

Final Report

Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate

Fraunhofer ITEM Study No. 02G08016

Number 1 of 2 Originals

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Executive Director:
[REDACTED]

Sponsor:
American Petroleum Institute
1220 L Street
NW Washington, DC 20005
USA

This final report consists of 350 pages

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1 Statements

1.1 Statement of Study Director

Study No.: 02G08016

Test Substance: Roofing Asphalt Fume Condensate

Title: Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate

This 28 day inhalation study was conducted in compliance with

- OECD Guideline for Testing of Chemicals 422 Adopted 22 March 1996 "Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test",
- EPA Health Effects Test Guidelines OPPTS 870.3650 Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test. EPA712-C-00-368 July 2000,
- OECD Guideline for Testing of Chemicals 474 Adopted 21 July 1997 "Mammalian Erythrocyte Micronucleus Test",
- EPA Health Effects Test Guidelines OPPTS 870.5395 Mammalian erythrocyte micronucleus test. EPA712 C 98 226, August 1998,

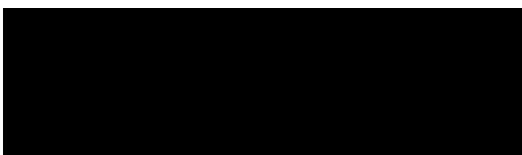
and in compliance with the Principles of Good Laboratory Practice (German Chemicals Law § 19a, Appendix 1, July 02, 2008).

This report provides a correct and accurate record of the results obtained.

I accept the responsibility for the validity of the study.

Date

07.07.09



1.2 Statement of Principal Scientists

Fraunhofer ITEM Study No.: 02G08016

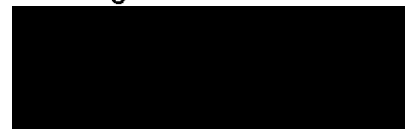
Test Substance: Roofing Asphalt Fume Condensate

Title: Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate

We, the undersigned, hereby declare that the work in this study was performed by us or under our supervision according to the procedures herein described and that this report provides a correct and faithful record of the results obtained.

Signature/Date

Animal House Veterinarian:



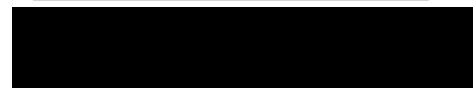
Aerosol Physicist:



Chemical Analysis:



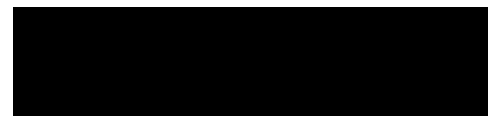
Clinical Chemistry:



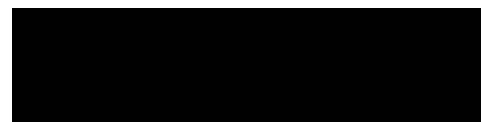
Histopathology:



Scientist responsible for
Micronucleus Test:



Biostatistics:



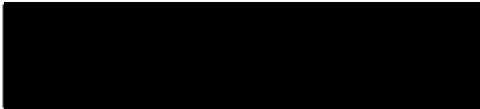
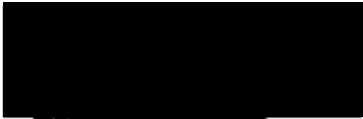
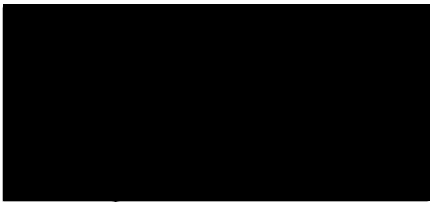
Principal Investigator:



see page 7

(responsible for tissue trimming and slide preparation)

1.3 Statement of the Principal Investigator

Fraunhofer ITEM Study/Protocol No. 02G08016	Phase Contract No. Fh-ITEM 02-2008
Histopathologist's Authentication and Statement of Compliance	
Fraunhofer ITEM Study/Protocol No. 02G08016 Nycomed Phase Contract No. Fh-ITEM 02-2008	
This study phase was conducted by me or under my supervision in accordance with the methods described in the Phase Contract and in full compliance with the current principles of Good Laboratory Practice Regulations as set forth the German Chemicals Law and the OECD- and EC-Regulations in their version being in force during the period of the study.	
	
Place, date	Signature
	
Place, date	
Head of the Institute of Pharmacology and Preclinical Drug Safety (IPAS) Nycomed GmbH	

1.4 Quality Assurance Statement

Fraunhofer ITEM Study No.: 02 G 08016

Test Substance: Roofing Asphalt Fume Condensate

Title: Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate

The Quality Assurance Unit (QAU) hereby declares that the study was inspected at intervals adequate to ensure the integrity of the study and that the findings were reported to the Study Director and the management of Fraunhofer ITEM. Exact dates of inspections and inspection reports are given below. This report describes the methods and procedures used in the study and the documented results reflect the raw data of the study.

Date of Inspection	Type of Inspection	Date of Inspection Report
May 22, 23, 27, 2008	Study Plan (draft 1)	May 28, 2008
June 18, 2008	Study Plan (draft 2)	June 18, 2008
July 16, 2008	Exp. Phase: Preparing animals for exposure	July 29, 2008
July 17, 2008	Exp. Phase: Start of exposure	July 29, 2008
July 28, 2008	Exp. Phase: End of daily exposure	July 29, 2008
July 31 – Aug. 1, 2008	Exp. Phase: Sampling of particles; Storage of test item	Aug. 01, 2008
Aug. 04. 2008	Exp. Phase: Mating	Aug. 04, 2008
Aug. 12, 2008	Exp. Phase: FOB, locomotor activity	Aug. 12, 2008
Aug. 13, 2008	Exp. Phase: Necropsy, spermatology, micronucleus test	Aug. 13, 2008

Aug. 21, 2008	Study plan amendment No. 2, Phase contract	Aug. 22, 2008
Aug. 25, 2008	Exp. Phase: Investigations in pups	Aug. 25, 2008
Aug. 26, 2008	Exp. Phase: Necropsy of dams	Aug. 26, 2008
Sept. 09, 2008	In life raw data: Provantis printouts	Sept. 09, 2008
Dec. 08, 12, 2008	Raw data of analytical investigations	Dec. 08, 2008
Nov. 26 – Dec. 04, 2008 Jan. 05 – 06, 2009	Final Report (draft 1)	Jan. 07, 2009
Jan. 29 . Feb. 04, 2009	Final Report (draft 2)	Feb. 04, 2009
April 21, 2009	Final Report (draft 3)	April 24, 2009

Date

July 09, 2009

Signature

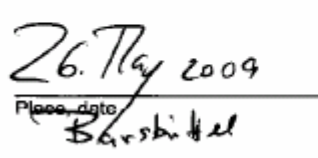


Fraunhofer Institute of Toxicology and Experimental Medicine
(Fraunhofer ITEM)

Head of Quality Assurance:



1.5 Quality Assurance Statement of the Test Site

Fraunhofer ITEM Study/Protocol No. 02G08016		Phase Contract No. Fh-ITEM 02-2008
QUALITY ASSURANCE STATEMENT		
Study/Protocol No.:	Fraunhofer ITEM No. 02G08016	
Test Facility:	Fraunhofer ITEM Nikolai-Fuchs-Str. 1, 30625 Hannover	
Test Site:	Nycomed GmbH Institute of Pharmacology and Preclinical Drug Safety (IPAS) Haldkrugsweg 1, 22885 Barsbüttel, Germany	
No. and Title of the PI phase:	Nycomed Phase Contract No. Fh-ITEM 02-2008 Preparation of histological slides	
Quality Assurance Programme:		
Inspections of the PI phase:	Inspection Dates	Dates of reporting to PI and to management:
PI phase protocol	18.08.2008	19.08.2008
Conduct of PI phase, raw data	04.09.2008	04.09.2008
The laboratory in which the study phase was performed is subject of regular process based audits. The conduct of the inspections, the reporting and assessment of the inspection results were in accordance with the Standard Operating Procedures of QAU being in force during the period of the study phase and in full compliance with the current principles of Good Laboratory Practice Regulations as set forth the German Chemicals Law and the OECD- and EC-Regulations in their version being in force during the period of the study.		
 Place, date Barsbüttel		 Signature

2 Executive Summary

The aim of the study was to evaluate subchronic, reproductive, developmental, and in vivo cytogenetic effects of roofing asphalt fume condensate (RAFC) following inhalation in Wistar (WU) rats, employing OECD protocol 422 and EPA OPPTS 870.3650 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus test [OECD 474] via Inhalation .

The animals were exposed to RAFC at target concentrations of 30, 100, and 300 mg/m³ THC (total hydrocarbons), resp., or clean air by nose only inhalation, 6 hours per day, 7 days per week. The average concentrations measured continuously during the whole exposure period by aerosol photometers were 30.0 mg/m³, 100.1 mg/m³ and 297.3 mg/m³ THC for the low, mid and high dose group.

Subchronic subgroup: males and females were exposed for 28 days.

Breeding females: daily exposure of the animals lasted for a 2 week period before mating and during the mating period. After successful mating, females were exposed daily from day 0 through day 20 p.c. Daily exposure of males and any females not successfully mated was continued until their sacrifice.

Results of the study indicated that body weight gain and food consumption were significantly reduced in male rats in the 300 mg/m³ THC group. As a result of an error of the randomisation program, females were assigned to the groups based on their body weight instead of randomising them, resulting in a statistically significant difference in absolute body weights between the control and the treated groups at study start. This had to be taken into account when interpreting the absolute body weight and organ weight data.

The absolute and relative lung weight was statistically significantly increased in the male 300 mg/m³ THC group. Absolute lung weight was also statistically significantly increased in all female groups including the breeding females (only 100 and 300 mg/m³ THC groups) exposed to roofing asphalt fume condensate. Relative lung weight (the more relevant endpoint) was statistically significantly increased in the female 100 and 300 mg/m³ THC groups as well as in the 300 mg/m³ THC group of the breeding females.

The absolute liver weight was dose dependently increased in all female groups treated with roofing asphalt fume condensate, this reaching statistical significance at 300 mg/m³ THC. Relative liver weights (the more relevant endpoint) were not statistically significantly different from controls.

No test item induced adverse effect was observed in hematology and clinical chemistry.

RAFC related findings were observed in the nasal cavity and in the lungs. In the nasal cavity, a statistically significant decrease of inflammatory cell infiltration was observed in the (300 mg/m³ THC) high dose group as compared to the control group. This observation was unexpected and is also in contrast to results of the dose range finding study with RAFC (Fraunhofer ITEM Study No. 02N07533), where inflammatory changes were observed in all groups but more frequently in the 300 and 1000 mg/m³ THC dose groups than in the respective control groups and is also in contrast to the breeding females of the present

study (nasal cavities of groups 1 and 4 examined), where a single control animal but 7/12 rats of the 300 mg/m³ THC high dose group showed (multi)focal very slight to slight mucosal mononuclear/inflammatory cell infiltration of the nasal cavity. The reason for this marked discrepancy between both subsets of females is presently unknown. The observed trend in the present study by no means can be considered an adverse test item related effect.

Minimal adverse effects of the 300 mg/m³ THC exposure occurred in the lungs, where a slight increase of alveolar macrophage accumulation was observed in combination with minimal mononuclear/inflammatory cell infiltration and minimal to slight (adaptive) alveolar hyperplasia of the bronchiolar type (alveolar bronchiolization) and is not considered to be preneoplastic. In all other organs, including larynx and trachea, no effects of the RAFC exposure could be observed.

No adverse effects were seen in spermatology or behavioral endpoints investigated. No effect of exposure could be observed on any of the investigated parameters of reproduction (mating and pregnancy rates, pregnancy and postpartum body weight, food and water consumption, and clinical observations), as well as early postnatal development of F1.

