13.85	13.31	13.60			
	N		15	5	20	20	20	20	20	10	10	10			
	2f	41		155.2	163.1	163.5	169.7	168.9	171.1						
		43		163.1	170.8	170.6	175.5	185.8	192.9						
		45		157.7	172.8	170.6	177.8	188.5	206.7						
		47		175.1	185.6	190.2	190.9	196.8	202.1						
		49		172.7	187.9	182.6	190.6	190.4	198.6						
		51		151.5	168.8	174.8	181.9	180.2	190.6						
		53		167.7	189.6	190.3	194.5	200.3	205.9						
		55		159.2	173.0	178.7	179.6	181.7	186.4						
		57		164.7	172.4	173.8	173.4	178.7	184.4						
		59		157.3	167.5	167.5	173.8	176.2	181.9						
		Mean		160.08	164.76	175.15	176.26	180.77	184.75	192.06					
		S.D.		6.35	8.86	9.20	9.13	8.51	9.57	11.48					
		N		5	5	10	10	10	10	10					

Appendix 2 Individual body weights (g)

Group Sex	Animal Number	Day numbers relative to Start Date									
		-4	-3	0	7	14	21	27			
3f	61	.	163.2	174.5	178.8	181.4	188.0	196.0			
	63	.	168.2	179.5	177.6	182.5	189.6	197.0			
	65	.	174.8	190.7	187.1	186.7	193.9	203.0			
	67	.	161.2	175.5	178.7	183.3	191.2	200.9			
	69	.	153.8	170.9	179.2	184.2	194.4	200.2			
	71	161.4	.	172.1	174.8	183.4	191.1	195.9			
	73	168.1	.	191.6	182.4	187.7	195.1	203.1			
	75	174.0	.	185.9	189.5	191.4	199.9	200.5			
	77	163.8	.	178.4	183.1	186.1	199.3	201.5			
	79	156.9	.	170.7	170.8	171.4	181.9	187.0			
Mean	164.84	164.24	178.98	180.20	183.81	192.44	198.51				
S.D.	6.53	7.85	7.88	5.55	5.25	5.35	4.84				
N	5	5	10	10	10	10	10				
4f	81	.	166.7	173.2	171.3	178.1	190.2	197.8			
	83	.	154.1	164.2	163.7	168.2	175.7	183.4			
	85	.	158.1	173.5	172.8	177.6	181.7	186.7			
	87	.	152.3	163.7	166.7	176.6	178.6	184.8			
	89	.	174.6	184.1	185.1	187.2	193.3	201.0			
	91	164.0	.	176.2	177.0	185.9	190.8	194.0			
	93	166.5	.	183.8	183.2	187.9	191.5	197.6			
	95	169.2	.	182.8	179.2	186.6	186.3	195.1			
	97	159.0	.	167.9	172.5	185.0	184.3	189.6			
	99	160.5	.	176.4	189.1	188.7	192.8	201.1			
Mean	163.84	161.16	174.58	176.06	182.18	186.52	193.11				
S.D.	4.20	9.34	7.62	8.16	6.72	6.24	6.58				
N	5	5	10	10	10	10	10				

Appendix 3 Food consumption per cage (g/rat/day)

Group Sex	Cage Number	No in Cage	Day numbers relative to Start Date																	
			From: 0	7	14	21	28	35	42	44										
1f	1	5	12.5	12.4	13.1	13.1	13.1													
	3	5	13.1	13.3	13.0	13.2	13.5													
	5	5	12.8	13.0	13.2	13.5	14.8	14.1	14.2	13.8	14.1	14.2								
	7	5	12.1	12.5	12.9	13.7	14.2	14.1	14.2	13.8	14.1	14.2								
			Mean	12.63	12.80	13.05	13.38	14.50	13.95	14.15	14.15									
			S.D.	0.43	0.42	0.13	0.28	0.42	0.21	0.07	0.07									
			N	4	4	4	4	2	2	2	2									
2f	9	5	12.1	12.1	12.7	13.0														
	11	5	12.0	12.2	12.1	12.5														
			Mean	12.05	12.15	12.40	12.75													
			S.D.	0.07	0.07	0.42	0.35													
			N	2	2	2	2													
3f	13	5	12.2	12.3	12.8	13.1														
	15	5	12.4	12.8	14.3	13.4														
			Mean	12.30	12.55	13.55	13.25													
			S.D.	0.14	0.35	1.06	0.21													
			N	2	2	2	2													
4f	17	5	11.8	12.1	12.6	12.9														
	19	5	12.7	12.9	12.6	13.2														
			Mean	12.25	12.50	12.60	13.05													
			S.D.	0.64	0.57	0.00	0.21													
			N	2	2	2	2													
5f	21	5	12.3	12.2	12.6	12.7														
	23	5	11.4	11.4	12.1	12.5														
	25	5	12.0	12.5	13.0	13.5														
	27	5	12.1	12.6	11.8	12.3														
			Mean	11.95	12.18	12.38	12.75	13.85	13.55	13.80	13.80									
			S.D.	0.39	0.54	0.53	0.53	0.07	0.21	0.14	0.14									
			N	4	4	4	4	2	2	2	2									

Food consumption was measured per cage (5 animals/cage) over successive periods of 7 days (6 or 2 days in the week prior to necropsy) and expressed as g/rat/day

Appendix 4.1 Individual haematology results: red blood cell and coagulation parameters (Main groups)

Group	Animal Sex Number	RBC 10E12/L	Hb mmol/L	PCV L/L	MCV fL	MCH fmol	MCHC mmol/L	Reticulo cytes %	Thrombo cytes 10E9/L	Prothrom Time s
3m	62	9.40	10.2	0.479	51.0	1.09	21.3	0.71	754	42.4
	64	8.63	9.6	0.454	52.6	1.11	21.1	0.85	1018	40.7
	66	8.84	9.5	0.448	50.7	1.07	21.2	1.02	935	34.7
	68	9.65	10.2	0.498	51.6	1.06	20.5	0.90	897	38.6
	70	8.83	10.0	0.475	53.8	1.13	21.1	1.13	841	37.0
	72	9.01	9.6	0.461	51.2	1.07	20.8	1.00	911	51.3
	74	8.65	9.7	0.445	51.4	1.12	21.8	0.82	1025	46.2
	76	9.02	10.0	0.483	53.5	1.11	20.7	1.78	823	36.8
	78	9.03	10.1	0.489	54.2	1.12	20.7	1.52	874	37.5
	80	9.50	9.8	0.487	51.3	1.03	20.1	1.15	939	38.8
Mean		9.056	9.87	0.4719	52.13	1.091	20.93	1.088	901.7	40.40
	S.D.	0.352	0.26	0.0186	1.28	0.032	0.47	0.332	84.2	5.03
	N	10	10	10	10	10	10	10	10	10
4m	82	9.11	9.8	0.460	50.5	1.08	21.3	0.75	950	35.9
	84	8.72	9.3	0.449	51.5	1.07	20.7	1.13	975	34.7
	86*									
	88	8.71	9.7	0.458	52.6	1.11	21.2	1.22	861	34.3
	90	8.48	9.8	0.468	55.2	1.16	20.9	1.41	915	33.8
	92	9.23	10.4	0.499	54.1	1.13	20.8	1.08	1023	38.8
	94	9.57	10.3	0.493	51.5	1.08	20.9	0.88	920	41.5
	96	9.16	10.1	0.500	54.6	1.10	20.2	1.60	796	45.3
	98	9.68	10.8	0.507	52.4	1.12	21.3	1.05	786	44.1
	100	9.13	10.1	0.488	53.5	1.11	20.7	1.32	932	41.3
Mean		9.088	10.03	0.4802	52.88	1.107	20.89	1.160	906.4	38.86
	S.D.	0.397	0.44	0.0215	1.58	0.028	0.35	0.262	78.9	4.39
	N	9	9	9	9	9	9	9	9	9
5m	102	9.30	10.0	0.491	52.8	1.08	20.4	1.00	893	38.0
	104	9.48	10.3	0.494	52.1	1.09	20.9	1.21	862	34.1
	106	9.18	9.9	0.472	51.4	1.08	21.0	1.15	925	35.3
	108	9.20	9.9	0.483	52.5	1.08	20.5	1.42	799	36.9
	110	9.13	10.0	0.478	52.4	1.10	20.9	1.08	888	36.7
	112	10.15	11.0	0.517	50.9	1.08	21.3	0.51	711	50.3
	114	9.39	10.5	0.490	52.2	1.12	21.4	0.63	905	48.0
	116	9.85	10.3	0.513	52.1	1.05	20.1	1.21	820	43.4
	118	9.32	10.0	0.494	53.0	1.07	20.2	1.00	979	43.0
	120	9.64	11.0	0.528	54.8	1.14	20.8	1.02	864	43.2
Mean		9.464	10.29	0.4960	52.42	1.089	20.75	1.023	864.6	40.89
	S.D.	0.328	0.42	0.0179	1.04	0.026	0.44	0.272	74.2	5.52
	N	10	10	10	10	10	10	10	10	10

* = blood could not be obtained, because animal (#86) was found dead in metabolism cage

Appendix 4.1 Individual haematology results: red blood cell and coagulation parameters (Main groups)

Group Sex	Animal Number	RBC 10E12/L	Hb mmol/L	PCV L/L	MCV fL	MCH fmol	MCHC mmol/L	Reticulo cytes %	Thrombo cytes 10E9/L	Prothrom Time s
3F	61	9.34	9.6	0.477	51.1	1.03	20.1	1.31	1012*	34.5
	63	8.60	9.6	0.460	53.5	1.12	20.9	1.20	904	35.4
	65	8.75	9.3	0.462	52.8	1.06	20.1	1.33	908	34.4
	67	8.92	9.4	0.451	50.6	1.05	20.8	1.17	1103	35.5
	69	8.76	9.2	0.451	51.5	1.05	20.4	0.90	1052	36.0
	71	9.50	9.8	0.473	49.8	1.03	20.7	0.64	1120	35.5
	73	8.97	9.8	0.463	51.6	1.09	21.2	0.79	1006	41.2
	75	8.74	9.7	0.466	53.3	1.11	20.8	0.85	840	38.7
	77	8.95	9.6	0.456	50.9	1.07	21.1	0.65	1079	36.5
	79	9.15	10.0	0.489	53.4	1.09	20.4	1.25	825	34.6
Mean		8.968	9.60	0.4648	51.85	1.070	20.65	1.009	984.9	36.23
S.D.		0.286	0.24	0.0120	1.31	0.032	0.39	0.272	108.4	2.15
N		10	10	10	10	10	10	10	10	10
4F	81	8.71	9.3	0.439	50.4	1.07	21.2	1.07	1049	39.7
	83	8.99	9.7	0.460	51.2	1.08	21.1	0.77	930	41.5
	85	8.96	9.3	0.454	50.7	1.04	20.5	1.17	950	41.4
	87	8.95	10.0	0.488	54.5	1.12	20.5	1.14	799	40.3
	89	9.28	10.4	0.496	53.4	1.12	21.0	1.14	781	35.5
	91	9.22	9.6	0.467	50.7	1.04	20.6	0.64	1022	37.6
	93	8.65	9.5	0.453	52.4	1.10	21.0	0.90	913	35.0
	95	8.75	9.3	0.457	52.2	1.06	20.4	1.51	898	35.0
	97	8.55	9.3	0.447	52.3	1.09	20.8	0.79	868	34.9
	99	8.71	9.3	0.451	51.8	1.07	20.6	1.22	1023	40.2
Mean		8.877	9.57	0.4612	51.96	1.079	20.77	1.035	923.3	38.11
S.D.		0.244	0.37	0.0179	1.30	0.029	0.29	0.259	91.7	2.80
N		10	10	10	10	10	10	10	10	10
5F	101	8.97	9.5	0.455	50.7	1.06	20.9	0.70	935	41.5
	103	8.64	9.6	0.459	53.1	1.11	20.9	0.91	971	34.7
	105	9.23	9.8	0.479	51.9	1.06	20.5	0.69	887	33.9
	107	9.00	9.8	0.468	52.0	1.09	20.9	1.04	916	41.0
	109	9.02	9.8	0.475	52.7	1.09	20.6	1.33	880	38.0
	111	9.13	9.6	0.475	52.0	1.05	20.2	1.11	977	40.0
	113	8.59	9.8	0.463	53.9	1.14	21.2	0.86	965	34.6
	115	8.99	9.5	0.458	50.9	1.06	20.7	0.75	1070	39.7
	117	9.26	9.7	0.471	50.9	1.05	20.6	0.77	918	46.0
	119	8.76	9.8	0.477	54.5	1.12	20.5	1.31	940	42.2
Mean		8.959	9.69	0.4680	52.26	1.083	20.70	0.947	945.9	39.16
S.D.		0.230	0.13	0.0087	1.29	0.032	0.28	0.240	54.8	3.88
N		10	10	10	10	10	10	10	10	10

* = Platelet clumps in sample

Appendix 5.1 Individual haematology results: total and differential white blood cell counts (absolute and relative numbers)
(Main groups)

Group	Animal Sex Number	WBC		Lympho		Neutro		Eosino		Baso		Lympho		Neutro		Eosino		Baso		Mono							
		10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%	Absolute 10E9/L	%				
3m	62	4.4	2.7	1.6	0.02	0.01	0.08	60.7	36.7	0.5	0.2	1.9	60.7	36.7	0.5	0.2	1.9	60.7	36.7	0.5	0.2	1.9	60.7	36.7	0.5	0.2	1.9
	64	6.7	4.9	1.5	0.05	0.04	0.12	73.7	23.1	0.8	0.6	1.8	73.7	23.1	0.8	0.6	1.8	73.7	23.1	0.8	0.6	1.8	73.7	23.1	0.8	0.6	1.8
	66	4.9	3.5	1.2	0.02	0.02	0.12	71.8	25.2	0.4	0.4	2.4	71.8	25.2	0.4	0.4	2.4	71.8	25.2	0.4	0.4	2.4	71.8	25.2	0.4	0.4	2.4
	68	5.6	4.2	1.1	0.06	0.03	0.17	75.2	20.1	1.0	0.6	3.0	75.2	20.1	1.0	0.6	3.0	75.2	20.1	1.0	0.6	3.0	75.2	20.1	1.0	0.6	3.0
	70	6.5	5.3	1.0	0.04	0.04	0.18	80.9	15.2	0.6	0.6	2.7	80.9	15.2	0.6	0.6	2.7	80.9	15.2	0.6	0.6	2.7	80.9	15.2	0.6	0.6	2.7
	72	5.5	4.3	0.8	0.08	0.03	0.23	79.0	15.0	1.4	0.5	4.2	79.0	15.0	1.4	0.5	4.2	79.0	15.0	1.4	0.5	4.2	79.0	15.0	1.4	0.5	4.2
	74	2.8	2.2	0.5	0.00	0.01	0.08	78.3	18.5	0.1	0.3	2.8	78.3	18.5	0.1	0.3	2.8	78.3	18.5	0.1	0.3	2.8	78.3	18.5	0.1	0.3	2.8
	76	7.5	5.8	1.4	0.07	0.05	0.20	77.5	18.3	0.9	0.7	2.6	77.5	18.3	0.9	0.7	2.6	77.5	18.3	0.9	0.7	2.6	77.5	18.3	0.9	0.7	2.6
	78	6.5	5.4	0.9	0.06	0.03	0.13	83.3	13.3	0.9	0.5	2.0	83.3	13.3	0.9	0.5	2.0	83.3	13.3	0.9	0.5	2.0	83.3	13.3	0.9	0.5	2.0
	80	9.2	7.8	1.0	0.07	0.07	0.22	84.7	11.3	0.8	0.8	2.4	84.7	11.3	0.8	0.8	2.4	84.7	11.3	0.8	0.8	2.4	84.7	11.3	0.8	0.8	2.4
Mean		5.96	4.61	1.10	0.047	0.033	0.153	76.51	19.67	0.74	0.52	2.58	76.51	19.67	0.74	0.52	2.58	76.51	19.67	0.74	0.52	2.58	76.51	19.67	0.74	0.52	2.58
S.D.		1.76	1.62	0.34	0.026	0.018	0.055	6.87	7.37	0.36	0.18	0.69	6.87	7.37	0.36	0.18	0.69	6.87	7.37	0.36	0.18	0.69	6.87	7.37	0.36	0.18	0.69
N		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
4m	82	3.5	2.4	0.9	0.01	0.01	0.14	69.1	26.3	0.2	0.4	4.0	69.1	26.3	0.2	0.4	4.0	69.1	26.3	0.2	0.4	4.0	69.1	26.3	0.2	0.4	4.0
	84	7.2	6.1	0.9	0.04	0.04	0.12	84.5	12.8	0.6	0.5	1.7	84.5	12.8	0.6	0.5	1.7	84.5	12.8	0.6	0.5	1.7	84.5	12.8	0.6	0.5	1.7
	86*	3.7	2.8	0.8	0.00	0.01	0.12	75.8	20.3	0.1	0.4	3.3	75.8	20.3	0.1	0.4	3.3	75.8	20.3	0.1	0.4	3.3	75.8	20.3	0.1	0.4	3.3
	90	4.6	3.4	1.1	0.01	0.01	0.06	74.4	23.7	0.2	0.3	1.3	74.4	23.7	0.2	0.3	1.3	74.4	23.7	0.2	0.3	1.3	74.4	23.7	0.2	0.3	1.3
	92	7.0	5.7	1.0	0.06	0.04	0.25	81.0	14.2	0.8	0.5	3.5	81.0	14.2	0.8	0.5	3.5	81.0	14.2	0.8	0.5	3.5	81.0	14.2	0.8	0.5	3.5
	94	5.8	4.7	0.8	0.05	0.03	0.24	80.7	13.9	0.8	0.6	4.1	80.7	13.9	0.8	0.6	4.1	80.7	13.9	0.8	0.6	4.1	80.7	13.9	0.8	0.6	4.1
	96	5.6	4.5	0.8	0.04	0.03	0.21	80.7	14.4	0.8	0.5	3.7	80.7	14.4	0.8	0.5	3.7	80.7	14.4	0.8	0.5	3.7	80.7	14.4	0.8	0.5	3.7
	98	4.3	3.6	0.5	0.03	0.02	0.10	83.9	12.5	0.7	0.4	2.4	83.9	12.5	0.7	0.4	2.4	83.9	12.5	0.7	0.4	2.4	83.9	12.5	0.7	0.4	2.4
	100	7.5	6.4	0.7	0.08	0.05	0.24	85.9	9.3	1.0	0.6	3.2	85.9	9.3	1.0	0.6	3.2	85.9	9.3	1.0	0.6	3.2	85.9	9.3	1.0	0.6	3.2
	Mean		5.47	4.40	0.83	0.036	0.027	0.164	79.56	16.38	0.58	0.47	3.02	79.56	16.38	0.58	0.47	3.02	79.56	16.38	0.58	0.47	3.02	79.56	16.38	0.58	0.47
S.D.		1.53	1.45	0.17	0.026	0.015	0.071	5.46	5.70	0.33	0.10	1.00	5.46	5.70	0.33	0.10	1.00	5.46	5.70	0.33	0.10	1.00	5.46	5.70	0.33	0.10	1.00
N		9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
5m	102	6.3	5.1	0.8	0.07	0.03	0.22	81.7	13.2	1.1	0.5	3.5	81.7	13.2	1.1	0.5	3.5	81.7	13.2	1.1	0.5	3.5	81.7	13.2	1.1	0.5	3.5
	104	5.5	4.4	0.8	0.07	0.03	0.17	80.7	14.4	1.3	0.6	3.0	80.7	14.4	1.3	0.6	3.0	80.7	14.4	1.3	0.6	3.0	80.7	14.4	1.3	0.6	3.0
	106	5.9	4.2	1.6	0.03	0.03	0.14	70.4	26.3	0.5	0.5	2.3	70.4	26.3	0.5	0.5	2.3	70.4	26.3	0.5	0.5	2.3	70.4	26.3	0.5	0.5	2.3
	108	4.4	3.4	0.8	0.04	0.01	0.10	77.9	18.7	0.8	0.3	2.2	77.9	18.7	0.8	0.3	2.2	77.9	18.7	0.8	0.3	2.2	77.9	18.7	0.8	0.3	2.2
	110	5.4	4.4	0.8	0.03	0.02	0.17	81.5	14.3	0.6	0.4	3.1	81.5	14.3	0.6	0.4	3.1	81.5	14.3	0.6	0.4	3.1	81.5	14.3	0.6	0.4	3.1
	112	2.9	2.1	0.6	0.01	0.00	0.13	74.0	21.2	0.3	0.1	4.5	74.0	21.2	0.3	0.1	4.5	74.0	21.2	0.3	0.1	4.5	74.0	21.2	0.3	0.1	4.5
	114	4.4	3.7	0.4	0.04	0.01	0.22	83.8	10.1	0.8	0.3	5.1	83.8	10.1	0.8	0.3	5.1	83.8	10.1	0.8	0.3	5.1	83.8	10.1	0.8	0.3	5.1
	116	5.6	4.5	0.8	0.05	0.02	0.15	81.2	14.8	0.9	0.4	2.6	81.2	14.8	0.9	0.4	2.6	81.2	14.8	0.9	0.4	2.6	81.2	14.8	0.9	0.4	2.6
	118	5.8	4.9	0.6	0.03	0.03	0.19	84.7	11.0	0.6	0.5	3.2	84.7	11.0	0.6	0.5	3.2	84.7	11.0	0.6	0.5	3.2	84.7	11.0	0.6	0.5	3.2
	120	5.2	4.1	0.8	0.01	0.02	0.29	79.3	14.5	0.2	0.4	5.6	79.3	14.5	0.2	0.4	5.6	79.3	14.5	0.2	0.4	5.6	79.3	14.5	0.2	0.4	5.6
Mean		5.14	4.08	0.80	0.038	0.020	0.178	79.52	15.85	0.71	0.40	3.51	79.52	15.85	0.71	0.40	3.51	79.52	15.85	0.71	0.40	3.51	79.52	15.85	0.71	0.40	3.51
S.D.		0.99	0.86	0.31	0.021	0.011	0.055	4.40	4.91	0.34	0.14	1.17	4.40	4.91	0.34	0.14	1.17	4.40	4.91	0.34	0.14	1.17	4.40	4.91	0.34	0.14	1.17
N		10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10

* = blood could not be obtained, because animal (#86) was found dead in metabolism cage

Appendix 6.1 Individual clinical chemistry results (Main groups)