RAFC did not induce any significant increases in micronucleus frequency in polychromatic erythrocytes of the bone marrow of exposed rats. Although no adverse effects were seen on blood formation in rats exposed to RAFC at concentrations up to 300 mg/m³ THC for 28 days, the ability of RAFC or RAFC components/metabolites to reach circulation and produce toxicity in the bone marrow was verified by the significant depression of blood formation in female rats exposed to 1000 mg/m³ THC in the dose range finding study (Fraunhofer ITEM Study No. 02N07533). Thus data from this study reflect an actual negative result. Under the restrictions of the micronucleus assay and the chosen target cells, roofing asphalt fume condensate is considered non mutagenic in immature bone marrow erythrocytes of Wistar (CrI:WU) rats.

In summary (see Table below), the low dose 30 mg/m³ was determined as the overall NOAEL for the study, with clear (mild) effects in the high dose and based on a significantly increased relative lung weight in mid dose subchronic females although, in the absence of any histopathological correlates. The results do not give any indication that the test item is a reproductive toxin or a mutagen at concentrations up to 300 mg/m³ THC..

No observed effect levels overview

End point	LOAEL mg/m ³ THC	NOAEL mg/m ³ THC
Subchronic – males	300	100
Subchronic – females	100	30
Reproductive – males	-	300
Reproductive – females	-	300
Developmental – males	-	Not applicable
Developmental – females	-	300
Systemic – maternal	100	30
Cytogenetic – males	-	300
Cytogenetic - females	-	300

3 Introduction

3.1 Objectives of the Study

The aim of the study was to evaluate subchronic, reproductive, developmental, and in vivo cytogenetic effects of roofing asphalt fume condensate (RAFC) following inhalation in Wistar (WU) rats.

Since the potential exposure route for humans is inhalation, the test item in this study was also administered via the inhalation route. The nose only inhalation method as a routine and validated procedure was chosen since a whole body inhalation exposure would require a much higher quantity of test item.

3.2 Guidelines for Conduct of the Study

The study was conducted according to

- OECD Guideline for Testing of Chemicals 422 Adopted 22 March 1996 "Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test",
- EPA Health Effects Test Guidelines OPPTS 870.3650 Combined Repeated Dose Toxicity Study With the Reproduction/Developmental Toxicity Screening Test. EPA712–C–00–368 July 2000,
- OECD Guideline for Testing of Chemicals 474 Adopted 21 July 1997 "Mammalian Erythrocyte Micronucleus Test",
- EPA Health Effects Test Guidelines OPPTS 870.5395 Mammalian erythrocyte micronucleus test. EPA712 C 98 226, August 1998,

and in compliance with the Principles of Good Laboratory Practice (German Chemicals Law § 19a, Appendix 1, July 02, 2008).

The study followed the regulations of the German Animal Protection Law (Tierschutzgesetz) of 18 May 2006.

3.3 Selection of Animal Species

For toxicity studies, rats are often used because of the economy in their use, the information available on physiology and development, and the susceptibility to different chemicals. Wistar (WU) rats are often used for this type of study in the laboratories of Fraunhofer ITEM.

3.4 Dates

Study Initiation Date:	June 25, 2008
Experimental Start Date: (day of first treatment)	July 15, 2008
Experimental Completion Date:	January 21, 2009
Study Completion Date	July 7, 2009

3.5 Study Staff

Study Director:	[REDACTED]
Deputy Study Director:	[REDACTED]
Animal House Veterinarian:	[REDACTED]
Aerosol Physicist:	[REDACTED]
Chemical Analysis:	[REDACTED]
Clinical Chemistry:	[REDACTED]
Histopathology:	[REDACTED]
Scientist responsible for Micronucleus Test:	[REDACTED]
Statistician:	[REDACTED]
Principal Investigator:	[REDACTED]
Sponsor's Study Representative:	[REDACTED]
Sponsor's Study Monitor:	[REDACTED]

3.6 Dose Level Selection

The selection of dose levels for treatment groups 2,3 and 4 was based on the results and the recommendation of the "Range Finding Testing for a Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate" (Fraunhofer ITEM Study No. 02N07533). Selected nominal target concentrations of RAFC measured as total hydrocarbons (THC) at the different inhalation units were 0, 30, 100 and 300 mg/m³ THC.

3.7 Frequency and Duration of Test Item Exposure

The animals in groups 1 to 4 were exposed to the test item or clean air by nose only inhalation daily, 6 hours per day, 7 days per week.

Subchronic subgroup: males and females were exposed for 28 days.

Breeding females: daily exposure of the animals lasted for a 2 week period before mating and during the mating period. After successful mating, females were exposed daily from day 0 through day 20 p.c. Daily exposure of males and any females not successfully mated was continued until their sacrifice.

3.8 Test Item

3.8.1 Characterization

The test item of the study was roofing asphalt fume condensate.

Test item source and preparation:

Details on the roofing asphalt fume condensate, delivered by the Heritage Research Group, used for this study and results of earlier chamber trials are summarized below, taken from the report "Collection, Validation and Generation of Asphalt Roofing Fumes for Reproductive/Developmental Toxicity Study", Heritage Research Group, 3 February 2006.

Identity and homogeneity of the test item:

API identification:	Sample # 06 01
CAS Nr:	64742-93-4
Density:	0.8745 g/ml
Kinematic Viscosity:	8.3616 centi stokes at 100°F
Refractive Index:	1.4831 at 25°C
Expiry Date:	August 2020

Specific information about density, fluorescence, and refractive index of the test item are provided by the sponsor for each separate of the five bottles filled with roofing asphalt fume condensate and confirmed the homogeneity of the batch.

Sample identity was confirmed by determination of density and refractive index of the test

item (see Fraunhofer ITEM study No. 02N07532 "Chamber Trials for the Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate").

3.8.2 Safety Protection, Storage and Handling

Safety precaution, storage and handling of the test item was carried out according to the TRGS 901 (Technische Regeln für Gefahrstoffe).

The test item was stored at -18°C except during use when it was kept at ambient room temperature and between daily dosing when it was kept at approx. 4 - 6°C. After completion of the study unused material will be returned to the sponsor.

4 Test System

4.1 Animal Model

Young adult males and virgin females (approx. 7 weeks of age at delivery) Wistar rats (CrI:WU), purchased from Charles River Deutschland, Sulzfeld, Germany, were used in this study. The study commenced with 53 young adult male and 101 virgin female rats.

4.2 Acclimation and Mating of Animals

Prior to the start of the exposure period, the following procedures were completed for all animals: Acclimation to the Fraunhofer ITEM laboratory conditions for approx. 3 weeks. Starting in the first week of the acclimation period, a training program was performed to acclimatize the animals to the exposure tubes for increasing periods of time. During the whole acclimation period, clinical observations were made once a day. Animals were accepted for the study only if they were in good health.

4.3 Animal Identification

A unique 4 digit individual identification number was assigned to each animal in the study. The first digit was the group number (i.e. 1 - 5), the last three digits were the consecutive animal number (e.g. 101-112 for males and 201 - 224 for females). The cages were labeled with the corresponding number. All data collected from an animal were filed under that number. The ears of the animals were tattooed according to this identification number.

4.4 Housing and Maintenance

Animals were individually housed in Makrolon® Type III cages. Absorbent softwood was used as bedding material in the cages (ssniff 3/4, Ssniff GmbH, Soest, Germany). Drinking water from the Hannover city water supplier was offered fresh weekly, in Makrolon® bottles (approximately 300 ml), ad libitum. Food was offered ad libitum fresh weekly. The diet used

(sniff V1534) was supplied by ssniff GmbH, Soest, Germany.

Temperature and relative humidity were recorded continuously. The temperature in the animal room was set at 22 ± 2 °C and the relative humidity at $55\% \pm 15\%$. Air exchange rate was about 15 times per hour. A 12-hour light/dark cycle was used for lighting controlled by an automatic timing device.

Biological waste material, including food, bedding and other disposable materials generated in the animal facility were collected and disposed of in compliance with local, state and federal regulations.

5 Procedures

5.1 Experimental Design and Randomisation

The rats were randomized by weight via a computer generated randomization program (PROVANTIS) into one of the clean air control or test item exposed groups.

Additionally, a positive control group treated with cyclophosphamide monohydrate (CP) with five males and five females was included for the micronucleus test (see section 11).

After assignment to treatment groups but prior to the start of exposure, all male groups were evaluated for homogeneity of mean body weights and variances. The weight variation per sex within or between groups did not exceed $\pm 20\%$ of the mean weight at the moment of randomization. As a result of an error of the randomisation program, females were assigned to the groups based on their body weight instead of randomising them, resulting in a statistically significant difference in absolute body weights between the control and the treated groups at study start (see **Table 2**). This had to be taken into account when interpreting the absolute body weight and organ weight data.

Animals were exposed according to the following scheme:

Group	No. of Animals/subgroup			Target concentration mg/m ³ THC** of the test item	Animal Numbers	
	breeding females	Sub chronic treatment	Micro nucleus test*		males (M)	females (F)
1 Clean Air Control	12 F	12 M 12 F	5 M + 5 F	-	1101 - 1112	1201 - 1224
2 Low Dose	12 F	12 M 12 F	5 M + 5 F	30	2101 - 2112	2201 - 2224
3 Medium Dose	12 F	12 M 12 F	5 M + 5 F	100	3101 - 3112	3201 - 3224
4 High Dose	12 F	12 M 12 F	5 M + 5 F	300	4101 - 4112	4201 - 4224
5 Positive Control (CP)***	-	-	5 M + 5 F	-	5101 - 5105	5201 - 5205

* Animals are taken from the subchronic subgroup

** Total hydrocarbons

*** for the micronucleus test: see section 11

Female animal numbers 201 - 212 were assigned to the breeding subgroup, while animal

numbers 213 - 225 formed the subchronic subgroup.

5.2 Inhalation Exposure

5.2.1 General

Technical setup for generation of exposure fumes was as in the study "Chamber Trials for the Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate" (Fraunhofer ITEM Study No.: 02N07532) and described in detail in the corresponding study report.

Exposure was conducted in animal room T1.033. The rats were exposed to asphalt fumes in a direct flow nose only inhalation exposure system. In this system the fume was supplied to each animal individually, and exhaled air was exhausted immediately. The rats were placed around the exposure cylinder in tapered acrylic glass tubes with adjustable backstops. The different exposure units were placed under separate laboratory hoods to avoid cross contamination.

5.2.2 Generation of the Exposure Atmosphere

The method developed by Koch (1993) used for regeneration of asphalt fume basically uses a free jet to recondense hot vapor in a stream of cool air. Since in this system heat and mass transfer are mainly determined by the free jet, the particle generation process is very robust, not sensitive to external factors, and yields a stable fume in respect to its physical and chemical composition.

In the free jet evaporation condensation generator, a well defined mass flux of vaporized liquid asphalt fume condensate is issued together with a carrier (nitrogen) at high velocity through a nozzle into a stream of slowly flowing cool air. An expanding turbulent jet is formed, as a result of the surrounding air mixing with the vapor stream. The asphalt vapor is cooled and diluted downstream of the nozzle, as the jet develops. The initial vapor phase contains very fine seed particles, originating from the vapor generation process. The vapor is generated by first nebulizing the condensate, using a pneumatic nebulization nozzle, and subsequently evaporating the droplets in a heated evaporation tube. The seed particles result from lower volatility constituents in the condensate. Due to the nonlinear temperature behavior of the saturation concentration, the saturation ratio (S) goes through a maximum as a function of distance from the nozzle. Depending on the temperature of the surrounding air in the generator and the mass flux of the vaporized material, supersaturation ($S > 1$) of the vapor is eventually achieved, leading to formation and growth of liquid aerosol droplets by condensation of the vapor phase on the seed particles. A peristaltic pump, driven by a stepping motor, maintains the pump feed rate of the asphalt fume condensate.