Group	Animal Sex Number	ALP U/L	ASAT U/L	ALAT U/L	GGT U/L	Bilirub Total umol/L	Total Protein g/L	Albumin g/L	Albumin/ Globulin	Glucose Plasma mmol/L
3m	62	147	282	37	0.1	2.8	55	29	1.12	7.87
	64	134	203	39	1.2	2.3	57	29	1.04	7.84
	66	135	190	39	0.0	2.7	57	29	1.04	9.95
	68	121	196	38	0.8	2.0	59	30	1.03	8.87
	70	151	212	39	1.8	2.9	57	29	1.04	6.60
	72	110	212	38	0.0	2.1	56	30	1.15	6.29
	74	125	172	33	0.1	1.8	56	30	1.15	12.28
	76	155	298	57	0.0	1.7	56	29	1.07	7.57
	78	147	284	59	0.4	2.1	60	31	1.07	6.07
	80	122	218	52	0.6	2.0	60	30	1.00	5.53
	Mean	134.7	226.7	43.1	0.50	2.24	57.3	29.6	1.071	7.887
	S.D.	15.0	44.4	9.2	0.61	0.42	1.8	0.7	0.052	2.046
	N	10	10	10	10	10	10	10	10	10
4m	82	195	238	33	0.7	1.9	57	30	1.11	10.74
	84	148	156	33	0.2	2.0	53	27	1.04	7.62
	86*	168	185	34	0.0	2.2	58	30	1.07	12.53
	90	145	174	34	0.5	2.4	60	30	1.00	9.65
	92	147	213	50	0.0	1.8	60	31	1.07	9.94
	94	194	256	49	0.4	1.9	59	31	1.11	7.85
	96	158	220	46	0.0	1.8	59	31	1.11	8.22
	98	167	314	60	0.1	1.9	61	32	1.10	7.45
	100	137	244	54	0.0	2.2	58	30	1.07	7.86
		Mean	162.1	222.2	43.7	0.21	2.01	58.3	30.2	1.076
	S.D.	21.0	48.1	10.4	0.26	0.21	2.3	1.4	0.037	1.741
	N	9	9	9	9	9	9	9	9	9
5m	102	141	184	42	0.0	1.9	56	29	1.07	8.34
	104	140	207	57	1.3	2.3	60	31	1.07	5.30
	106	130	247	41	0.0	2.0	55	28	1.04	10.71
	108	148	206	44	1.2	2.0	57	30	1.11	9.87
	110	164	288	62	0.3	2.5	62	32	1.07	6.95
	112	203	336	57	1.3	2.4	61	33	1.18	8.98
	114	163	217	52	0.0	2.2	59	31	1.11	9.54
	116	123	197	48	0.2	2.1	60	31	1.07	9.47
	118	176	176	57	0.1	2.2	59	31	1.11	7.36
	120	149	237	55	0.4	2.3	60	31	1.07	9.08
	Mean	153.7	229.5	51.5	0.48	2.19	58.9	30.7	1.090	8.560
	S.D.	23.6	49.8	7.3	0.56	0.19	2.2	1.4	0.039	1.608
	N	10	10	10	10	10	10	10	10	10

* = blood could not be obtained, because animal (#86) was found dead in metabolism cage

Appendix 6.1 Individual clinical chemistry results (Main groups)

Group	Animal Sex Number	Cholest erol mmol/L	Phospho lipids mmol/L	Triglyc erides mmol/L	Creatin ine umol/L	Urea mmol/L	PO4 mmol/L	Ca mmol/L	Cl mmol/L	K mmol/L	Na mmol/L
3m	62	1.30	1.28	0.51	26	6.0	2.50	2.59	104	5.1	144
	64	1.59	1.33	0.50	27	8.5	2.43	2.58	104	4.3	144
	66	1.72	1.47	0.71	27	8.9	2.55	2.63	105	3.7	145
	68	1.54	1.34	0.46	29	8.5	2.62	2.68	103	4.2	145
	70	1.37	1.29	0.71	32	8.4	2.53	2.63	106	4.2	147
	72	1.73	1.57	0.78	27	7.0	2.26	2.51	104	4.4	143
	74	1.74	1.39	0.42	22	6.6	2.20	2.64	104	4.1	142
	76	1.64	1.40	0.47	28	8.4	2.51	2.59	106	4.7	145
	78	2.03	1.58	0.53	28	8.4	2.56	2.64	106	4.6	145
	80	1.44	1.15	0.34	29	9.2	2.44	2.64	106	3.9	145
Mean		1.610	1.380	0.543	27.5	7.99	2.460	2.613	104.8	4.32	144.5
S.D.		0.213	0.133	0.143	2.5	1.06	0.134	0.047	1.1	0.40	1.4
N		10	10	10	10	10	10	10	10	10	10
4m	82	1.89	1.47	0.50	23	8.4	2.19	2.65	103	4.1	143
	84	2.05	1.63	0.85	25	6.5	2.52	2.68	106	4.3	143
	86*										
	88	1.85	1.58	0.77	21	6.0	2.12	2.64	103	3.8	143
	90	1.98	1.59	0.69	24	8.2	2.51	2.69	104	3.8	146
	92	2.02	1.71	0.56	31	11.2	2.19	2.55	103	3.9	142
	94	1.33	1.25	0.61	27	9.0	2.37	2.67	105	3.8	143
	96	1.21	1.15	0.40	28	8.7	2.43	2.58	107	4.2	144
	98	1.23	1.12	0.29	30	10.1	2.61	2.73	106	4.9	145
	100	1.58	1.29	0.45	27	9.0	2.68	2.64	105	3.8	144
Mean		1.682	1.421	0.569	26.2	8.57	2.402	2.648	104.7	4.07	143.7
S.D.		0.348	0.222	0.181	3.3	1.61	0.199	0.055	1.5	0.37	1.2
N		9	9	9	9	9	9	9	9	9	9
5m	102	1.62	1.46	0.58	26	9.0	2.50	2.68	104	4.1	143
	104	1.80	1.60	0.91	27	9.7	2.46	2.71	103	3.9	143
	106	1.67	1.38	0.56	24	5.8	2.52	2.61	106	4.5	143
	108	1.63	1.37	0.52	31	9.7	2.75	2.64	104	4.3	144
	110	1.55	1.40	0.37	30	11.3	2.97	2.68	105	4.0	147
	112	1.08	1.12	0.38	27	6.9	2.15	2.57	103	4.6	143
	114	1.40	1.25	0.37	30	9.7	2.29	2.63	106	4.4	144
	116	1.53	1.31	0.41	27	9.1	2.39	2.59	104	4.7	144
	118	1.19	1.16	0.40	27	10.1	2.70	2.62	106	4.2	144
	120	1.32	1.18	0.34	30	11.1	2.48	2.65	108	3.9	146
Mean		1.479	1.323	0.484	27.9	9.24	2.521	2.638	104.9	4.26	144.1
S.D.		0.227	0.149	0.173	2.2	1.71	0.236	0.043	1.6	0.29	1.4
N		10	10	10	10	10	10	10	10	10	10

* = blood could not be obtained, because animal (#86) was found dead in metabolism cage

Appendix 7.1 Individual volume, creatinine content and relative fluoride content of the urine (16-hour samples) collected on day 27-28 (Main groups)

Group	Animal Sex Number	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/nmol	
1m	2	12.9	5074	0.91	0.18	
	4	18.0	4174	0.99	0.24	
	6	13.7	4822	1.26	0.26	
	8	19.7	3802	1.11	0.29	
	10	13.0	4717	1.33	0.28	
	12	14.4	4436	0.90	0.20	
	14	31.9	2371	0.53	0.22	
	16	8.8	7791	0.20	0.03	
	18	7.8	9128	1.86	0.20	
	20	20.0	3494	0.73	0.21	
	Mean		16.02	4980.9	0.98	0.21
	S.D.		6.93	2015.5	0.46	0.07
	N		10	10	10	10
	2m	42	13.3	4883	4.22	0.86
		44	13.0	4756	5.70	1.20
		46	13.5	4722	6.98	1.48
		48	8.6	7432	8.60	1.16
		50	13.0	4349	5.61	1.29
		52	14.3	5258	7.97	1.52
		54	12.8	4656	6.38	1.37
56		10.0	6875	7.19	1.05	
58		8.2	8115	8.22	1.01	
60		10.3	4847	5.92	1.22	
Mean			11.70	5589.3	6.68	1.22
S.D.			2.21	1351.7	1.37	0.21
N			10	10	10	10

Appendix 7.1 Individual volume and creatinine content of the urine (16-hour samples) collected on day 27-28 (Main groups)

Group Sex	Animal Number	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/mmol
3m	62	7.9	6286	9.31	1.48
	64	14.2	4134	5.46	1.32
	66	10.2	5417	8.08	1.49
	68	10.0	5915	8.23	1.39
	70	5.9	11502	12.99	1.13
	72	4.6	12379	18.15	1.47
	74	4.0	12509	17.96	1.44
	76	6.9	8162	12.37	1.52
	78	7.8	8172	11.27	1.38
	80	9.7	7547	9.75	1.29
	Mean	8.12	8202.3	11.36	1.39
	S.D.	3.04	2991.2	4.15	0.12
	N	10	10	10	10
4m	82	9.2	6476	8.58	1.32
	84	9.6	6903	10.31	1.49
	86	10.9*	4928	8.31	1.69
	88	8.8	6598	9.81	1.49
	90	9.6	6303	8.82	1.40
	92	9.7	6222	11.59	1.86
	94	8.8	6480	11.86	1.83
	96	6.9	9322	17.09	1.83
	98	12.3	5415	8.89	1.64
	100	7.9	8610	15.32	1.78
	Mean	9.37	6725.7	11.06	1.63
	S.D.	1.49	1326.8	3.00	0.20
	N	10	10	10	10
5m	102	10.7	5067	10.33	2.04
	104	10.0	6475	2.63	0.41
	106	8.0	7633	12.62	1.65
	108	10.6	5428	10.39	1.91
	110	10.8	5320	9.38	1.76
	112	8.9	5998	15.71	2.62
	114	18.6	3219	6.35	1.97
	116	7.2	7362	15.09	2.05
	118	10.1	5825	12.30	2.11
	120	15.4	4002	8.60	2.15
	Mean	11.03	5632.9	10.34	1.87
	S.D.	3.45	1366.9	3.94	0.57
	N	10	10	10	10

* = Animal found dead in metabolism cage

Appendix 7.1 Individual volume and creatinine content of the urine (16-hour samples) collected on day 27-28 (Main groups)

Group	Animal Sex Number	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/mmol	
1f	1	20.7*	1971	0.67	0.34	
	3	5.1	7810	2.02	0.26	
	5	15.3	3200	0.89	0.28	
	7	20.5	2288	0.59	0.26	
	9	3.4	9485	1.77	0.19	
	11	18.6	1832	0.71	0.39	
	13	18.0	2512	0.86	0.34	
	15	8.4	4871	0.25	0.05	
	17	18.8	2588	0.73	0.28	
	19	17.5	2416	0.86	0.35	
	Mean	14.63	3897.3	0.93	0.27	
	S.D.	6.50	2674.1	0.54	0.10	
	N	10	10	10	10	
	2f	41	13.2	2783	1.61	0.58
		43	4.7	6733	4.47	0.66
		45	5.2	7211	5.37	0.74
		47	7.6	5278	3.41	0.65
		49	4.6	7736	6.44	0.83
		51	10.5	3867	3.11	0.81
53		5.3	7402	6.74	0.91	
55		9.8	3903	3.68	0.94	
57		5.6	6484	5.93	0.91	
59		15.0	2433	3.53	1.45	
Mean	8.15	5383.0	4.43	0.85		
S.D.	3.78	1998.7	1.65	0.25		
N	10	10	10	10		

Appendix 7.1 Individual volume and creatinine content of the urine (16-hour samples) collected on day 27-28 (Main groups)

Group Sex	Animal Number	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/mmol
3f	61	5.4	7467	6.55	0.88
	63	4.4	7293	5.51	0.76
	65	4.0	9368	7.55	0.81
	67	4.0	8051	5.89	0.73
	69	7.3	6290	4.01	0.64
	71	6.9	5405	6.40	1.18
	73	3.4	11390	8.12	0.71
	75	4.0	6879	6.46	0.94
	77	6.1	6833	5.40	0.79
	79	5.0	7990	7.09	0.89
	Mean	5.05	7696.6	6.30	0.83
	S.D.	1.34	1683.5	1.18	0.15
	N	10	10	10	10
4f	81	8.8	4022	4.36	1.08
	83	6.2	5299	6.60	1.25
	85	6.5	5632	5.89	1.05
	87	7.2	5130	5.88	1.15
	89	5.7	7830	6.10	0.78
	91	9.3	4330	4.21	0.97
	93	3.9	9628	7.88	0.82
	95	6.6	5562	6.57	1.18
	97	5.0	9390	7.94	0.85
	99	6.2	6212	6.11	0.98
	Mean	6.54	6303.5	6.15	1.01
	S.D.	1.61	1983.4	1.23	0.16
	N	10	10	10	10
5f	101	5.9	6227	7.61	1.22
	103	3.1	10188	10.21	1.00
	105	6.6	5625	6.99	1.24
	107	7.8	6487	6.64	1.02
	109	8.5	4598	5.12	1.11
	111	9.3	4380	5.42	1.24
	113	6.6	4949	7.14	1.44
	115	6.8	5347	5.63	1.05
	117	8.1	4478	7.28	1.63
	119	5.0	7429	9.47	1.28
	Mean	6.77	5970.8	7.15	1.22
	S.D.	1.81	1777.6	1.66	0.20
	N	10	10	10	10

Appendix 7.2 Individual volume and creatinine content of the urine (16-hour samples) collected on day 44-45 (Recovery groups)

Group	Animal Sex Number	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/mmol	
1m	22	20.6	3716	0.86	0.23	
	24	20.1	4165	0.86	0.21	
	26	9.5	6359	1.20	0.19	
	28	12.8	5183	1.61	0.31	
	30	19.3	3366	0.58	0.17	
	32	25.1	3102	0.68	0.22	
	34	21.6	3859	0.81	0.21	
	36	124.2*	517	0.25	0.48	
	38	7.7	8966	1.97	0.22	
	40	11.0	8006	1.40	0.17	
		Mean	27.19	4723.9	1.02	0.24
		S.D.	34.58	2492.2	0.52	0.09
	N	10	10	10	10	
5m	122	33.4	2359	0.77	0.33	
	124	9.9	8679	2.55	0.29	
	126	23.4	3428	1.01	0.30	
	128	13.2	5899	1.66	0.28	
	130	15.2	5623	1.69	0.30	
	132	12.3	6372	2.00	0.31	
	134	32.9	2735	0.91	0.33	
	136	18.1	4087	1.33	0.32	
	138	12.6	5860	2.01	0.34	
	140	10.8	6548	2.42	0.37	
		Mean	18.18	5159.0	1.64	0.32
		S.D.	8.81	1969.4	0.62	0.03
	N	10	10	10	10	

* = water bottle had emptied in the urine collector, value not included in the statistics

Appendix 7.2 Individual volume and creatinine content of the urine (16-hour samples) collected on day 44-45 (Recovery groups)

Group	Animal Sex Number	Urinary Volume mL	Urinary Creat umol/L	Urinary Fluoride mg/L	Fluoride/creat mg/mmol
1f	21	14.7	3303	0.97	0.29
	23	9.3	4344	1.18	0.27
	25	5.0	9356	2.02	0.22
	27	23.6	2419	0.59	0.24
	29	17.9	2818	0.68	0.24
	31	13.4	3828	0.87	0.23
	33	4.6	9400	2.03	0.22
	35	9.3	5154	0.77	0.15
	37	13.1	3861	0.79	0.21
	39	4.8	11217	2.10	0.19
	Mean	11.57	5570.0	1.20	0.23
	S.D.	6.22	3182.7	0.61	0.04
	N	10	10	10	10
5f	121	7.7	7188	2.08	0.29
	123	7.7	6512	1.93	0.30
	125	27.8	1884	0.57	0.30
	127	25.1	1885	0.57	0.30
	129	4.9	9342	3.18	0.34
	131	11.6	4567	1.42	0.31
	133	16.6	2770	0.89	0.32
	135	23.6	2089	0.51	0.24
	137	26.3	1823	0.54	0.30
	139	9.8	5243	1.21	0.23
	Mean	16.11	4330.3	1.29	0.29
	S.D.	8.85	2680.0	0.88	0.03
	N	10	10	10	10

Appendix 8.1 Individual terminal body weights and absolute organ weights (Main groups)

Group	Animal Sex Number	Terminal body wgt g	Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen		Testes		
			g	%	g	%	g	%	g	%	g	%	g	%	g	%	g	%	
1m	2	299.0	1.82	1.28	1.04	0.51	1.95	7.86	0.598	3.09									
	4	330.0	1.83	1.33	1.19	0.48	2.24	9.71	0.725	3.24									
	6	279.6	1.93	1.20	1.02	0.52	1.86	7.82	0.585	3.27									
	8	313.7	1.86	1.35	1.07	0.56	2.12	8.91	0.660	3.14									
	10	272.8	1.81	1.23	1.00	0.41	1.85	8.10	0.560	3.63									
	12	295.2	1.86	1.37	0.95	0.41	1.84	8.59	0.611	3.22									
	14	291.1	1.87	1.21	1.06	0.43	1.94	8.02	0.663	2.82									
	16	301.4	1.81	1.32	1.08	0.47	1.84	7.87	0.567	3.06									
	18	291.3	1.84	1.31	1.14	0.51	2.12	8.77	0.653	3.14									
	20	290.6	1.90	1.31	1.06	0.50	1.99	8.00	0.610	3.21									
	Mean		296.47	1.853	1.291	1.061	0.480	1.975	8.365	0.6232	3.182								
	S.D.		16.29	0.039	0.059	0.068	0.0050	0.141	0.618	0.0514	0.203								
	N		10	10	10	10	10	10	10	10	10								
	2m	42	299.3	1.90	1.15	1.18	0.44	2.01	9.10	0.659	3.25								
		44	302.9	1.83	1.35	1.23	0.60	2.17	9.06	0.618	3.15								
		46	280.9	1.76	1.33	1.03	0.47	1.92	8.52	0.555	3.18								
		48	285.0	1.74	1.27	0.98	0.45	1.77	7.68	0.690	2.38								
		50	294.2	1.70	1.30	1.01	0.45	1.99	9.29	0.613	2.80								
		52	321.1	1.81	1.31	1.13	0.46	2.15	9.76	0.649	2.48								
		54	285.5	1.82	1.22	1.10	0.48	1.94	8.52	0.522	3.04								
56		296.1	1.86	1.23	1.04	0.49	1.98	9.04	0.620	3.32									
58		293.0	1.80	1.26	1.19	0.45	2.04	8.57	0.632	3.00									
60		278.3	1.81	1.33	1.09	0.58	1.92	8.31	0.712	3.47									
Mean			293.63	1.803	1.275	1.098	0.487	1.989	8.785	0.6270	3.007								
S.D.			12.55	0.058	0.062	0.084	0.0057	0.116	0.585	0.0570	0.355								
N			10	10	10	10	10	10	10	10	10								

Appendix 8.1 Individual terminal body weights and absolute organ weights (Main groups)

Group Sex	Animal Number	Terminal body wgt g	Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen		Testes	
			g	%	g	%	g	%	g	%	g	%	g	%	g	%	g	%
3m	62	225.1	1.84	1.16	0.85	0.044	1.71	5.95	0.464	1.15*								
	64	309.9	1.88	1.37	1.18	0.056	2.16	9.26	0.687	3.14								
	66	286.7	1.81	1.17	0.98	0.043	1.98	8.60	0.594	2.95								
	68	291.3	1.85	1.25	1.27	0.046	2.05	8.46	0.607	3.23								
	70	298.9	1.89	1.43	1.27	0.046	2.05	8.46	0.607	3.23								
	72	265.5	1.74	1.08	0.97	0.043	1.82	7.81	0.506	3.35								
	74	268.5	1.85	1.43	1.07	0.057	1.84	7.75	0.465	3.25								
	76	280.1	1.73	1.25	1.18	0.054	1.93	8.62	0.641	3.11								
	78	284.7	1.74	1.23	1.01	0.053	1.83	8.15	0.644	2.99								
	80	310.0	1.91	1.36	1.24	0.045	2.11	8.84	0.742	3.34								
Mean		282.07	1.824	1.273	1.102	0.0487	1.944	8.234	0.5926	3.001								
S.D.		25.08	0.066	0.120	0.146	0.0056	0.143	0.933	0.0925	0.672								
N		10	10	10	10	10	10	10	10	10								
4m	82	269.0	1.75	1.50	1.02	0.050	1.82	7.80	0.632	2.82								
	84	298.4	1.87	1.51	1.14	0.046	2.03	9.04	0.688	3.29								
	88	273.3	1.79	1.34	0.98	0.060	1.84	8.48	0.667	3.18								
	90	280.1	1.79	1.29	1.03	0.047	1.94	8.41	0.617	3.58								
	92	274.8	1.81	1.12	0.99	0.046	1.77	9.45	0.563	2.81								
	94	305.2	1.85	1.31	1.10	0.050	2.08	9.44	0.540	3.32								
	96	299.2	1.82	1.24	1.20	0.059	2.07	9.72	0.609	3.51								
	98	270.1	1.85	1.12	0.94	0.038	1.80	8.50	0.461	3.17								
	100	305.4	1.90	1.29	1.31	0.051	2.10	9.81	0.706	2.94								
	Mean		286.17	1.826	1.302	1.079	0.0497	1.939	8.961	0.6092	3.180							
S.D.		15.56	0.046	0.139	0.120	0.0068	0.134	0.695	0.0778	0.279								
N		9	9	9	9	9	9	9	9	9								
5m	102	262.3	1.81	1.14	1.00	0.049	1.98	8.34	0.520	3.22								
	104	293.2	1.80	1.21	1.12	0.051	2.01	9.13	0.580	2.70								
	106	264.4	1.85	1.23	1.20	0.056	1.90	7.81	0.529	3.09								
	108	290.6	1.83	1.23	1.21	0.055	1.81	8.92	0.635	3.22								
	110	272.5	1.84	1.12	0.99	0.054	1.85	7.90	0.491	3.06								
	112	224.9	1.83	1.11	1.19	0.051	1.72	7.10	0.405	1.21*								
	114	274.4	1.84	1.15	1.02	0.048	1.89	8.83	0.510	3.13								
	116	272.2	1.78	1.18	0.98	0.053	1.89	8.51	0.502	2.81								
	118	287.7	1.85	1.19	1.05	0.045	1.94	8.78	0.515	3.25								
	120	281.1	1.76	1.18	1.20	0.049	1.84	8.46	0.547	2.61								
Mean		272.33	1.819	1.174	1.096	0.0511	1.883	8.378	0.5234	2.830								
S.D.		19.72	0.031	0.043	0.098	0.0034	0.084	0.618	0.0597	0.613								
N		10	10	10	10	10	10	10	10	10								