For the nose only system used in the inhalation studies and for the concentrations envisaged, the feed rate was adjusted accordingly. The condensate was pumped via a stainless steel tube directly into the pneumatic dispersion nozzle. This nozzle was operated with heated nitrogen (160 °C) at a flow rate of 5 l/min and generated droplets with a mean diameter of about 6 µm. The droplets were fed directly into a tube heated at approx.

220 °C, where they evaporated. The vapor was then issued through the nozzle and was recondensed in the condensation section as described, by mixing with cool air.

5.2.3 Inhalation Units and Dilution

From the generator, the fume was directed through stainless steel tubes to the inhalation units. Flow resistors controlled the flow of asphalt fume to each inhalation unit. The flow rate through these resistors was maintained by keeping a constant pressure difference between the inhalation units and the generator controlling the flow rate of the cooling air in the generator. The final concentrations were achieved by mixing the asphalt fume with dilution air, regulated by mass flow controllers. The whole inhalation system was microprocessor controlled and supervised by a computer.

5.2.4 Measurement of the Exposure Atmosphere

The temperature and the relative humidity in the fume supply to the inhalation units were measured. Data were collected by a computer. 10 minute average values were stored for documentation.

The fume concentration was determined by sampling from the nose only units using a combination of a glass fiber filter and a XAD absorption tube with a sample flow rate of approx. 2 l/min. Samples were taken from each exposure unit. An average of two samples per unit a week was taken. The material collected on the filter and the XAD tube was extracted and analyzed separately by IR spectroscopy according to BIA guideline #6305. The concentrations are given in mg Total Hydrocarbons (THC)/m³ aerosol and vapor phase. For the comparison of the asphalt fume concentration determined according to the BIA method with the absolute asphalt fume concentration, samples of defined concentrations of asphalt condensate were analyzed using the BIA method (see study 02N07532). In the report figures for the THC concentrations in the aerosol and vapor phase are presented. Parallel to the determination of THC the UV fluorescence determined as diphenylanthracene equivalents [mg DPA/kg] was measured in all exposed groups once a week. For continuous monitoring of the total hydrocarbon exposure concentration aerosol photometers as described in the report to the Fraunhofer ITEM Study No. 02N07532 were used. Periodic checking and optional recalculation of the photometer sensitivity during the inhalation study were carried out using the results of chemical analyses (mg THC/m³). Particle size distributions were determined once using a scanning mobility particle sizer (SMPS, TSI - Inc.) which gave a number size distribution in a size range of about 7 - 300 nm (SMPS measurements were not carried out under GLP conditions).

5.3 Daily and Weekly Observations

Animals were inspected at least once daily. Cages in which animals exhibited unusual behavior or appearance were tagged for inspection by the veterinarian or his designate. Once per week, all animals were inspected outside their home cages. The results of these examinations were documented.

Individual body weight of the animals was recorded to the nearest 0.1 g.

Subchronic subgroup: males and females at least once weekly

Breeding females: After detection of sperm, body weight of the females was determined on day 0, 7, 14, and 21 p.c. (post conceptionem) as well as on day 0 and 4 p.p. (post partum, day of birth = day 0 p.p.).

Individual food and water consumption in the animals was recorded to the nearest 0.1 g by the difference between initial and remaining food and water weight.

Subchronic subgroup: males and females weekly

Breeding females: After detection of sperm, food and water consumption of the females was determined on day 0, 7, 14, and 21 p.c. as well as on day 0 and 4 p.p.

6 Mating

Animals were mated beginning two weeks after the start of treatment for two consecutive weeks or until successful mating. Overnight mating was performed with 1 male and 1 female of the same dose group. Vaginal smears were taken the next morning. Mating was considered successful if sperm and/or a vaginal plug was found. The day of finding sperm was considered day 0 post conceptionem (p.c.).

Time to successful insemination (precoital time) was determined.

7 Locomotor Activity

Spontaneous locomotor activity over 90 minutes using the „Actimot“ computerized light beam system (TSE, Homburg/Ts., Germany) was determined around day 28 in all animals of the subchronic subgroup. The data were analyzed in 15 minutes intervals. In addition, the total values for distance, time in rest, time in movement, rearing time, and number of rearings were determined.

8 Functional Observational Battery

A functional observational battery (FOB) based on Gad (1982) and Moser et al. (1991) was determined around day 28 in all animals of the subchronic subgroup. In addition to the determination of forelimb grip strength (Meyer et al., 1979), the FOB included the following endpoints:

Righting reflex, body temperature, salivation, startle response, respiration, urination, mouth breathing, convulsions, pineal response, piloerection, diarrhea, pupil response, lacrimation, impaired gait, stereotypy, toe pinch, tail pinch, wire maneuver, hind leg splay, tremors, extensor thrust, positive geotropism, activity and limb rotation.

9 Clinical Laboratory Data

9.1 General

Hematological and clinical chemistry analyses (hematology and serum chemistry) were performed immediately before final necropsy for all rats from the subchronic subgroup. Blood samples were obtained following overnight (16h) fasting of the rats.

Blood samples were obtained by puncture of the retro bulbar venous plexus under light Isofluran^R anesthesia and collected for hematological and serum chemistry analysis in tubes coated with K₂ EDTA (1.5 - 2 mg/ml) and heparin lithium salt (>7.5 IU/ml), respectively. The samples were analyzed in a randomized sequence. Samples were deep frozen (-18°C) for later analysis.

For determination of prothrombin and thromboplastin times, blood was drawn from the v. cava caudalis using a syringe with 10% (v/v) of citric acid sodium salt (0.11 mmol/l) as anticoagulant.

9.2 Hematology

Erythrocyte count, hemoglobin, hematocrit, mean erythrocyte volume, mean erythrocyte hemoglobin mass, mean erythrocyte hemoglobin concentration, total and differential leukocyte count, platelet count, prothrombin time, and thromboplastin time were recorded. Extra blood smears were prepared for a possible later analysis of reticulocytes.

9.3 Clinical Chemistry

Aspartate aminotransferase (EC 2.6.1.1), alanine aminotransferase (EC 2.6.1.2), gamma glutamyl transferase (EC 2.3.2.2), alkaline phosphatase (EC 3.1.3.1), sorbitol dehydrogenase (EC 1.1.1.14), cholinesterase (EC 3.1.1.8), creatin kinase (EC 2.7.3.2), total bilirubin, urea, creatinine, total protein, albumin, cholesterol, glucose, sodium, potassium, calcium, chloride, inorganic phosphate and triglyceride were measured. Globulin and albumin/globulin ratio were calculated from the albumin and total protein data.

9.4 Quality Control

Clinical laboratory data were checked using commercially available control samples.

10 Post Mortem Investigations

Animals were sacrificed by CO₂ overdose and subsequent exsanguination. Necropsy was performed under the supervision of a veterinarian or pathologist.

Subchronic subgroup: after 28 days of exposure

Breeding females: Dams with offspring on day 4 p.p.; females without evidence of offspring approx. 14 days after the end of cohabitation

10.1 Spermatology

One epididymis per male was used for sperm collection. The number of cauda epididymal sperm reserves was determined. Epididymal sperm motility was estimated immediately after sacrifice. A morphological evaluation of an epididymal sperm sample was performed.

10.2 Gross Pathology and Histopathology

10.2.1 Gross Pathology

Necropsy and organ weighing was performed in all animals as scheduled.

Breeding females: The number of implantation sites was determined, using ammonium sulphide staining in case of no macroscopically visible implantations. Corpora lutea were counted.

In addition to the terminal body weight, selected organs listed below were weighed (paired organs separately; only pregnant females of the breeding subgroup were included in group mean organ weight calculation).

Lung (including 2/3 of trachea)	Kidneys
Heart	Testes
Liver	Epididymides
Spleen	Thymus
Brain	Ovaries
Adrenals	Uterus

The following organs and tissues were collected from each rat and fixed in 10% neutral buffered formalin:

Brain, pituitary, tongue, eyes, lacrimal glands, nasal and paranasal cavities, larynx, pharynx, trachea, thyroid, parathyroids, lungs, thymus, heart, aorta, lung associated lymph nodes, salivary glands, mandibular lymph nodes, liver, pancreas, spleen, kidneys, adrenals, oesophagus, forestomach, glandular stomach, duodenum, jejunum, ileum, caecum, colon, rectum, mesenterium and lymph nodes, urinary bladder, testes (fixation in modified Davidson's fluid), one epididymis (fixation in modified Davidson's fluid), prostate, seminal vesicles, ovaries with oviduct (fixation in modified Davidson's fluid), uterus, vagina, mammary glands, skeletal muscle, one femur including joint, vertebrae with spinal cord, skin, peripheral nerve, sternum with bone marrow, gross lesions.

10.2.2 Histopathology

Tissues for microscopic examination were fixed for at least one week in 10% neutral buffered formalin or for 1 day in modified Davidson's fixative followed by at least 6 days in 10 % neutral buffered formalin, embedded in paraffin, sectioned at 3 - 4 µm, and stained with hematoxylin and eosin. Bones were decalcified prior to embedding.

Trimming and slide preparation, except for testes, were done at IPAS (Institut für

Präklinische Arzneimittelsicherheit, Nycomed GmbH, Haidkrugsweg 1, 22885 Barsbüttel, Germany. Principal investigator: Dr. T. Wöhrmann) according to Ruehl Fehlert et al. 2003, Kittel et al. 2004, Morawietz et al. 2004. A complete histopathological examination was conducted in all rats (12 M + 12 F) of the subchronic subgroups of group 1 (control), and 4 (high dose). In testes, staging of the seminal epithelium was performed.

Additionally the respiratory tract of the animals in the low and mid dose group (12 m + 12 f each) as well as the nasal and paranasal cavities of the breeding females (12 per group) from the control and high dose were investigated, since histopathological changes were observed between the respiratory tract of the control and high dose animals in the subchronic treatment group.

11 Investigations in F₁

Litters were inspected at least once daily. Cages in which dams or litters exhibit unusual behavior or appearance were tagged for inspection by the veterinarian or his designate.

Number of offspring and the occurrence of any dead pups (differentiated between still born and alive/died pups based on lung flotation test) or abnormalities were recorded for all groups. Individual pup weight was recorded to the nearest 0.1 g on day 0 and 4 p.p.

On day 4 p.p., all pups were sacrificed by CO₂ overdose and subsequent exsanguination. All dead pups as well as pups sacrificed were carefully examined externally for gross abnormalities.

12 Micronucleus Test

12.1 General Procedure

The bone marrow micronucleus assay *in vivo* was performed in five male and five female animals per group (group 1 – 4) of the subchronic subgroup, alive at the moment of terminal sacrifice to assess the potential mutagenic activity of roofing asphalt fume condensate.

Additionally, a positive control group using cyclophosphamide monohydrate (CP; SIGMA, Germany, lot 076K1050; 60 mg/kg body weight, dissolved in water) with five males and five females was included. The positive control cyclophosphamide monohydrate was administered orally once 24 hrs before final sacrifice using an aqueous solution of 10 ml/kg body weight (concentration of cyclophosphamide monohydrate: 60 mg/10 ml).

12.2 Preparation of Bone Marrow and Slide Reading

Five animals of the clean air and test item groups (group 1 – 4, selected at random) were killed about 24 h after the start of the last exposure. The positive control animals were sacrificed 24 h after oral application of cyclophosphamide monohydrate. At the time of necropsy one femur of each rat was collected and cleaned from the surrounding muscle tissue. Ends of the femur were cut off. The bone marrow of each animal was washed out

with 5 ml of foetal calf serum and transferred into a tube. The cell suspension in the tube was then pulled gently up and down till a fine cell suspension was observed in the foetal calf serum.

The resulting bone marrow suspension was subsequently cleaned from nucleated cells by a cellulose column procedure (adopted from Sun et al., 1999) to facilitate the erythrocyte counts and to eliminate granulocytes which might have led to artefacts with scoring of micronuclei in erythrocytes.