* = Testes small (bilateral)

Appendix 8.1 Individual terminal body weights and absolute organ weights (Main groups)

Group Sex	Animal Number	Terminal body wgt		Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen	
		g		g	g	g	g	g	g	g	g	g	g	g	g	g	g
3f	61	173.4	1.72	0.89	0.67	0.049	1.21	5.41	0.409								
	63	172.4	1.71	0.99	0.74	0.055	1.27	4.90	0.397								
	65	177.8	1.76	0.98	0.83	0.060	1.37	5.20	0.396								
	67	174.1	1.66	0.88	0.68	0.055	1.16	4.93	0.352								
	69	180.3	1.65	0.86	0.72	0.050	1.36	5.47	0.392								
	71	174.9	1.69	0.98	0.76	0.053	1.48	5.32	0.395								
	73	178.4	1.67	0.93	0.75	0.059	1.36	5.08	0.447								
	75	177.8	1.65	0.95	0.81	0.065	1.46	5.96	0.413								
	77	179.5	1.76	1.03	0.78	0.064	1.22	5.31	0.378								
	79	162.7	1.61	0.91	0.67	0.054	1.17	5.07	0.406								
	Mean	175.13	1.688	0.940	0.741	0.0564	1.306	5.265	0.3985								
	S.D.	5.13	0.049	0.055	0.057	0.0055	0.116	0.311	0.0244								
	N	10	10	10	10	10	10	10	10								
4f	81	169.6	1.69	0.88	0.61	0.059	1.82	5.95	0.467								
	83	161.8	1.70	0.86	0.64	0.056	1.31	5.37	0.297								
	85	165.9	1.66	0.91	0.62	0.053	1.30	5.30	0.353								
	87	161.8	1.67	0.88	0.66	0.051	1.24	4.72	0.356								
	89	178.0	2.30*	0.90	0.72	0.058	1.22	5.00	0.383								
	91	172.5	1.65	0.87	0.81	0.044	1.30	5.36	0.362								
	93	175.9	1.69	0.88	0.72	0.064	1.27	5.46	0.419								
	95	174.4	1.63	0.99	0.71	0.051	1.22	5.39	0.404								
	97	171.5	1.63	1.00	0.66	0.061	1.32	5.09	0.477								
	99	180.7	1.75	0.94	0.67	0.056	1.28	5.09	0.364								
	Mean	171.21	1.737	0.911	0.682	0.0553	1.328	5.273	0.3882								
	S.D.	6.48	0.201	0.050	0.060	0.0058	0.177	0.329	0.0550								
	N	10	10	10	10	10	10	10	10								
5f	101	169.6	1.67	0.88	0.66	0.052	1.23	5.13	0.374								
	103	162.9	1.62	0.87	0.81	0.054	1.17	5.10	0.359								
	105	163.1	1.66	0.89	0.66	0.048	1.20	5.60	0.326								
	107	194.8	1.72	0.93	0.73	0.051	1.39	5.83	0.458								
	109	171.4	1.74	0.96	0.65	0.056	1.31	5.54	0.377								
	111	177.5	1.70	0.93	0.73	0.067	1.28	5.67	0.436								
	113	158.4	1.62	0.86	0.60	0.055	1.26	5.05	0.339								
	115	159.9	1.64	0.89	0.71	0.048	1.12	4.30	0.353								
	117	173.8	1.66	0.88	0.65	0.061	1.24	5.83	0.328								
	119	164.2	1.60	0.90	0.66	0.058	1.24	5.74	0.334								
	Mean	169.56	1.663	0.899	0.686	0.0550	1.244	5.379	0.3684								
	S.D.	10.82	0.046	0.031	0.059	0.0059	0.075	0.484	0.0453								
	N	10	10	10	10	10	10	10	10								

* = Fluid at the bottom of the skull; brains distorted

Appendix 8.2 Individual terminal body weights and absolute organ weights (Recovery groups)

Group Sex	Animal Number	Terminal body wgt										
		g	Brain	Lungs	Heart	Adrenals	Kidneys	Liver	Spleen	g	g	g
1f	21	197.8	1.69	1.01	0.77	0.057	1.30	5.93	0.523			
	23	189.4	1.71	0.90	0.70	0.047	1.24	5.08	0.499			
	25	187.6	1.72	1.02	0.68	0.048	1.30	5.23	0.486			
	27	228.4	1.82	1.04	0.83	0.055	1.48	5.56	0.455			
	29	216.7	1.71	1.08	0.75	0.058	1.32	5.48	0.499			
	31	203.5	1.65	0.99	0.85	0.059	1.39	5.33	0.510			
	33	197.9	1.67	1.00	0.71	0.057	1.39	5.25	0.519			
	35	196.8	1.72	0.94	0.67	0.059	1.32	5.33	0.430			
	37	211.6	1.68	0.96	0.76	0.053	1.37	5.34	0.549			
	39	221.4	1.74	1.04	0.83	0.052	1.41	6.17	0.517			
Mean		205.11	1.711	0.998	0.755	0.0545	1.352	5.470	0.4987			
S.D.		13.80	0.047	0.053	0.065	0.0044	0.069	0.337	0.0346			
N		10	10	10	10	10	10	10	10			
5f	121	188.7	1.65	1.00	0.68	0.059	1.30	5.45	0.490			
	123	199.6	1.77	0.96	0.73	0.051	1.35	5.04	0.460			
	125	213.8	1.67	0.95	0.80	0.058	1.38	6.55	0.571			
	127	192.2	1.73	0.91	0.74	0.045	1.20	4.92	0.539			
	129	201.7	1.74	0.97	0.74	0.064	1.40	6.17	0.508			
	131	204.7	1.77	0.99	0.72	0.050	1.52	5.40	0.409			
	133	201.6	1.70	0.98	0.68	0.050	1.31	5.54	0.496			
	135	201.7	1.75	0.96	0.74	0.054	1.35	5.28	0.488			
	137	195.1	1.69	1.01	0.79	0.059	1.28	5.60	0.449			
	139	189.5	1.70	0.92	0.66	0.048	1.22	4.60	0.424			
Mean		198.86	1.717	0.965	0.728	0.0538	1.331	5.455	0.4834			
S.D.		7.68	0.041	0.032	0.046	0.0060	0.093	0.574	0.0499			
N		10	10	10	10	10	10	10	10			

Appendix 9.1 Individual terminal body weights and relative organ weights (Main groups)

Group Sex	Animal Number	Terminal body wgt g	Brain		Lungs		Heart		Adrenals		Kidneys		Liver		Spleen	
			rel. wgt g/kg	body wgt												
3f	61	173.4	9.92	5.13	3.86	0.283	6.98	31.2	2.36							
	63	172.4	9.92	5.74	4.29	0.319	7.37	28.4	2.30							
	65	177.8	9.90	5.51	4.67	0.337	7.71	28.2	2.23							
	67	174.1	9.53	5.05	3.91	0.316	6.66	28.3	2.02							
	69	180.3	9.15	4.77	3.99	0.277	7.54	30.3	2.17							
	71	174.9	9.66	5.60	4.35	0.303	8.46	30.4	2.26							
	73	178.4	9.36	5.21	4.20	0.331	7.62	28.5	2.51							
	75	177.8	9.28	5.34	4.56	0.366	8.21	33.5	2.32							
	77	179.5	9.81	5.74	4.35	0.357	6.80	29.6	2.11							
	79	162.7	9.90	5.59	4.12	0.332	7.19	31.2	2.50							
Mean		175.13	9.643	5.368	4.230	0.3221	7.454	30.06	2.278							
S.D.		5.13	0.295	0.323	0.268	0.0289	0.582	1.63	0.157							
N		10	10	10	10	10	10	10	10							
4f	81	169.6	9.96	5.19	3.60	0.348	10.73	35.1	2.75							
	83	161.8	10.51	5.32	3.96	0.346	8.10	33.2	1.84							
	85	165.9	10.01	5.49	3.74	0.319	7.84	31.9	2.13							
	87	161.8	10.32	5.44	4.08	0.315	7.66	29.2	2.20							
	89	178.0	12.92	5.06	4.04	0.326	6.85	28.1	2.15							
	91	172.5	9.57	5.04	4.70	0.255	7.54	31.1	2.10							
	93	175.9	9.61	5.00	4.09	0.364	7.22	31.0	2.38							
	95	174.4	9.35	5.68	4.07	0.292	7.00	30.9	2.32							
	97	171.5	9.50	5.83	3.85	0.356	7.70	29.7	2.78							
	99	180.7	9.68	5.20	3.71	0.310	7.08	28.2	2.01							
Mean		171.21	10.143	5.325	3.984	0.3231	7.772	30.84	2.266							
S.D.		6.48	1.043	0.281	0.306	0.0329	1.114	2.20	0.303							
N		10	10	10	10	10	10	10	10							
5f	101	169.6	9.85	5.19	3.89	0.307	7.25	30.2	2.21							
	103	162.9	9.94	5.34	4.97	0.331	7.18	31.3	2.20							
	105	163.1	10.18	5.46	4.05	0.294	7.36	34.3	2.00							
	107	194.8	8.83	4.77	3.75	0.262	7.14	29.9	2.35							
	109	171.4	10.15	5.60	3.79	0.327	7.64	32.3	2.20							
	111	177.5	9.58	5.24	4.11	0.377	7.21	31.9	2.46							
	113	158.4	10.23	5.43	3.79	0.347	7.95	31.9	2.14							
	115	159.9	10.26	5.57	4.44	0.300	7.00	26.9	2.21							
	117	173.8	9.55	5.06	3.74	0.351	7.13	33.5	1.89							
	119	164.2	9.74	5.48	4.02	0.353	7.55	35.0	2.03							
Mean		169.56	9.831	5.314	4.055	0.3249	7.341	31.72	2.169							
S.D.		10.82	0.439	0.256	0.387	0.0343	0.290	2.36	0.166							
N		10	10	10	10	10	10	10	10							

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668sl

Animal	Group:1	Contr.	Males
A0002	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Very slight focal mononuclear cell infiltrate			
KIDNEYS : Very slight basophilic tubules			
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes			
NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI			
A0004	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
KIDNEYS : Very slight basophilic tubules			
LARYNX : Slight focal mononuclear cell infiltrate			
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes			
NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI			
A0006	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
KIDNEYS : Slight basophilic tubules Slight focal transitional cell hyperplasia			
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes			
NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI			

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:1	Contr.	Males
A0008	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	KIDNEYS :	Slight focal transitional cell hyperplasia Uni-lateral pelvic dilatation	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LARYNX, LIVER, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI		
A0010	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	KIDNEYS :	Very slight basophilic tubules	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI		
A0012	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	KIDNEYS :	Slight basophilic tubules Slight focal transitional cell hyperplasia Very slight medullary mineralisation	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI		