On the day preceding necropsy 2 cellulose columns were prepared for each animal by mixing equal amounts of type 50 cellulose (instead of type 50350 which is equivalent) and α -cellulose (both from Sigma, Taufkirchen, Germany), suspending the mixture in Hank's balanced salt solution (HBSS) and transferring 2 ml of the suspension in a Poly-Prep column that contained a 30 μ m pore size filter bed (BioRad, München, Germany). After sedimentation of the cellulose fraction, columns were rinsed once with HBSS and then kept at room temperature overnight until use. On the day of necropsy, the bone marrow suspensions were pre filtered through microscope cleaning paper, carefully loaded onto the cellulose columns, and allowed to drain into 15 ml centrifuge tubes.

The cleaned bone marrow was then centrifuged and most of the supernatant was discarded. The cell pellet was carefully re-suspended in a very small volume of foetal calf serum, resulting in about 2 drops of bone marrow cell suspension per animal. From this suspension two smears (A and B) were prepared on defatted slides. The smears were fixed for 10 min in absolute methanol and subsequently stained according to Pappenheim with May Grünwald and Giemsa solution. The slides were coded prior to microscopic analysis.

The slides were analyzed microscopically under 630 - 1000 x magnification. For each animal, the incidence of micronucleated cells per 2.000 polychromatic erythrocytes (PCE) of the bone marrow was determined. In addition, the ratio of PCE (immature) to normochromatic erythrocytes (NCE, mature) was calculated by counting the number of PCE per 500 red blood cells (RBC), as any toxic effects of the test item on immature nucleated erythrocytes may lead to a reduction in cell division. This in turn leads to a reduction in cell number in the bone marrow. To compensate loss of cellular volume, peripheral blood is shunted into the bone marrow. If the ratio of PCE to NCE in the bone marrow is determined and is found to be significantly less than the control value, this is taken as an indication of toxicity. A reduction in the proportion of immature among total erythrocytes thus indicates that the test item or its metabolites reached the bone marrow. For both endpoints one of the two existing (A or B) bone marrow smears was used (smear B was intended to be used only in the case smear A was not evaluable).

12.3 Data Evaluation

The micronucleus assay is judged as valid if the clean air controls demonstrate low spontaneous frequencies of micronucleus induction and if the positive controls demonstrate significantly higher frequencies of micronucleus induction as compared to the clean air controls. In addition, in test item treated animals the PCE ratio should not fall below 20% of the clean air control values to avoid unspecific effects due to excessive cytotoxicity in the bone marrow.

In the mammalian erythrocyte micronucleus test a genotoxic effect is claimed if a dose related increase in the number of micronucleated polychromatic erythrocytes or a statistically significant increase in the number of micronucleated polychromatic erythrocytes in a single dose group at a single sampling time is observed, but biological relevance of the

results is considered first.

13 Data Collection, Documentation and Reporting

Clinical observations, body weights, food and water consumption, mating and pregnancy data, sacrifice data, organ weights and general study comments were recorded as computer output (TASC: Toxicology Analysis System Customized, version 0 and PROVANTIS 7.1.0.0 and 8.2.0.1) and/or on special data forms. Necropsy data and organ weights were recorded on individual looseleaf sheets (one or more per animal) or as direct instrument or computer output.

14 Statistical Methods

Statistical comparison of groups were performed at the level of $\alpha=0.05$. Body weights, food and water consumption, and organ weight data were analyzed using analysis of variance (ANOVA). If the group means differed significantly according to this method, the means of the treatment groups were compared with the mean of the control group 1 using Dunnett's modification of the t test. Kruskal Wallis ANOVA (H-test) and Mann Whitney U test were applied in the case of non homogeneous data (e.g. micronucleus test).

Qualitative data were analyzed using the two tailed FISHER test with Bonferroni correction or Chi square test.

15 Storage and Retention of Materials

One original copy of the study plan, one original copy of the final report, all raw data, and all other material (and data) listed in the study plan and a sample of the test item are stored in the GLP-archives of Fraunhofer ITEM, Hannover, Germany at least for the period of time required by the GLP principles as laid down in the German regulations (15 years for records). The sponsor has to inform Fraunhofer ITEM if further archiving is required.

16 Results

16.1 Exposure Atmosphere

The exposure conditions are shown in **Table 1**, and graphs of the particle size distribution are shown in **Appendix A**.

The average concentrations of the asphalt fume measured by chemical analysis approx. 2 hrs after start of the exposure were 27.4 mg/m³, 90.2 mg/m³ and 267.5 mg/m³ THC for the low, mid and high dose group. The average concentrations measured continuously during the whole exposure period by aerosol photometers were 30.0 mg/m³, 100.1 mg/m³ and 297.3 mg/m³ THC for the low, mid and high dose group. Note: THC denotes the absolute mass concentration. To compare with results obtained by BIA method divide by a factor of 1.26. Differences between photometer measurements and chemical analysis are due to the measuring method of the photometers (for details see Fraunhofer ITEM study 02N07532, Chamber Trials for the Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate)

The UV fluorescence response measured as DPA equivalent was 251 mg/kg, 260 mg/kg, and 252 mg/kg for the low, mid and high dose group indicating that the composition of the atmosphere was similar in all exposure chambers. The UV fluorescence of the test item was determined in the study "Chamber Trial for the Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate" (Fraunhofer ITEM Study No. 02N07532) was 320 mg DPA / kg.

16.2 In Life Observations

16.2.1 Clinical Observations

Individual data are given in **Appendix B**.

No adverse test item related clinical signs were observed in rats during the course of the study, neither during the daily post-exposure (e.g. staining around the nose and eyes, which were considered minor and not related to the test item) nor the weekly cageside observations.

16.2.2 Mortality

No mortality occurred during the course of the study.

16.2.3 Body Weight

The data for body weight and body weight gain in rats are summarized in **Tables 2 and 3**.

Individual data are given in **Appendix C**.

In males, the body weight gain was significantly reduced in the 300 mg/m³ THC group.

In females no effect was observed on body weight gain. The only statistically significant differences from the control group were observed for absolute body weights as a result of an error of the randomisation program, that assigned animals to the groups based on their body weight instead of randomising them.

16.2.4 Food Consumption

The data for food consumption are presented in **Table 4**. Individual data are given in **Appendix D**.

The food consumption was decreased in the male 300 mg/m³ THC group. The biological relevance of the decrease in food consumption of the females however is limited due to the randomisation problems (see 5.1).

16.2.5 Water Consumption

The data for water consumption are presented in **Table 5**. Individual data are given in **Appendix E**.

No influence of the test item on water consumption was observed.

16.2.6 Locomotor Activity

The data for locomotor activity are presented in **Table 6**.

No influence of the test item on locomotor activity was observed.

16.2.7 Functional Observational Battery

The data for the functional observational battery are presented in **Table 7**. Individual data are given in **Appendix F**.

None of the investigated endpoints was affected by the test item exposure.

16.3 Post Mortem Observations

16.3.1 Gross Pathology

Macroscopic findings on day 28 are summarized in **Table 8**.

No test item related effects were observed during necropsy.

16.3.2 Organ Weights

Organ weight data are given in **Tables 9 - 12** with individual data presented in **Appendices G, H**. The non pregnant animals no. 1201, 2204, 2206, 2209, 3209, and 4205 as well as animal no. 4207 (see 16.4.1) were excluded from the calculation of mean values. For the calculation of the relative organ weights the terminal body weight determined in the post mortem room at terminal sacrifice (after overnight fasting) was used.

The absolute and relative lung weight was statistically significantly increased in the male 300 mg/m³ THC group. Absolute lung weight was also statistically significantly increased in all female groups including the breeding females (only 100 and 300 mg/m³ THC groups) exposed to roofing asphalt fume condensate. Relative lung weight (the more relevant endpoint) was statistically significantly increased in the female 100 and 300 mg/m³ THC groups as well as in the 300 mg/m³ THC group of the breeding females.

The absolute liver weight was dose dependently increased in all female groups treated with roofing asphalt fume condensate, this reaching statistical significance at 300 mg/m³ THC. Relative liver weights (the more relevant endpoint) were not statistically significantly different from controls.

Other statistically significant differences observed in absolute and relative organ weights are considered incidental and therefore of no toxicological relevance.

16.3.3 Hematology

Hematology data are presented in **Table 13 - 16** with individual data given in **Appendix J**.

No test item induced adverse effects were observed in hematology.

Sporadically occurring statistically significant differences are considered incidental and therefore of no toxicological relevance.

16.3.4 Clinical Chemistry

Clinical chemistry data are presented in **Table 17 - 19** with individual data given in **Appendix K**.

No test item induced adverse effect were observed in clinical chemistry.

Sporadically occurring statistically significant differences are considered incidental and therefore of no toxicological relevance.

16.3.5 Histopathological Examination

Histopathological findings are summarized in **Tables 20, 20a, 21 and 21a** with individual data presented in **Appendix L**.

The respiratory tract (nasal and paranasal cavities, larynx, laryngo-pharynx, trachea, lungs and lung-associated lymph nodes) was examined in all groups, while all other organs were examined only in the control group and in the 300 mg/m³ THC high dose group. In addition, the nasal and paranasal cavities of the breeding females of the control group and the 300 mg/m³ THC high dose group was examined histopathologically.

Test item related findings

Test item related findings were only observed in the nasal and paranasal cavities and in the lungs.

Nasal and Paranasal Cavities

A high percentage of male and female control rats showed (multi)focal very slight (minimal) to slight mucosal inflammatory cell infiltration, mainly of the transitional and respiratory epithelium in levels 1 and 2 of the 4 nasal cavity sections. Incidences and severity grades of this finding in the high-dosed animals (300 mg/m³ THC), however, were markedly lower (males) or even completely absent (females) as compared to the control group. In males, 9/12 (2/12 very slight, 7/12 slight) rats of the control group and 5/12 (2/12 very slight, 3/12 slight) rats of the (300 mg/m³ THC) high dose group revealed mucosal inflammatory cell infiltration, while 8/12 (5/12 very slight, 3/12 slight) females of the control group but not a single female (0/12) of the (300 mg/m³ THC) high dose group showed this change. In females, the difference between both groups was statistically significant. In addition to mucosal inflammatory cell infiltration, a single male control rat showed slight focal erosion(s) of the epithelium in level 1 of the nasal cavity.

The incidences of (multi)focal very slight to slight mucosal inflammatory cell infiltration in males and females of the low- (30 mg/m³ THC) and medium dose groups (100 mg/m³ THC) were about the same in both groups, but were lower than in the control and higher than in the high-dosed animals (300 mg/m³ THC). In males, 7/12 (30 mg/m³ THC) low dose group: 4/12 very slight, 3/12 slight; (100 mg/m³ THC) medium dose group: 3/12 very slight, 4/12 slight) rats each of the (30 mg/m³ THC) low- and (100 mg/m³ THC) medium dose groups as well as 4/12 (1/12 very slight, 3/12 slight) and 5/12 (4/12 very slight, 1/12 slight) females of the respective groups revealed this change.

(Multi)focal mucous (goblet) cell hyperplasia was diagnosed in 3/12 (2/12 very slight, 1/12 slight), 3/12 (2/12 very slight, 1/12 slight), 3/12 (all very slight) and 4/12 (1/12 very slight, 3/12 slight) males of the control, (30 mg/m³ THC) low-, (100 mg/m³ THC) medium- and (300 mg/m³ THC) high dose group, respectively, while 4/12 (3/12 very slight, 1/12 slight), 3/12 (all very slight), 1/12 (very slight) and 1/12 (very slight) females of the respective groups showed this finding. Mucous (goblet) cell hyperplasia was predominantly observed in the respiratory epithelial lining of the nasal septum in levels 1 and 2 of the nasal cavity sections. In addition, up to 2/12 males or females of different groups showed very slight to slight focal (mineralized) mucosal psammoma bodies as a spontaneous finding.

Nasal and Paranasal Cavities, Breeding Females of Groups 1 (control) and 4 (300 mg³ THC high dose)

With respect to the incidence of mucosal mononuclear/inflammatory cell infiltration, the findings in the nasal cavities of the breeding females of the control and (300 mg/m³ THC) high dose group were in contrast to the ones observed in the females of the subchronic part. A single female of the control group showed very slight focal mucosal mononuclear cell infiltration in level 1, while 7/12 females (5/12 very slight, 2/12 slight) of the (300 mg/m³ THC) high dose group revealed multifocal mucosal inflammatory cell infiltration, mainly in levels 1 and 2 of the nasal cavity. The difference between both groups is statistically significant. Further findings such as mucous (goblet) cell hyperplasia, mucosal psammoma bodies and dilatation of the submucosal glands occurred in single animals of the (300 mg/m³ THC) high dose group only.

Lungs

(Multi)focal very slight to slight (increased) alveolar accumulation of macrophages (alveolar histiocytosis) was observed in 2/12 (1/12 very slight, 1/12 slight), 4/12 (3/12 very slight, 1/12 slight), 2/12 (1/12 very slight and slight each) and 12/12 (3/12 very slight, 9/12 slight) males of the control, (30 mg/m³ THC) low, (100 mg/m³ THC) medium and (300 mg/m³ THC) high dose group, respectively. In females, 1/12 (very slight), 2/12 (very slight) and 12/12 (6/12 very slight, 6/12 slight) rats of the control, (100 mg/m³ THC) medium- and (300 mg/m³ THC) high dose group, respectively, showed this change with no occurrence in the (30 mg/m³ THC) low dose group. For both sexes, the difference between the control group and the (300 mg/m³ THC) high dose group was statistically significant. The alveolar macrophages in the (300 mg/m³ THC) high dose group were predominantly located in the alveolar duct regions of the lungs and many of them had a foamy (vacuolated) cytoplasm. Although small aggregates of alveolar macrophages occurred in all of the (300 mg/m³ THC) high dose exposed lungs, degeneration and decay of the alveolar macrophages was not observed.

Another statistically significant test item related finding, all males and females (12/12 each) of the (300 mg/m³ THC) high dose group only developed multifocal very slight to slight (males: 3/12 very slight, 9/12 slight; females: 6/12 very slight and slight, resp.) bronchiolo-alveolar hyperplasia of the bronchiolar type (alveolar bronchiolization). This adaptive type of hyperplasia describes the presence of bronchiolar epithelium within alveolar ducts and adjacent alveoli. In addition, a single male and 3/12 females of the (300 mg/m³ THC) high dose group revealed (multi)focal very slight bronchial mucous (goblet) cell hyperplasia.

(Multi)focal interstitial mononuclear or (mixed) inflammatory cell infiltration occurred in a single male control animal (very slight), in 5/12 (very slight) males and in 6/12 (5/12 very slight, 1/12 slight) females of the (300 mg/m³ THC) high dose group. This finding was not observed in the female control group. In the (30 mg/m³ THC) low- and (100 mg/m³ THC) medium dose groups, between 1/12 and 2/12 males or females per group were affected by very slight to slight interstitial mononuclear/inflammatory cell infiltration.

Further pulmonary findings such as alveolar inflammatory cell infiltration, foreign-body granuloma, osseous metaplasia, alveolar dilatation, alveolar haemorrhage, chronic passive congestion and (acute) congestion were incidental and unrelated to the test item exposure.

Non test item related noteworthy findings in other organs

Eyes, Harderian glands

Due to retrobulbar blood collection, between 7/12 and 10/12 males and females per group showed mainly unilateral slight to severe retrobulbar haemorrhage. Single males of the (300 mg/m³ THC) high dose group revealed additional unilateral slight intra-ocular haemorrhage or unilateral slight retrobulbar mononuclear cell infiltration. Both lesions were also related to blood sampling, as were changes in the Harderian glands such as slight (multi)focal haemorrhage (incidence up to 4/12 animals per group and sex), slight focal necrosis (incidence up to 2/12 females per group), slight focal atrophy and slight focal pigment deposits (1/12 and 2/12 males of the (300 mg/m³ THC) high dose group, respectively).

Heart

Eight of 12 and 7/12 males of the control and (300 mg/m³ THC) high dose group, respectively, were affected by spontaneous, mainly very slight (multi)focal myocardial mononuclear cell infiltration which in 1/12 males of the (300 mg/m³ THC) high dose group was associated with focal very slight myocardial (myofibre) degeneration. In females, mainly very slight (multi)focal myocardial mononuclear cell infiltration was seen in 3/12 and 4/12 rats of the control and (300 mg/m³ THC) high dose group, respectively.

Liver

Between 9/12 and 11/12 males and females per group showed very slight to slight (multi)focal microgranulomas. Up to 2/12 males and females per group revealed also (multi)focal small areas of (acute) hepatocellular necrosis (grade: slight).

Kidneys, Renal pelvis

(Multi)focal very slight basophilic tubules were observed in 5/12 males each of the control and (300 mg/m³ THC) high dose group as well as in a single control female. Further incidental lesions such as congenital hydronephrosis, interstitial mononuclear cell infiltration, tubular mineralisation, tubular dilatation and dilatation of the renal pelvis affected up to 2/12 males or females.

Testes and Epididymides

A detailed qualitative examination of a segmental cross-section of the testes (transverse section of one testis, longitudinal section of the other testis) was made, taking into account the tubular stages of the spermatogenic cycle. The examination was conducted in order to identify treatment-related effects such as missing germ cell layers or types, retained spermatids, multinucleate or apoptotic germ cells and disorganization of the germinal epithelium.

The randomly scanned seminiferous tubules of 10/12 males of the control and 9/12 males of the (300 mg/m³ THC) high dose group showed the appropriate cell layers in their approximate normal numbers, this means that stages I-VIII contained a layer of spermatogonia, a layer of pachytene spermatocytes and several layers of round spermatids interspersed with elongated spermatids. Stages IX-XIV contained a layer of spermatogonia and prepachytene spermatocytes, several layers of late pachytene or dividing (stage XIV) spermatocytes and several layers of elongated spermatids. There was no evidence of degenerating spermatids or spermatocytes.

The testis of up to 2/12 males each of the control and (300 mg/m³ THC) high dose group showed slight to severe degeneration and depletion of spermatids and spermatocytes which in one male of each group was associated with slight to moderate Sertoli-cell vacuolation and spermatid retention (very slight to slight). Single males of both groups were also affected by very slight focal sloughing of germ cells into the tubular lumen, slight tubular atrophy or slight tubular dilatation.

Very slight (multi)focal interstitial mononuclear cell infiltration was recorded in the epididymides of up to 5/12 males per group. Further incidental findings of the epididymides were sloughing of germ cells into the lumen (2/12 males of the control group) and aspermia (1/12 males of the 300 mg/m³ THC high dose group). The latter finding was associated with severe degeneration and depletion of spermatids/spermatocytes in the corresponding testis.

Prostate

Single males from the control and (300 mg/m³ THC) high dose group showed a multifocal moderate non-suppurative inflammation, while (multi)focal very slight to slight interstitial mononuclear or inflammatory cell infiltration was observed in up to 3/12 males per group.

Uterus

Oestrus cycle-related slight to moderate dilatation (distension) of the uterus (prooestrus) was observed in 3/12 females of the control and (300 mg/m³ THC) high dose group, respectively.

Other organs

Several further findings in various organs were noted which occurred incidentally and at low frequencies and were not unusual for rats of this strain and age.

16.3.6 Spermatology

The summary of the spermatology data is provided in **Table 22**. The individual animal data are reported in **Appendix M**.

No statistically significant effect was observed on sperm count, sperm motility and percent abnormal sperm, although there is a statistically non significant but dose dependent trend towards a decrease in sperm number in all exposed groups. However all values are within historical control data of the test facility with a minimum of 16.4 million sperm per epididymis.

16.4 Mating and Pregnancy Data

16.4.1 Mating and Pregnancy Rates

The summary of the F₀ cohabitation data is provided in **Table 23**. The individual animal data

are reported in **Appendix N**.

For the four groups, mating yielded 10, 10, 11, and 10 sperm positive females, in groups 1 (control), 2 (low dose), 3 (medium dose), and 4 (high dose), respectively. This resulted in 11, 9, 11, and 11 pregnancies and 11, 9, 11, and 10 females with liveborn offspring, respectively (**Table 32**). No influence on precoital time and duration of pregnancy was observed.

Animal nos. 1201, 2206, 2209, 3209, and 4205 did not become pregnant although sperm was detected in their vaginal smears. Conversely, animal nos. 1203, 1205, 2201, 3206, 4207, and 4211 became pregnant although no sperm was detected in vaginal smears, which was obviously due to successful mating early in the evening. All these animals gave birth to their litters. Only animal no. 4207 was declared as non pregnant and was therefore killed at the last day of exposure, but was found pregnant with 12 implantation sites. Animal no. 2204 was not found sperm positive and was also not pregnant at sacrifice.

In summary, no effect of exposure could be observed on mating and pregnancy rates.

16.4.2 Pregnancy and Postpartum Body Weight, Food and Water Consumption, and Clinical Observations

The summary of the maternal gestation and postpartum body weights and body weight gains is given in **Table 24 - 25** and **28 - 29**. The individual animal data are reported in **Appendix N**. The summary of the maternal gestation and postpartum food and water consumption is given in **Table 26 - 27** and **30 - 31**. The individual animal data are also reported in **Appendix N**.

No statistically significant differences from the control group 1 were observed on body weight, except an increased body weight in the exposed groups (statistically significant for group 3 and 4) due to the randomization problems described in 4.1 and 15.2.3. Gestation body weight gain was slightly (but statistically non significantly) decreased in the high dose group 4 (**Table 25**), accompanied by a decreased gestation food consumption in the same group (**Table 26**). These effects can be interpreted as a slight maternally toxic effect as requested for the high dose group by OECD Guideline 422.

The only clinical observations were poor condition in animal nos. 1204 (control group) and 4209 (high dose) on day 0 p.p., which is considered to be a common finding and not exposure related.

No effects were observed on any of the other investigated parameters.

16.4.3 Investigations in F₁

A summary of the delivery and litter data is given in **Table 32**, the individual data are reported in **Appendix N**.

No adverse effects were observed on any of the investigated endpoints. The observed decrease in the number of pups dying between days 0 and 4 p.p. in all exposed groups compared to the control group 1 is due to the fact that the litter of animal no. 1204 (control group 1) had to be killed on day 0 p.p. due to lack of maternal care, and is by no means an adverse effect of the exposure.

Sporadically occurring clinical findings reflected poor condition with no influence of the

treatment.

Based on these findings, no effect of the exposure could be detected on any of the investigated parameters in F₁ pups.

16.5 Blood Formation and Micronucleus Induction

Results are summarized in **Table 33** with individual data shown in **Appendix O**.

After 28 days of exposure the test item RAFC (30 - 300 mg/m³ THC, 6 h/day, 7 days/week) mediated no tendency towards repression of red blood cell (RBC) formation in both male and female animals, as compared to controls (see Table 33 and Appendix O).

This does not mean that RAFC or components of RAFC were not systemically available, because in a range finding study (Fraunhofer ITEM Study No. 02N07533) using a concentration of 1000 mg/m³ THC blood formation was significantly depressed in female animals, thus indicating that RAFC or components of RAFC are able to reach the bone marrow as target organ for the mammalian erythrocyte micronucleus test.

There was no evidence of a significantly enhanced mean frequency of micronucleated erythrocytes (MN per 2000 PCE) due to RAFC exposure, as compared to the respective clean air groups (see Table 33 and Appendix O). In contrast, animals treated with the positive control cyclophosphamide monohydrate (CP, 60 mg/kg b.w.) exhibited highly significant enhancement of mean micronucleus frequency, amounting to 15.0 ± 3.00 (males) and 12.8 ± 1.30 micronuclei per 2000 PCE, compared to 1.0 ± 1.00 (males) and 1.0 ± 0.71 (females) in the clean air group, respectively.