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:1	Contr.	Males
A0014	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI		
A0016	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	KIDNEYS :	Slight basophilic tubules Slight focal transitional cell hyperplasia	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI		
A0018	survivor killed on day 28		
	Macroscopic findings		
	LUNGS :	Petechia(e) medial lobe , 2 mm	
	Microscopic findings		
	KIDNEYS :	Slight focal transitional cell hyperplasia Very slight basophilic tubules	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
	LUNGS :	Alveolar microhaemorrhage(s)	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, LARYNX, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI		

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:1	Contr.	Males
A0020	survivor		killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

KIDNEYS : Very slight focal transitional cell hyperplasia
Bi-lateral pelvic dilatation
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TESTES, TRACHEA/BRONCHI

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8658s1

Animal	Group:1	Contr.	Females
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A0001 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

KIDNEYS : Very slight basophilic tubules

LIVER : Very slight hepatocellular micro-vesicular vacuolation

NO ABNORMALITIES DETECTED IN:

ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

A0003 survivor
killed on day 28

Macroscopic findings

THYMUS : Red patches

Microscopic findings

KIDNEYS : Very slight basophilic tubules

LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes

THYMUS : Microhaemorrhage(s)

NO ABNORMALITIES DETECTED IN:

ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

A0005 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes

NO ABNORMALITIES DETECTED IN:

ADRENALS, BRAIN, HEART, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TRACHEA/BRONCHI

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:1	Contr.	Females
A0007	survivor killed on day 28		
Macroscopic findings			
	THYMUS :	Uni-lateral red patches	
Microscopic findings			
	LARYNX :	Very slight focal mixed inflammatory-cell infiltration	
	LIVER :	Very slight hepatocellular micro-vesicular vacuolation	
	THYMUS :	Microhaemorrhage(s)	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, KIDNEYS, LUNGS, NASAL CAVITY, SPLEEN, TRACHEA/BRONCHI		
A0009	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
Microscopic findings			
	LIVER :	Very slight hepatocellular micro-vesicular vacuolation	
	TRACHEA/BRONCHI :	Very slight focal mononuclear cell infiltrate	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, HEART, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN		
A0011	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
Microscopic findings			
	HEART :	Slight focal mononuclear cell infiltrate	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
		Very slight hepatocellular micro-vesicular vacuolation	
	NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TRACHEA/BRONCHI		

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 Individual data pathology at the end of the treatment period

Study:8668sl

Animal	Group:1	Contr.	Females
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A0013 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

BRAIN : Slight focal pineal gland mononuclear cell infiltrate
Pineal gland cyst(s)
HEART : Slight focal mononuclear cell infiltrate
KIDNEYS : Uni-lateral pelvic dilatation
Very slight focal transitional cell hyperplasia
Very slight basophilic tubules
LIVER : Very slight mononuclear cell aggregates/necrotic
hepatocytes

NO ABNORMALITIES DETECTED IN:
ADRENALS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TRACHEA/BRONCHI

A0015 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

LARYNX : Very slight focal mononuclear cell infiltrate
LIVER : Very slight mononuclear cell aggregates/necrotic
hepatocytes

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, HEART, KIDNEYS, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

A0017 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

KIDNEYS : Very slight basophilic tubules
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Very slight hepatocellular micro-vesicular vacuolation

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-i-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:l	Contr.	Females
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A0017 Continued...

Microscopic findings

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

A0019 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

KIDNEYS : Very slight basophilic tubules
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Very slight hepatocellular micro-vesicular vacuolation

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, HEART, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:2	500ppm	Males
B0042	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Slight multifocal mononuclear cell infiltrate Very slight focal endocardial inflammatory cell infiltrate	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
B0044	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight multifocal mononuclear cell infiltrate	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
B0046	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight endocardial mixed inflammatory-cell infiltration	
	LIVER :	Very slight focal mononuclear cell infiltrate Slight hepatocellular micro-vesicular vacuolation	
B0048	survivor killed on day 28		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1 ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:2	500ppm	Males
B0050	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
		NO ABNORMALITIES DETECTED IN: HEART	
B0052	survivor killed on day 28		
	Macroscopic findings		
	KIDNEYS :	Uni-lateral flabby	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate Slight myocardial vacuolation	
	KIDNEYS :	Uni-lateral pelvic dilatation Very slight basophilic tubules	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
B0054	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate Slight myocardial vacuolation	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes Slight hepatocellular micro-vesicular vacuolation	

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:2	500ppm	Males
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B0056 survivor
killed on day 28

Macroscopic findings

THORACIC CAVITY : Hydrothorax

Microscopic findings

HEART : Slight multifocal mononuclear cell infiltrate
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes
THORACIC CAVITY : Microscopy not applicable

B0058 survivor
killed on day 28

Macroscopic findings

KIDNEYS : Uni-lateral flabby

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight focal mononuclear cell infiltrate
Very slight focal endocardial inflammatory cell infiltrate
KIDNEYS : Uni-lateral pelvic dilatation
Very slight focal transitional cell hyperplasia
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes

B0060 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Very slight focal mononuclear cell infiltrate
Slight myocardial vacuolation
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:2	500ppm	Females
B0041	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
		NO ABNORMALITIES DETECTED IN:	
		HEART, LIVER	
B0043	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight multifocal mononuclear cell infiltrate	
		Slight myocardial vacuolation	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	
B0045	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal endocardial mixed inflammatory-cell infiltration	
		Slight multifocal mononuclear cell infiltrate	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
B0047	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Slight myocardial vacuolation	
		Very slight multifocal mononuclear cell infiltrate	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:2	500ppm	Females
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B0049 survivor
killed on day 28

Macroscopic findings

THORACIC CAVITY : Slight hydrothorax
THYMUS : Red patches

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
THORACIC CAVITY : Microscopy not applicable
THYMUS : Microhaemorrhage(s)

NO ABNORMALITIES DETECTED IN:
LIVER

B0051 survivor
killed on day 28

Macroscopic findings

THYMUS : Red patches

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes
THYMUS : Microhaemorrhage(s)

B0053 survivor
killed on day 28

Macroscopic findings

THYMUS : Red patches

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes
Slight hepatocellular micro-vesicular vacuolation
THYMUS : Microhaemorrhage(s)

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:2	500ppm	Females
B0055	survivor killed on day 28		
Macroscopic findings			
	THYMUS :	Uni-lateral red patches	
Microscopic findings			
	HEART :	Very slight multifocal mononuclear cell infiltrate	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
	THYMUS :	Microhaemorrhage(s)	
B0057	survivor killed on day 28		
Macroscopic findings			
	HEART :	Red apical elevation(s)	
	THYMUS :	Red patches	
Microscopic findings			
	HEART :	Very slight multifocal mononuclear cell infiltrate No microscopic evidence of macroscopic finding Slight myocardial vacuolation	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes Slight hepatocellular micro-vesicular vacuolation	
	THYMUS :	Microhaemorrhage(s)	
B0059	survivor killed on day 28		
Macroscopic findings			
	HEART :	Red apical elevation(s)	
Microscopic findings			
	HEART :	Slight focal mononuclear cell infiltrate Slight myocardial vacuolation Focal congestion	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	

Sub-acute(4 week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:3	1,500ppm	Males
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C0062 survivor
killed on day 28

Macroscopic findings

TESTES : Small
THORACIC CAVITY : Slight hydrothorax

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
TESTES : Very severe seminiferous tubular atrophy
Slight interstitial cell proliferation
Very slight seminiferous tubular mineralisation
THORACIC CAVITY : Microscopy not applicable

C0064 survivor
killed on day 28

Macroscopic findings

THORACIC CAVITY : Hydrothorax

Microscopic findings

HEART : Slight multifocal mononuclear cell infiltrate
Very slight focal endocardial inflammatory cell infiltrate
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
THORACIC CAVITY : Microscopy not applicable

C0066 survivor
killed on day 28

Macroscopic findings

THORACIC CAVITY : Hydrothorax

Microscopic findings

HEART : Slight multifocal mononuclear cell infiltrate
Very slight focal endocardial inflammatory cell infiltrate
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
THORACIC CAVITY : Microscopy not applicable

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group	1,500ppm	Males
C0068	survivor		
	killed on day 28		
Macroscopic findings			
THORACIC CAVITY : Hydrothorax			
Microscopic findings			
HEART :	Very slight focal mononuclear cell infiltrate		
LIVER :	Slight hepatocellular micro-vesicular vacuolation mainly periportal		
	Very slight mononuclear cell aggregates/necrotic hepatocytes		
THORACIC CAVITY : Microscopy not applicable			
C0070	survivor		
	killed on day 28		
Macroscopic findings			
HEART :	Right ventricular flabby		
	Right ventricular red area , 3 mm		
KIDNEYS :	Uni-lateral flabby		
THORACIC CAVITY : Hydrothorax			
Microscopic findings			
HEART :	Very slight multifocal mononuclear cell infiltrate		
	Focal congestion		
KIDNEYS :	Uni-lateral pelvic dilatation		
	Very slight focal transitional cell hyperplasia		
LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes		
THORACIC CAVITY : Microscopy not applicable			
C0072	survivor		
	killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART :	Slight myocardial vacuolation		
	Very slight multifocal mononuclear cell infiltrate		
	Very slight focal endocardial inflammatory cell infiltrate		
LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes		

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:3	1,500ppm	Males
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C0074 survivor
killed on day 28

Macroscopic findings
THORACIC CAVITY : Hydrothorax

Microscopic findings
HEART : Very slight focal mononuclear cell infiltrate
THORACIC CAVITY : Microscopy not applicable

NO ABNORMALITIES DETECTED IN:
LIVER

C0076 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings
HEART : Slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Slight hepatocellular micro-vesicular vacuolation mainly periportal

C0078 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings
HEART : Very slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
LIVER : Slight hepatocellular micro-vesicular vacuolation mainly periportal

C0080 survivor
killed on day 28

MACROSCOPY : No gross lesions

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:3	1,500ppm	Males
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C0080 Continued.. .

Microscopic findings

HEART :	Slight multifocal mononuclear cell infiltrate
	Slight myocardial vacuolation
LIVER :	Slight hepatocellular micro vesicular vacuolation mainly periportal
	Very slight mononuclear cell aggregates/necrotic hepatocytes

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:	1,500ppm	Females
C0061	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight multifocal mononuclear cell infiltrate Slight myocardial vacuolation	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes Slight hepatocellular micro-vesicular vacuolation	
C0063	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight multifocal mononuclear cell infiltrate	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
C0065	survivor killed on day 28		
	Macroscopic findings		
	THORACIC CAVITY :	Slight hydrothorax	
	THYMUS :	Red patches	
	Microscopic findings		
	HEART :	Very slight multifocal mononuclear cell infiltrate	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
	THORACIC CAVITY :	Microscopy not applicable	
	THYMUS :	Microhaemorrhage(s)	
C0067	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:3	1,500ppm	Females
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C0067 Continued....