17 Discussion and Conclusions

The animals were exposed to RAFC or clean air by nose only inhalation, 6 hours per day, 7 days per week. The average concentrations measured continuously during the whole exposure period by aerosol photometers were 30.0 mg/m³, 100.1 mg/m³ and 297.3 mg/m³ THC for the low, mid and high dose group.

Subchronic subgroup: males and females were exposed for 28 days.

Breeding females: daily exposure of the animals lasted for a 2 week period before mating and during the mating period. After successful mating, females were exposed daily from day 0 through day 20 p.c. Daily exposure of males and any females not successfully mated was continued until their sacrifice.

Results of the study indicated that body weight gain and food consumption were significantly reduced in male rats in the 300 mg/m³ THC group. As a result of an error of the randomisation program, females were assigned to the groups based on their body weight instead of randomising them, resulting in a statistically significant difference in absolute body weights between the control and the treated groups at study start (see **Table 2**). This had to be taken into account when interpreting the absolute body weight and organ weight data.

The absolute and relative lung weight was statistically significantly increased in the male

300 mg/m³ THC group. Absolute lung weight was also statistically significantly increased in all female groups including the breeding females (only 100 and 300 mg/m³ THC groups) exposed to roofing asphalt fume condensate. Relative lung weight (the more relevant endpoint) was statistically significantly increased in the female 100 and 300 mg/m³ THC groups as well as in the 300 mg/m³ THC group of the breeding females.

The absolute liver weight was dose dependently increased in all female groups treated with roofing asphalt fume condensate, this reaching statistical significance at 300 mg/m³ THC. Relative liver weights (the more relevant endpoint) were not statistically significantly different from controls.

No test item induced adverse effect was observed in hematology and clinical chemistry.

RAFC related findings were observed in the nasal cavity and in the lungs. In the nasal cavity, a statistically significant decrease of inflammatory cell infiltration was observed in the (300 mg/m³ THC) high dose group as compared to the control group. This observation was unexpected and is also in contrast to results of the dose range finding study with RAFC (Fraunhofer ITEM Study No. 02N07533), where inflammatory changes were observed in all groups but more frequently in the 300 and 1000 mg/m³ THC dose groups than in the respective control groups and is also in contrast to the breeding females of the present study (nasal cavities of groups 1 and 4 examined), where a single control animal but 7/12 rats of the 300 mg/m³ THC high dose group showed (multi)focal very slight to slight mucosal mononuclear/inflammatory cell infiltration of the nasal cavity. The reason for this marked discrepancy between both subsets of females is presently unknown. The observed trend in the present study by no means can be considered an adverse test item related effect. Minimal adverse effects of the 300 mg/m³ THC exposure occurred in the lungs, where a slight increase of alveolar macrophage accumulation was observed in combination with minimal mononuclear/inflammatory cell infiltration and minimal to slight (adaptive) alveolar hyperplasia of the bronchiolar type (alveolar bronchiolization). This type of hyperplasia is considered to be non-preneoplastic and is interpreted as an attempt to facilitate a more efficient removal of inhaled materials via the mucociliary escalator by extension of the bronchiolar epithelium into the alveolar ducts. In all other organs, including larynx and trachea, no effects of the RAFC exposure could be observed.

No adverse effects were seen in spermatology or behavioral endpoints investigated.

No effect of exposure could be observed on any of the investigated parameters of reproduction (mating and pregnancy rates, pregnancy and postpartum body weight, food and water consumption, and clinical observations), as well as early postnatal development of F1.

RAFC did not induce any significant increases in micronucleus frequency in polychromatic erythrocytes of the bone marrow of exposed rats. Negative results obtained in the present study might on the one hand reflect that RAFC administered by nose only inhalation has no clastogenic or aneugenic potential in the bone marrow of Wistar (CrI:WU) rats. On the other hand, the absence of micronucleus induction in polychromatic erythrocytes might represent a false negative result. In the case of a false negative result, one might hypothesize that the test item did not reach the target cells, as there was no effect of RAFC on blood formation after 28 days of exposure. Concentration of RAFC in the target organ, insufficient to induce

micronucleus formation, might in this case reflect limited absorption of RAFC components via the lung or enhanced elimination of potentially mutagenic components. However, in a dose range finding study (Fraunhofer ITEM Study No. 02N07533), using 1000 mg/m³ THC as maximum concentration, blood formation was significantly depressed in female animals, thus indicating that RAFC or RAFC components/metabolites are able to reach circulation and the bone marrow and to mediate toxic effects. Data thus reflect an actual negative result. Under the restrictions of the micronucleus assay and the chosen target cells, roofing asphalt fume condensate is considered non mutagenic in immature bone marrow erythrocytes of Wistar (CrI:WU) rats.

In summary, the low dose 30 mg/m³ was determined as the overall NOAEL for systemic toxicity in the study, with clear (mild) effects in the high dose and based on a significantly increased relative lung weight in mid dose subchronic females although, in the absence of any histopathological correlates. The results give no indication that test item was a reproductive toxin or a mutagen at concentrations up to 300 mg/m³ THC.

18 References

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19 Tables

Table 1 : Exposure Conditions with Mean and Standard Deviation

	Control	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
Daily Exposure time (hrs)	6	6	6	6
Temperature (°C)	22.3 ± 0.4	22.7 ± 0.6	22.2 ± 0.7	22.4 ± 0.7
Humidity (% r. h.)	59.1 ± 2.7	51.8 ± 2.3	52.3 ± 3.1	48.0 ± 3.2
Air inflow (l/min)	35.0	39.2	39.5	46.7
Air outflow (l/min) [§]	30.6	32.8	34.8	40.7
THC (mg/m ³) [§]	-0.04 ± 0.06	27.4 ± 1.2	90.2 ± 6.6	267.5 ± 16.9
n=	4	13	12	13
THC (mg/m ³) [#]		30.0 ± 2.2	100.1 ± 8.4	297.3 ± 21.5
n=		44	41	44
Fluorescence (mg/kg) [*]		251 ± 15	260 ± 15	252 ± 9
n=		7	6	7

§ generating a slight overpressure in the inhalation system

\$ from chemical analysis (2 hrs after start of exposure)

from photometric measurements (total exposure period)

* Fluorescence as DPA equivalent

Note:

Note: THC denotes the absolute mass concentration. To compare with results obtained by BIA method divide by a factor of 1.26. Differences between photometer measurements and chemical analysis are due to the measuring method of the photometers (for details see Fraunhofer ITEM study 02N07532, Chamber Trials for the Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate)

Table 2: Body Weight

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Bodyweights Intergroup Comparison of Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g) Identity (No Transformation)

Group	Sex		Day numbers relative to Start Date				
			0	7	14	21	27
1	m	Mean	277.79	294.54	314.58	329.85	343.13
		S.D.	12.22	16.18	16.60	19.55	19.40
		N	12	12	12	12	12
2	m	Mean	281.65	293.82	314.37	327.87	345.87
		S.D.	12.56	13.49	14.06	14.33	17.70
		N	12	12	12	12	12
3	m	Mean	286.22	297.56	320.18	333.73	349.08
		S.D.	9.72	13.36	12.89	14.60	16.32
		N	12	12	12	12	12
4	m	Mean	284.76	286.53	300.81	314.73	328.12
		S.D.	12.22	10.53	12.76	11.62	13.66
		N	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 2: Body Weight (cont'd)

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Bodyweights Intergroup Comparison of Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

		Bodyweight (g)	Identity (No Transformation)				
Group	Sex		Day numbers relative to Start Date				
			0	7	14	21	27
1	f	Mean	173.28	182.18	190.54	203.77	206.06
		S.D.	7.55	7.66	7.56	11.37	10.17
		N	24	24	24	12	12
2	f	Mean	177.70*	185.12	193.81	204.52	209.24
		S.D.	5.19	6.67	6.76	6.53	7.55
		N	24	24	24	12	12
3	f	Mean	180.70**	187.33*	197.30**	204.33	209.00
		S.D.	4.25	5.27	6.72	6.63	6.21
		N	24	24	24	12	12
4	f	Mean	188.38**	192.05**	200.13**	214.10**	219.63**
		S.D.	5.58	6.80	8.89	7.24	8.83
		N	24	24	24	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 3: Body Weight Gain

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		Bodyweights	Intergroup Comparison of Bodyweight Gains						
08016		Combined Repeated Toxicity screening	Dose Toxicity Test	Study with the Reproduction/Developmental and Mammalian Erythrocyte Micronucleus Test					
		Body Weight Gain (g)		Transformation: Identity (No Transformation)					
		Day numbers relative to Start Date							
Group	Sex	Base Weight Day 0	From: To:	0 7	7 14	14 21	21 27	Abs Gain 0 27	% Gain 0 27
1	m	277.79 12.22 12	Mean S.D. N	16.75 7.98 12	20.04 3.39 12	15.27 4.48 12	13.28 3.46 12	65.34 9.23 12	23.48 2.81 12
2	m	281.65 12.56 12	Mean S.D. N	12.17 3.64 12	20.55 3.49 12	13.50 5.48 12	18.00* 4.69 12	64.22 8.01 12	22.79 2.54 12
3	m	286.22 9.72 12	Mean S.D. N	11.34 5.05 12	22.62 4.33 12	13.56 4.42 12	15.35 4.05 12	62.87 8.15 12	21.93 2.43 12
4	m	284.76 12.22 12	Mean S.D. N	1.77** 7.30 12	14.28** 3.35 12	13.92 2.81 12	13.39 4.83 12	43.36** 12.64 12	15.32** 4.62 12

Abs Gain = absolute bodyweight gain between base period and end of the analysis period

% Gain = percentage bodyweight gain between base period and end of the analysis period

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 3: Body Weight Gain (cont'd)

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		Bodyweights	Intergroup Comparison of Bodyweight Gains						
08016		Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test							
		Body Weight Gain (g)		Transformation: Identity (No Transformation)					
Group	Sex	Base Weight Day 0	From: To:	Day numbers relative to Start Date				Abs Gain 0 27	% Gain 0 27
				0 7	7 14	14 21	21 27		
1	f	173.28	Mean	8.90	8.36	10.69	2.29	29.17	16.50
		7.55	S.D.	3.47	2.64	6.04	3.51	6.85	3.76
		24	N	24	24	12	12	12	12
2	f	177.70*	Mean	7.42	8.69	7.82	4.73	29.65	16.52
		5.19	S.D.	3.59	2.39	2.12	4.07	5.50	3.11
		24	N	24	24	12	12	12	12
3	f	180.70**	Mean	6.63*	9.96	7.43	4.68	28.28	15.68
		4.25	S.D.	3.06	3.25	3.43	2.23	6.46	3.79
		24	N	24	24	12	12	12	12
4	f	188.38**	Mean	3.67**	8.08	8.71	5.53	28.08	14.67
		5.58	S.D.	2.80	4.33	4.00	5.39	7.34	3.87
		24	N	24	24	12	12	12	12

Abs Gain = absolute bodyweight gain between base period and end of the analysis period

% Gain = percentage bodyweight gain between base period and end of the analysis period

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 4: Food Consumption

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			Food Consumption		Intergroup Food Consumption by Animal			
08016			Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test					
			Day numbers relative to Start Date					
Group	Sex	From:	0	7	14	21	Mean	Total
		To:	7	14	21	27	0 27	0 27
1	m	Mean	19.22262	20.09643	12.20833	18.10694	17.40858	469.33333
		S.D.	1.17890	1.24656	5.45788	7.60245	3.40933	88.36521
		N	12	12	12	12	12	12
2	m	Mean	19.20833	20.29881	12.43452	18.46528	17.60174	474.38333
		S.D.	1.36829	1.45097	6.09756	7.30858	2.95331	75.76220
		N	12	12	12	12	12	12
3	m	Mean	18.87143	20.33929	13.36548	19.67639	18.06314	486.09167
		S.D.	1.15246	0.98802	4.81374	5.41290	2.64154	69.12308
		N	12	12	12	12	12	12
4	m	Mean	16.80714**	18.13452**	9.27738	16.69444	15.22837	409.70000
		S.D.	1.32766	1.06127	4.82256	6.74228	2.87617	74.25669
		N	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 4: Food Consumption (cont'd)