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes

C0069 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
LIVER : Slight hepatocellular micro-vesicular vacuolation

C0071 survivor
killed on day 28

Macroscopic findings

KIDNEYS : Flabby

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
KIDNEYS : Bi-lateral pelvic dilatation
Slight focal basophilic tubules

NO ABNORMALITIES DETECTED IN:
LIVER

C0073 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight multifocal mononuclear cell infiltrate

NO ABNORMALITIES DETECTED IN:
LIVER

Sub-acute(4 week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:3	1,500ppm	Females
C0075	survivor killed on day 28		
Macroscopic findings			
	HEART :	Red area	
	THYMUS :	Uni-lateral red patches	
Microscopic findings			
	HEART :	Slight myocardial vacuolation Very slight multifocal mononuclear cell infiltrate No microscopic evidence of macroscopic finding	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	
	THYMUS :	Microhaemorrhage(s)	
C0077	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	
Microscopic findings			
	HEART :	Very slight focal mononuclear cell infiltrate Very slight focal endocardial inflammatory cell infiltrate	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	
C0079	survivor killed on day 28		
	MACROSCOPY :	No gross lesions	
Microscopic findings			
	HEART :	Slight myocardial vacuolation Very slight focal mononuclear cell infiltrate	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Males
D0082	survivor		
	killed on day 28		
Macroscopic findings			
THORACIC CAVITY : Hydrothorax			
Microscopic findings			
HEART :	Slight endocardial mixed inflammatory-cell infiltration		
	Slight focal mononuclear cell infiltrate		
LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes		
THORACIC CAVITY :	Microscopy not applicable		
D0084	survivor		
	killed on day 28		
Macroscopic findings			
THORACIC CAVITY : Hydrothorax			
THYROID :	Uni-lateral white nodule , 2 mm		
Microscopic findings			
HEART :	Very slight multifocal mononuclear cell infiltrate		
	Slight focal endocardial inflammatory cell infiltrate		
LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes		
THORACIC CAVITY :	Microscopy not applicable		
THYROID :	Ectopic thymic tissue with an increased number of single cell necrosis		
NO ABNORMALITIES DETECTED IN:			
THYROID			
D0086	found dead		
	on day 28		
Macroscopic findings			
HEART :	Bi-lateral atrial enlarged		
TESTES :	Cryptorchism		
Microscopic findings			
HEART :	Very slight focal mononuclear cell infiltrate		
	* Atrial congestion		
* = PROBABLE CAUSE OF DEATH			

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Males
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D0086 Continued...

Microscopic findings

KIDNEYS : Slight basophilic tubules
LUNGS : Slight focal perivascular oedema

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LIVER, SPLEEN, TESTES,
TRACHEA/BRONCHI

D0088 survivor
killed on day 28

Macroscopic findings

THORACIC CAVITY : Hydrothorax

Microscopic findings

HEART : Very slight focal mononuclear cell infiltrate
LIVER : Very slight mononuclear cell aggregates/necrotic
hepatocytes
THORACIC CAVITY : Microscopy not applicable

D0090 survivor
killed on day 28

Macroscopic findings

THORACIC CAVITY : Hydrothorax

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
Very slight endocardial mixed inflammatory-cell
infiltration
LIVER : Very slight mononuclear cell aggregates/necrotic
hepatocytes
THORACIC CAVITY : Microscopy not applicable

D0092 survivor
killed on day 28

MACROSCOPY : No gross lesions

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Males
D0092	Continued....		
Microscopic findings			
HEART :	Slight myocardial vacuolation		
	Very slight focal mononuclear cell infiltrate		
LIVER :	Slight hepatocellular micro-vesicular vacuolation mainly periportal		
	Slight mononuclear cell aggregates/necrotic hepatocytes		
D0094	survivor		
	killed on day 28		
	MACROSCOPY : No gross lesions		
Microscopic findings			
HEART :	Slight myocardial vacuolation		
	Slight focal mononuclear cell infiltrate		
LIVER :	Slight hepatocellular micro-vesicular vacuolation mainly periportal		
	Slight mononuclear cell aggregates/necrotic hepatocytes		
D0096	survivor		
	killed on day 28		
	MACROSCOPY : No gross lesions		
Microscopic findings			
HEART :	Slight multifocal mononuclear cell infiltrate		
	Very slight focal endocardial inflammatory cell infiltrate		
LIVER :	Slight hepatocellular micro-vesicular vacuolation mainly periportal		
	Slight mononuclear cell aggregates/necrotic hepatocytes		
D0098	survivor		
	killed on day 28		
	MACROSCOPY : No gross lesions		
Microscopic findings			
HEART :	Very slight focal mononuclear cell infiltrate		
	Slight myocardial vacuolation		

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10 1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Males
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D0098 Continued...

Microscopic findings

LIVER : Slight hepatocellular micro-vesicular vacuolation mainly periportal
Very slight mononuclear cell aggregates/necrotic hepatocytes

D0100 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight focal mononuclear cell infiltrate
LIVER : Slight hepatocellular micro-vesicular vacuolation
Very slight mononuclear cell aggregates/necrotic hepatocytes

Sub acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop 1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Females
D0081	survivor		
	killed on day 28		
Macroscopic findings			
	KIDNEYS :	Uni-lateral flabby	
Microscopic findings			
	HEART :	Slight myocardial vacuolation	
		Very slight focal mononuclear cell infiltrate	
	KIDNEYS :	Uni-lateral pelvic dilatation	
		Slight focal transitional cell hyperplasia	
		Slight pyelitis	
	LIVER :	Slight mononuclear cell aggregates/necrotic hepatocytes	
		Slight hepatocellular micro-vesicular vacuolation	
D0083	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
Microscopic findings			
	HEART :	Slight myocardial vacuolation	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	
D0085	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
Microscopic findings			
	HEART :	Slight focal mononuclear cell infiltrate	
		Slight myocardial vacuolation	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	
D0087	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
Microscopic findings			
	HEART :	Very slight focal mononuclear cell infiltrate	
		Slight myocardial vacuolation	

Sub acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Females
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D0087 Continued....

Microscopic findings

LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes

D0089 survivor
killed on day 28

Macroscopic findings

BRAIN : Hydrocephalus
Malformation
HEART : Right ventricular dark elevation(s)

Microscopic findings

BRAIN : Hydrocephalus
Focal gliosis
HEART : Very slight multifocal mononuclear cell infiltrate
Congestion
Very slight focal endocardial inflammatory cell infiltrate
LIVER : Slight hepatocellular micro-vesicular vacuolation

D0091 survivor
killed on day 28

Macroscopic findings

THYMUS : Red patches

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight focal mononuclear cell infiltrate
Very slight focal endocardial inflammatory cell infiltrate
THYMUS : Microhaemorrhage(s)

NO ABNORMALITIES DETECTED IN:
LIVER

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:	5,000ppm	Females
D0093	survivor		
	killed on day 28		
Macroscopic findings			
	HEART :	Red area	
	THYMUS :	Red patches	
Microscopic findings			
	HEART :	Slight focal mononuclear cell infiltrate	
	LIVER :	Slight hepatocellular micro-vesicular vacuolation	
	THYMUS :	Microhaemorrhage(s)	
D0095	survivor		
	killed on day 28		
Macroscopic findings			
	HEART :	Red apical elevation(s)	
Microscopic findings			
	HEART :	Slight multifocal mononuclear cell infiltrate	
		Slight myocardial vacuolation	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
D0097	survivor		
	killed on day 28		
	MACROSCOPY :	No gross lesions	
Microscopic findings			
	HEART :	Very slight multifocal mononuclear cell infiltrate	
		Slight myocardial vacuolation	
	LIVER :	Very slight mononuclear cell aggregates/necrotic hepatocytes	
D0099	survivor		
	killed on day 28		
Macroscopic findings			
	KIDNEYS :	Uni-lateral pitted area	
	LIVER :	Pale appearance	

Sub-acute(4-week) inhalation toxicity study with 1,1,1-trifluoroethane in
rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:4	5,000ppm	Females
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D0099 Continued....

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight focal mononuclear cell infiltrate
KIDNEYS : No microscopic evidence of macroscopic finding
LIVER : Slight hepatocellular micro-vesicular vacuolation
periportal and mid-zonal

NO ABNORMALITIES DETECTED IN:
KIDNEYS

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Males
E0102	survivor killed on day 28		
Macroscopic findings			
ADRENALS : Uni-lateral dark red area			
Microscopic findings			
ADRENALS : Slight uni-lateral focal hyperaemia			
HEART : Slight multifocal mononuclear cell infiltrate			
Slight myocardial vacuolation			
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes			
Very slight hepatocellular micro-vesicular vacuolation			
mainly periportal			
NO ABNORMALITIES DETECTED IN:			
BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI			
E0104	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Very slight multifocal mononuclear cell infiltrate			
KIDNEYS : Very slight basophilic tubules			
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes			
Very slight hepatocellular micro-vesicular vacuolation			
mainly periportal			
NO ABNORMALITIES DETECTED IN:			
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TESTES, TRACHEA/BRONCHI			
E0106	survivor killed on day 28		
Macroscopic findings			
THORACIC CAVITY : Hydrothorax			
Microscopic findings			
HEART : Slight multifocal mononuclear cell infiltrate			

Sub-acute(4 week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Males
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E0106 Continued...

Microscopic findings

HEART : Very slight focal endocardial inflammatory cell infiltrate
KIDNEYS : Slight basophilic tubules
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes
THORACIC CAVITY : Microscopy not applicable

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TESTES, TRACHEA/BRONCHI

E0108 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
KIDNEYS : Very slight focal mononuclear cell infiltrate
Very slight basophilic tubules
LARYNX : Slight focal mononuclear cell infiltrate
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Very slight hepatocellular micro-vesicular vacuolation

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LUNGS, NASAL CAVITY, SPLEEN, TESTES,
TRACHEA/BRONCHI

E0110 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight myocardial vacuolation
Slight focal mononuclear cell infiltrate
KIDNEYS : Very slight focal transitional cell hyperplasia
Very slight basophilic tubules
LARYNX : Slight focal mononuclear cell infiltrate

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Males
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E0110 Continued....

Microscopic findings

LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Slight hepatocellular micro-vesicular vacuolation mainly periportal

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LUNGS, NASAL CAVITY, SPLEEN, TESTES,
TRACHEA/BRONCHI

E0112 survivor
killed on day 28

Macroscopic findings

EPIDIDYMIDES : Small
TESTES : Small

Microscopic findings

EPIDIDYMIDES : Slight focal interstitial mononuclear cell infiltrate
Decreased number of spermatozoa
HEART : Slight myocardial vacuolation
LIVER : Very slight mononuclear cell aggregates/necrotic hepatocytes
Slight hepatocellular micro-vesicular vacuolation throughout the liver
TESTES : Very severe seminiferous tubular atrophy
Slight interstitial cell proliferation
Very slight seminiferous tubular mineralisation

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

E0114 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight focal endocardial mixed inflammatory-cell infiltration

Sub-acute(4 week) inhalation toxicity study with 3,3,3 trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Males
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E0114 Continued....

Microscopic findings

HEART : Very slight focal mononuclear cell infiltrate
KIDNEYS : Very slight focal transitional cell hyperplasia
Very slight basophilic tubules
LIVER : Slight hepatocellular micro-vesicular vacuolation
periportal and mid-zonal
Very slight mononuclear cell aggregates/necrotic
hepatocytes
TESTES : Very slight seminiferous tubular atrophy

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TRACHEA/BRONCHI

E0116 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight myocardial vacuolation
KIDNEYS : Very slight focal transitional cell hyperplasia
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Slight hepatocellular micro-vesicular vacuolation mainly
periportal

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TESTES, TRACHEA/BRONCHI

E0118 survivor
killed on day 28

Macroscopic findings

HEART : Right ventricular flabby

Microscopic findings

HEART : Very slight focal mononuclear cell infiltrate
Slight myocardial vacuolation
No microscopic evidence of macroscopic finding
KIDNEYS : Uni-lateral pelvic dilatation

Sub acute(4 week) inhalation toxicity study with 3,3,3 trifluoroprop-1 ene in rats
TNO Quality of Life
Appendix 10.1 Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Males
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E0118 Continued....