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			Food Consumption		Intergroup Food Consumption by Animal						
08016			Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test								
			Day numbers relative to Start Date								
Group	Sex	From:	0	7	14	21	Mean	Total			
		To:	7	14	21	27	0	0			

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 5: Water Consumption

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			Water Consumption		Intergroup Water Consumption by Animal				
08016			Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test						
			Day numbers relative to Start Date						
Group	Sex	From:	0	7	14	21	Mean	Total	
		To:	7	14	21	27	0	0	
							27	27	
1	m	Mean	24.90952	25.10238	15.30238	21.75417	21.76711	587.72500	
		S.D.	2.72513	2.65597	7.81784	9.05275	4.25937	111.09859	
		N	12	12	12	12	12	12	
2	m	Mean	25.41429	25.80119	15.36667	22.73611	22.32956	602.49167	
		S.D.	2.45147	3.47265	7.66669	9.85148	3.81117	97.81731	
		N	12	12	12	12	12	12	
3	m	Mean	25.13571	26.00833	17.93214	25.65139	23.68189	637.44167	
		S.D.	3.09711	2.75857	6.39229	8.27919	4.47713	117.35178	
		N	12	12	12	12	12	12	
4	m	Mean	24.90357	25.31667	12.79286	23.15000	21.54077	579.99167	
		S.D.	2.02667	2.15729	6.34392	9.43956	3.62315	93.00573	
		N	12	12	12	12	12	12	

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 5: Water Consumption (cont'd)

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			Water Consumption		Intergroup Water Consumption by Animal			
08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test								
Day numbers relative to Start Date								
Group	Sex	From: To:	0	7	14	21	Mean	Total
			7	14	21	27	0 27	0 27
1	f	Mean	19.29167	19.47619	20.51667	19.63750	19.77336	534.01667
		S.D.	1.67858	2.05227	1.83055	2.26539	1.57212	42.13713
		N	24	24	12	12	12	12
2	f	Mean	19.90476	20.89167	20.77738	20.03472	20.60570	556.92500
		S.D.	2.40697	1.62769	2.13869	1.93655	1.81813	49.36339
		N	24	24	12	12	12	12
3	f	Mean	20.26964	21.18571	20.57262	19.43889	20.15198	544.81667
		S.D.	2.91642	2.78312	2.70633	2.76800	2.34804	63.31949
		N	24	24	12	12	12	12
4	f	Mean	20.86488	21.49881*	21.40238	20.90833	20.98125	566.56667
		S.D.	2.72870	3.20365	1.90600	1.96323	1.46948	39.68992
		N	24	24	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 6: Locomotor Activity

08016 males

		DG			
		1	2	3	4
TR-15	Mean	451.2833	459.3500	443.8583	439.3083
	Std	52.7989	60.8074	155.0305	67.5517
	N	12.0000	12.0000	12.0000	12.0000
TM-15	Mean	448.7167	440.6417	456.1417	460.6917
	Std	52.7989	60.8121	155.0305	67.5517
	N	12.0000	12.0000	12.0000	12.0000
DI-15	Mean	148.2000	142.4417	158.7833	149.1000
	Std	22.8856	27.3996	62.4741	36.1726
	N	12.0000	12.0000	12.0000	12.0000
RT-15	Mean	313.7750	341.5167	293.5333	275.2083
	Std	127.1725	161.7469	153.9679	74.1546
	N	12.0000	12.0000	12.0000	12.0000
RE-15	Mean	87.6667	82.4167	86.7500	90.9167
	Std	13.7665	22.2648	34.0030	14.7861
	N	12.0000	12.0000	12.0000	12.0000
TR-30	Mean	643.4167	651.3500	633.5250	636.9667
	Std	105.9195	104.8598	142.6781	115.9777
	N	12.0000	12.0000	12.0000	12.0000
TM-30	Mean	256.5833	248.6500	266.4667	263.0250
	Std	105.9195	104.8598	142.6800	115.9815
	N	12.0000	12.0000	12.0000	12.0000
DI-30	Mean	77.2083	74.3583	86.4667	80.8000
	Std	34.8461	37.4640	55.1256	41.7873

Abbreviations:
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 Interval in minutes
 T - total period
 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 males

		DG			
		1	2	3	4
DI-30	N	12.0000	12.0000	12.0000	12.0000
RT-30	Mean	216.0333	272.5250	268.2833	215.7667
	Std	143.6797	213.5808	187.7204	120.1197
	N	12.0000	12.0000	12.0000	12.0000
RE-30	Mean	49.4167	50.0833	51.0000	53.5000
	Std	25.3501	19.4163	27.4359	25.0654
	N	12.0000	12.0000	12.0000	12.0000
TR-45	Mean	732.9167	740.9833	742.3833	760.8917
	Std	116.4537	70.4674	95.3892	94.3819
	N	12.0000	12.0000	12.0000	12.0000
TM-45	Mean	167.0917	159.0417	157.6250	139.1250
	Std	116.4539	70.4553	95.3908	94.3668
	N	12.0000	12.0000	12.0000	12.0000
DI-45	Mean	49.2667	44.4417	45.8750	38.3250
	Std	36.8829	20.2452	30.5325	27.5859
	N	12.0000	12.0000	12.0000	12.0000
RT-45	Mean	174.5000	172.1167	145.2417	119.0417
	Std	133.4445	217.8180	160.6263	98.9397
	N	12.0000	12.0000	12.0000	12.0000
RE-45	Mean	33.6667	25.1667	26.1667	26.3333
	Std	24.2087	16.4584	21.3747	16.2163
	N	12.0000	12.0000	12.0000	12.0000

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 Numbers indicate
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 Interval in minutes
 T - total period
 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 males

		DG			
		1	2	3	4
TR-60	Mean	785.5333	811.8333	782.6333	816.1000
	Std	129.4013	67.3886	87.2058	77.8629
	N	12.0000	12.0000	12.0000	12.0000
TM-60	Mean	114.4750	88.1583	117.3750	83.9000
	Std	129.4058	67.3794	87.2123	77.8803
	N	12.0000	12.0000	12.0000	12.0000
DI-60	Mean	33.9417	22.9167	34.4833	22.3667
	Std	42.5212	18.2461	26.1904	22.0503
	N	12.0000	12.0000	12.0000	12.0000
RT-60	Mean	76.4500	128.4917	116.4167	51.8583
	Std	72.8510	188.3408	172.9763	63.7260
	N	12.0000	12.0000	12.0000	12.0000
RE-60	Mean	16.4167	16.9167	17.6667	15.2500
	Std	16.1440	12.9436	16.7567	16.0404
	N	12.0000	12.0000	12.0000	12.0000
TR-75	Mean	836.9583	826.1750	858.8833	858.3167
	Std	116.8266	104.8589	58.4934	52.6270
	N	12.0000	12.0000	12.0000	12.0000
TM-75	Mean	63.0333	73.8250	41.1167	41.6833
	Std	116.8305	104.8336	58.4934	52.6270
	N	12.0000	12.0000	12.0000	12.0000
DI-75	Mean	19.0417	21.2417	11.8917	10.8667
	Std	38.5164	31.6944	17.3662	14.3252

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 T - total period
 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 males

		DG			
		1	2	3	4
DI-75	N	12.0000	12.0000	12.0000	12.0000
RT-75	Mean	10.5583	97.9833	17.1083	20.5417
	Std	15.9400	188.4979	26.4487	24.9593
	N	12.0000	12.0000	12.0000	12.0000
RE-75	Mean	2.9167	13.0833	5.4167	5.5000
	Std	3.7040	20.7472	6.9079	7.1795
	N	12.0000	12.0000	12.0000	12.0000
TR-90	Mean	850.6333	857.3500	865.7833	872.4083
	Std	83.7725	70.8935	63.7683	32.0080
	N	12.0000	12.0000	12.0000	12.0000
TM-90	Mean	49.3667	42.6500	34.2250	27.6000
	Std	83.7754	70.8935	63.7637	32.0037
	N	12.0000	12.0000	12.0000	12.0000
DI-90	Mean	13.9250	11.4000	9.1250	7.1667
	Std	23.6526	19.7763	16.3669	7.8334
	N	12.0000	12.0000	12.0000	12.0000
RT-90	Mean	45.2833	95.3750	12.6000	22.1750
	Std	92.9401	201.5919	19.5256	41.6643
	N	12.0000	12.0000	12.0000	12.0000
RE-90	Mean	9.0000	7.5833	4.5833	4.5000
	Std	18.7714	15.6464	6.8684	6.9740
	N	12.0000	12.0000	12.0000	12.0000

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 Interval in minutes
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 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 males

		DG			
		1	2	3	4
TRM	Mean	716.7903	724.5069	721.1778	730.6653
	Std	69.7050	61.4691	69.8774	39.2832
	N	12.0000	12.0000	12.0000	12.0000
TMM	Mean	183.2111	175.4944	178.8250	169.3375
	Std	69.7074	61.4600	69.8756	39.2878
	N	12.0000	12.0000	12.0000	12.0000
DIM	Mean	56.9306	52.8000	57.7708	51.4375
	Std	24.1795	20.6965	25.8232	15.4329
	N	12.0000	12.0000	12.0000	12.0000
RTM	Mean	139.4333	184.6681	142.1972	117.4319
	Std	74.3066	177.9005	102.4731	49.0992
	N	12.0000	12.0000	12.0000	12.0000
REM	Mean	33.1806	32.5417	31.9306	32.6667
	Std	11.4001	14.5352	14.5603	9.1458
	N	12.0000	12.0000	12.0000	12.0000

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 Numbers indicate
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 Interval in minutes
 T - total period
 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
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 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 females

		DG			
		1	2	3	4
TR-15	Mean	392.9167	425.3500	418.8583	411.9500
	Std	65.9065	50.9328	76.2869	70.1671
	N	12.0000	12.0000	12.0000	12.0000
TM-15	Mean	507.0833	474.6500	481.1333	488.0500
	Std	65.9065	50.9328	76.2793	70.1671
	N	12.0000	12.0000	12.0000	12.0000
DI-15	Mean	189.0583	167.0833	167.4833	174.3083
	Std	41.6024	25.0625	36.5598	41.4432
	N	12.0000	12.0000	12.0000	12.0000
RT-15	Mean	254.5583	214.6667	194.3917	187.9833
	Std	122.3364	99.9507	92.8839	31.2678
	N	12.0000	12.0000	12.0000	12.0000
RE-15	Mean	100.4167	88.0000	86.7500	88.1667
	Std	29.4663	24.6060	22.7601	17.1720
	N	12.0000	12.0000	12.0000	12.0000
TR-30	Mean	630.9000	683.6250	632.7667	667.8667
	Std	88.4749	84.3547	71.5977	91.2356
	N	12.0000	12.0000	12.0000	12.0000
TM-30	Mean	269.0917	216.3833	267.2417	232.1417
	Std	88.4656	84.3509	71.5970	91.2355
	N	12.0000	12.0000	12.0000	12.0000
DI-30	Mean	91.3833	66.0583	83.1583	73.2083
	Std	36.7953	27.0660	26.7111	30.7993

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 Interval in minutes
 T - total period
 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 females