Microscopic findings

KIDNEYS : Slight focal transitional cell hyperplasia
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Very slight hepatocellular micro-vesicular vacuolation
mainly periportal
TRACHEA/BRONCHI : Very slight focal mononuclear cell infiltrate

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TESTES

E0120 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight focal mononuclear cell infiltrate
Slight myocardial vacuolation
LIVER : Slight hepatocellular micro-vesicular vacuolation mainly
periportal
Very slight mononuclear cell aggregates/necrotic
hepatocytes

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TESTES, TRACHEA/BRONCHI

Sub acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Females
E0101	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Slight multifocal mononuclear cell infiltrate Slight myocardial vacuolation Very slight focal endocardial inflammatory cell infiltrate			
KIDNEYS : Very slight corticomedullary mineralisation			
LIVER : Very slight hepatocellular micro-vesicular vacuolation mainly periportal			
NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TRACHEA/BRONCHI			
E0103	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Slight multifocal mononuclear cell infiltrate Slight myocardial vacuolation			
LIVER : Very slight hepatocellular micro-vesicular vacuolation periportal and mid-zonal			
NO ABNORMALITIES DETECTED IN: ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY, SPLEEN, TRACHEA/BRONCHI			
E0105	survivor killed on day 28		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Slight myocardial vacuolation			
KIDNEYS : Very slight medullary mineralisation Very slight basophilic tubules			

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Females
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E0105 Continued....

Microscopic findings

LIVER : Slight hepatocellular micro-vesicular vacuolation
periportal and mid-zonal

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TRACHEA/BRONCHI

E0107 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight myocardial vacuolation
Slight multifocal mononuclear cell infiltrate
KIDNEYS : Very slight basophilic tubules
LIVER : Slight hepatocellular micro-vesicular vacuolation
throughout the liver

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TRACHEA/BRONCHI

E0109 survivor
killed on day 28

Macroscopic findings

THYMUS : Uni-lateral red appearance
Uni-lateral red patches

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight multifocal mononuclear cell infiltrate
LIVER : Slight hepatocellular micro-vesicular vacuolation
THYMUS : Microhaemorrhage(s)

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats

TNO Quality of Life

Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Females
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E0111 survivor
killed on day 28

Macroscopic findings

SKIN/SUBCUTIS : Sparsely haired
THYMUS : Red patches

Microscopic findings

HEART : Very slight multifocal mononuclear cell infiltrate
Slight myocardial vacuolation
KIDNEYS : Very slight basophilic tubules
LIVER : Slight hepatocellular micro-vesicular vacuolation
SKIN/SUBCUTIS : No microscopic evidence of macroscopic finding
THYMUS : Microhaemorrhage(s)

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY,
SKIN/SUBCUTIS, SPLEEN, TRACHEA/BRONCHI

E0113 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

ADRENALS : Very slight focal cortical mononuclear cell infiltrate
HEART : Very slight focal endocardial mixed inflammatory-cell
infiltration
KIDNEYS : Uni-lateral pelvic dilatation
Slight focal mononuclear cell infiltrate
Very slight basophilic tubules
LIVER : Very slight hepatocellular micro-vesicular vacuolation

NO ABNORMALITIES DETECTED IN:
BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TRACHEA/BRONCHI

E0115 survivor
killed on day 28

Macroscopic findings

THYMUS : Uni-lateral red patches

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.1 - Individual data pathology at the end of the treatment period

Study:8668s1

Animal	Group:5	15,000ppm	Females
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E0115 Continued...

Microscopic findings

HEART : Slight myocardial vacuolation
Very slight multifocal mononuclear cell infiltrate
KIDNEYS : Uni-lateral pelvic dilatation
LIVER : Slight mononuclear cell aggregates/necrotic hepatocytes
Very slight hepatocellular micro vesicular vacuolation
THYMUS : Microhaemorrhage(s)

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, LARYNX, LUNGS, NASAL CAVITY, SPLEEN,
TRACHEA/BRONCHI

E0117 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight myocardial vacuolation
LIVER : Very slight hepatocellular micro-vesicular vacuolation

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

E0119 survivor
killed on day 28

MACROSCOPY : No gross lesions

Microscopic findings

HEART : Slight multifocal mononuclear cell infiltrate
LIVER : Slight hepatocellular micro-vesicular vacuolation

NO ABNORMALITIES DETECTED IN:
ADRENALS, BRAIN, KIDNEYS, LARYNX, LUNGS, NASAL CAVITY,
SPLEEN, TRACHEA/BRONCHI

*** Listing Complete ***

Sub-acute(4-week) inhalation toxicity study with 3,3,3 trifluoroprop 1 ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:1	Contr.	Males
A0022	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART : Slight focal mononuclear cell infiltrate		
A0024	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART : Very slight focal mononuclear cell infiltrate		
A0026	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN: HEART		
A0028	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN: HEART		
A0030	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN: HEART		

Sub-acute(4-week) inhalation toxicity study with 3,3,3 trifluoroprop 1-ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:1	Contr.	Males
A0032	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight multifocal mononuclear cell infiltrate	
A0034	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
A0036	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Slight focal mononuclear cell infiltrate	
A0038	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN: HEART		
A0040	survivor killed on day 45		
	Macroscopic findings		
	THORACIC CAVITY :	Hydrothorax	
	THYMUS :	Uni-lateral red patches	

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:1	Contr.	Males
A0040	Continued...		

Microscopic findings

HEART : Very slight focal mononuclear cell infiltrate

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:	Contr	Females
A0021	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
A0023	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
A0025	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN:	HEART	
A0027	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN:	HEART	
A0029	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN:	HEART	

Sub-acute(4 week) inhalation toxicity study with 3,3,3-trifluoroprop-1 ene in rats
TNO Quality of Life
Appendix 10.2 Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:1	Contr.	Females
A0031	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
A0033	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
A0035	survivor killed on day 45		
	MACROSCOPY : No gross lesions		
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN: HEART		
A0037	survivor killed on day 45		
	Macroscopic findings		
	THYMUS :	Uni-lateral red patches	
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN: HEART		
A0039	survivor killed on day 45		
	MACROSCOPY : No gross lesions		

Sub-acute(4-week) innalation toxicity study with 3,3,3 trifluoroprop-1-ene in
rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:1	Contr.	Females
A0039	Continued...		

Microscopic findings
NO ABNORMALITIES DETECTED IN:
HEART

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:5	15,000ppm	Males
E0122	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
E0124	survivor killed on day 45		
	Macroscopic findings		
	HEART :	Right ventricular flabby	
	Microscopic findings		
	HEART :	No microscopic evidence of macroscopic finding Very slight focal mononuclear cell infiltrate	
E0126	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Slight multifocal mononuclear cell infiltrate	
E0128	survivor killed on day 45		
	Macroscopic findings		
	HEART :	Right ventricular flabby	
	Microscopic findings		
	HEART :	Slight focal mononuclear cell infiltrate	
E0130	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	

Sub-acute(4-week) inhalation toxicity study with 3,3,3 trifluoroprop-1 ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:5	15,000ppm	Males
E0130	Continued....		
Microscopic findings			
NO ABNORMALITIES DETECTED IN: HEART			
E0132	survivor killed on day 45		
MACROSCOPY : No gross lesions			
Microscopic findings			
NO ABNORMALITIES DETECTED IN: HEART			
E0134	survivor killed on day 45		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Very slight focal mononuclear cell infiltrate			
E0136	survivor killed on day 45		
Macroscopic findings			
THYMUS : Uni-lateral red patches			
Microscopic findings			
NO ABNORMALITIES DETECTED IN: HEART			
E0138	survivor killed on day 45		
MACROSCOPY : No gross lesions			
Microscopic findings			
HEART : Very slight focal mononuclear cell infiltrate			

Sub-acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in rats
TNO Quality of Life
Appendix 10.2 Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:5	15,000ppm	Males
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E0140	survivor		
	killed on day 45		

MACROSCOPY : No gross lesions

Microscopic findings

NO ABNORMALITIES DETECTED IN:
HEART

Sub-acute(4-week) inhalation toxicity study with 3,3,3 trifluoroprop-1 ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:5	15,000ppm	Females
E0121	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
E0123	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN:		
	HEART		
E0125	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	HEART :	Very slight focal mononuclear cell infiltrate	
E0127	survivor killed on day 45		
	MACROSCOPY :	No gross lesions	
	Microscopic findings		
	NO ABNORMALITIES DETECTED IN:		
	HEART		
E0129	survivor killed on day 45		
	Macroscopic findings		
	THORACIC CAVITY :	Hydrothorax	
	THYMUS :	Uni-lateral red patches	

Sub-acute(4-week) inhalation toxicity study with 3,3,3 trifluoroprop-1 ene in rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:5	15,000ppm	Females
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E0129 Continued....

Microscopic findings
NO ABNORMALITIES DETECTED IN:
HEART

E0131 survivor
killed on day 45

Macroscopic findings
LUNGS : Petechia(e) left lung
THORACIC CAVITY : Hydrothorax

Microscopic findings
HEART : Very slight focal mononuclear cell infiltrate

E0133 survivor
killed on day 45
MACROSCOPY : No gross lesions

Microscopic findings
NO ABNORMALITIES DETECTED IN:
HEART

E0135 survivor
killed on day 45
MACROSCOPY : No gross lesions

Microscopic findings
NO ABNORMALITIES DETECTED IN:
HEART

E0137 survivor
killed on day 45
MACROSCOPY : No gross lesions

Microscopic findings
NO ABNORMALITIES DETECTED IN:
HEART

Sub acute(4-week) inhalation toxicity study with 3,3,3-trifluoroprop-1-ene in
rats
TNO Quality of Life
Appendix 10.2 - Individual data pathology at the end of the recovery period

Study:8668s2

Animal	Group:5	15,000ppm	Females
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E0139	survivor		
	killed on day 45		

MACROSCOPY : No gross lesions

Microscopic findings

NO ABNORMALITIES DETECTED IN:
HEART

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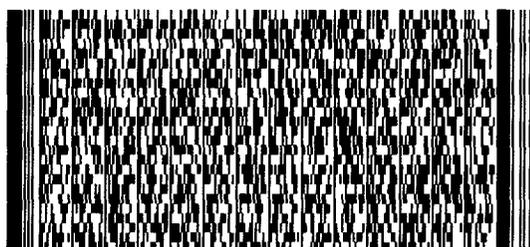


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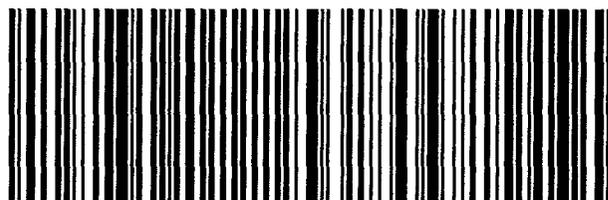
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