		DG			
		1	2	3	4
DI-30	N	12.0000	12.0000	12.0000	12.0000
RT-30	Mean	147.3917	104.5833	117.4083	97.0167
	Std	113.6397	90.8501	98.0581	45.7794
	N	12.0000	12.0000	12.0000	12.0000
RE-30	Mean	40.5833	33.0000	37.4167	30.8333
	Std	26.1654	17.5032	20.8826	14.1539
	N	12.0000	12.0000	12.0000	12.0000
TR-45	Mean	746.6750	768.5833	768.6917	785.7083
	Std	113.0602	89.2694	99.6444	92.5304
	N	12.0000	12.0000	12.0000	12.0000
TM-45	Mean	153.3250	131.4250	131.3167	114.2750
	Std	113.0602	89.2806	99.6468	92.5299
	N	12.0000	12.0000	12.0000	12.0000
DI-45	Mean	49.8667	37.6333	40.6167	36.4750
	Std	43.5636	26.6859	36.3231	33.2003
	N	12.0000	12.0000	12.0000	12.0000
RT-45	Mean	80.2917	60.9917	33.4583	39.9500
	Std	105.6016	83.0812	31.5210	48.5945
	N	12.0000	12.0000	12.0000	12.0000
RE-45	Mean	19.6667	17.1667	13.9167	13.6667
	Std	26.2032	18.0042	13.0625	15.8650
	N	12.0000	12.0000	12.0000	12.0000

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 2: 30 mg/m³
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 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 females

		DG			
		1	2	3	4
TR-60	Mean	808.7000	836.6917	793.2750	796.5167
	Std	113.9814	89.7673	141.3006	107.6408
	N	12.0000	12.0000	12.0000	12.0000
TM-60	Mean	91.3083	63.3000	106.7333	103.4917
	Std	113.9889	89.7722	141.2943	107.6389
	N	12.0000	12.0000	12.0000	12.0000
DI-60	Mean	30.8333	17.6333	38.1667	35.3500
	Std	39.9540	26.0608	55.6658	47.0964
	N	12.0000	12.0000	12.0000	12.0000
RT-60	Mean	57.1583	24.1417	27.8167	21.4417
	Std	108.9326	35.4248	44.4878	29.9634
	N	12.0000	12.0000	12.0000	12.0000
RE-60	Mean	14.5000	6.7500	12.7500	6.6667
	Std	25.1595	9.4784	23.1207	7.2780
	N	12.0000	12.0000	12.0000	12.0000
TR-75	Mean	811.5500	868.8667	859.6667	846.3083
	Std	117.7540	46.1676	67.5583	99.1103
	N	12.0000	12.0000	12.0000	12.0000
TM-75	Mean	88.4500	31.1333	40.3333	53.6917
	Std	117.7540	46.1676	67.5583	99.1103
	N	12.0000	12.0000	12.0000	12.0000
DI-75	Mean	30.3167	7.9750	12.3083	20.0750
	Std	40.8846	12.6856	22.9970	43.0027

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 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 females

		DG			
		1	2	3	4
DI-75	N	12.0000	12.0000	12.0000	12.0000
RT-75	Mean	39.3417	8.9083	5.3000	13.6500
	Std	72.3782	23.8576	13.2515	27.2998
	N	12.0000	12.0000	12.0000	12.0000
RE-75	Mean	8.9167	3.0000	3.3333	3.0000
	Std	14.7861	7.8277	8.2719	5.9696
	N	12.0000	12.0000	12.0000	12.0000
TR-90	Mean	812.4583	867.7833	858.5000	833.5167
	Std	109.5644	58.9692	83.5269	158.2418
	N	12.0000	12.0000	12.0000	12.0000
TM-90	Mean	87.5417	32.2250	41.4917	66.4750
	Std	109.5644	58.9659	83.5116	158.2455
	N	12.0000	12.0000	12.0000	12.0000
DI-90	Mean	30.2667	9.1417	15.1750	21.7250
	Std	41.4450	17.0334	32.3121	55.8057
	N	12.0000	12.0000	12.0000	12.0000
RT-90	Mean	36.6583	14.6000	15.0500	7.0833
	Std	76.1482	27.0652	35.7956	19.4753
	N	12.0000	12.0000	12.0000	12.0000
RE-90	Mean	10.9167	4.3333	4.8333	2.8333
	Std	25.2819	9.1784	11.5115	7.3464
	N	12.0000	12.0000	12.0000	12.0000

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 Interval in minutes
 T - total period
 1: Control
 2: 30 mg/m³
 3: 100 mg/m³
 4: 300 mg/m³
 DG: Dose Group

Table 6: Locomotor Activity (cont'd)

08016 females

		DG			
		1	2	3	4
TRM	Mean	700.5333	741.8167	721.9597	723.6444
	Std	62.9474	40.1206	68.8655	65.4611
	N	12.0000	12.0000	12.0000	12.0000
TMM	Mean	199.4667	158.1861	178.0417	176.3542
	Std	62.9467	40.1204	68.8619	65.4611
	N	12.0000	12.0000	12.0000	12.0000
DIM	Mean	70.2875	50.9208	59.4847	60.1903
	Std	26.4466	12.1170	28.5665	27.0483
	N	12.0000	12.0000	12.0000	12.0000
RTM	Mean	102.5667	71.3153	65.5708	61.1875
	Std	79.2989	49.7977	38.6342	16.6548
	N	12.0000	12.0000	12.0000	12.0000
REM	Mean	32.5000	25.3750	26.5000	24.1944
	Std	17.1252	9.8594	9.4332	5.9691
	N	12.0000	12.0000	12.0000	12.0000

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 4: 300 mg/m³
 DG: Dose Group

Table 7: Functional Observational Battery**FOB Study No: 02G08016, Males**

Group no.	1 Control				2 Low Dose				3 Medium Dose				4 High Dose			
	Mean	SD	N	+/-	Mean	SD	N	+/-	Mean	SD	N	+/-	Mean	SD	N	+/-
Body temperature, °C	35.9	0.7	12		35.7	0.5	12		36.1	0.3	12		36.0	0.7	12	
Forelimb grip strength, g	499.6	116.9	12		462.1	85.6	12		574.2	88.7	12		501.7	79.4	12	
Positive geotropism				7/5				8/4				7/5				3/9
Wire maneuver				7/5				9/3				8/4				7/5
Stereotypy	0.0	0.0	12		0.0	0.0	12		0.0	0.0	12		0.0	0.0	12	
Toe pinch	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Tail pinch	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Tremors				0/12				0/12				0/12				0/12
Extensor thrust				12/0				12/0				12/0				12/0
Limb rotation	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Activity	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Salivation				0/12				0/12				0/12				0/12
Startle response				12/0				12/0				12/0				12/0
Respiration	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Urination	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Mouth breathing				0/12				0/12				0/12				0/12
Convulsions				0/12				0/12				0/12				0/12
Pineal response				12/0				12/0				12/0				12/0
Piloerection				0/12				0/12				0/12				0/12
Diarrhea	0.0	0.0	12		0.0	0.0	12		0.0	0.0	12		0.0	0.0	12	
Lacrimation				0/12				0/12				0/12				0/12
Impaired gait	0.0	0.0	12		0.0	0.0	12		0.0	0.0	12		0.0	0.0	12	
Pupil response				12/0				12/0				12/0				12/0
Hind leg splay, cm	10.4	1.4	12		9.2	1.8	12		9.2	1.2	12		9.8	2.0	12	
Righting reflex	0.4	0.4	12		0.4	0.3	12		0.2	0.3	12		0.3	0.4	12	

Table 7: Functional Observational Battery (cont'd)**FOB Study No: 02G08016, Females**

Group no.	1 Control				2 Low Dose				3 Medium Dose				4 High Dose			
	Mean	SD	N	+/	Mean	SD	N	+/	Mean	SD	N	+/	Mean	SD	N	+/
Body temperature, °C	37.4	0.3	12		37.4	0.3	12		37.4	0.6	12		37.4	0.4	12	
Forelimb grip strength, g	377.1	69.6	12		374.2	107.6	12		424.6	74.6	12		442.5	83.6	12	
Positive geotropism				7/5				8/4				6/6				6/6
Wire maneuver				11/1				12/0				11/1				12/0
Stereotypy	0.0	0.0	12		0.0	0.0	12		0.0	0.0	12		0.0	0.0	12	
Toe pinch	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Tail pinch	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Tremors				0/12				0/12				0/12				0/12
Extensor thrust				12/0				12/0				12/0				12/0
Limb rotation	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Activity	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Salivation				0/12				0/12				0/12				0/12
Startle response				12/0				12/0				12/0				12/0
Respiration	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Urination	3.0	0.0	12		3.0	0.0	12		3.0	0.0	12		3.0	0.0	12	
Mouth breathing				0/12				0/12				0/12				0/12
Convulsions				0/12				0/12				0/12				0/12
Pineal response				12/0				12/0				12/0				12/0
Piloerection				0/12				0/12				0/12				0/12
Diarrhea	0.0	0.0	12		0.0	0.0	12		0.0	0.0	12		0.0	0.0	12	
Lacrimation				0/12				0/12				0/12				0/12
Impaired gait	0.0	0.0	12		0.0	0.0	12		0.0	0.0	12		0.0	0.0	12	
Pupil response				12/0				12/0				12/0				12/0
Hind leg splay, cm	8.7	1.4	12		8.5	1.5	12		8.5	1.0	12		8.6	1.6	12	
Righting reflex	0.4	0.2	12		0.4	0.3	12		0.3	0.2	12		0.3	0.3	12	

Table 8: Main Macroscopic findings (day 28)

Group/ Observation	Group 1 Control		Group 2 30 mg/m ³		Group 3 100 mg/m ²		Group 4 300 mg/m ²	
Sex	m	f	m	f	m	f	m	f
n	12	12	12	12	12	12	12	12
Mandibular Glands								
red areas							1	
Thymus								
red areas	1	3		1		1	2	1
Lung								
red/brown area						1	1	
Heart								
enlarged in size						1		
Spleen								
enlarged					1			
Kidney(s)								
dilated		2	2		1		4	1
Uterus								
cystic enlarged		4		2		3		2
Testes/Epididymides								
reduced in size			1		1		1	

Table 9: Organ Weights

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Group	Sex		Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Epid. left g	Epid. right g	Heart Weight g	Kidney Wt left g
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	m	Mean	0.0218	0.0215	1.879	0.641	0.639	1.213	1.226
		S.D.	0.0014	0.0030	0.050	0.092	0.099	0.106	0.138
		N	12	12	12	12	12	12	12
2	m	Mean	0.0221	0.0215	1.868	0.620	0.629	1.203	1.248
		S.D.	0.0030	0.0030	0.046	0.052	0.057	0.081	0.103
		N	12	12	12	12	12	12	12
3	m	Mean	0.0233	0.0229	1.898	0.653	0.650	1.228	1.321
		S.D.	0.0031	0.0022	0.049	0.070	0.074	0.074	0.083
		N	12	12	12	12	12	12	12
4	m	Mean	0.0234	0.0217	1.885	0.586	0.635	1.143	1.193
		S.D.	0.0019	0.0026	0.039	0.104	0.075	0.102	0.074
		N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 9: Organ Weights (cont'd)

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Generalised Results			Group Summary by Parameter				Fixed Time		
08016			Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test						
			Day: 28 relative to Start Date						
			Kidney Wt right g	Liver Weight g	Lung Weight g	Spleen Weight g	Testis Wt left g	Testis Wt right g	Thymus Weight g
Up	Sex		Identity	Identity	Identity	Identity	Identity	Identity	Identity
m	Mean	1.237	10.613	1.3992	0.594	1.653	1.649	0.427	
	S.D.	0.099	0.767	0.2063	0.069	0.088	0.102	0.048	
	N	12	12	12	12	12	12	12	
m	Mean	1.284	10.739	1.3778	0.638	1.603	1.588	0.451	
	S.D.	0.082	0.983	0.0928	0.059	0.153	0.118	0.070	
	N	12	12	12	12	12	12	12	
m	Mean	1.334*	11.182	1.4278	0.632	1.640	1.647	0.412	
	S.D.	0.079	1.102	0.0852	0.081	0.193	0.176	0.065	
	N	12	12	12	12	12	12	12	
m	Mean	1.236	10.525	1.5499*	0.597	1.572	1.686	0.417	
	S.D.	0.067	0.957	0.1468	0.050	0.364	0.089	0.080	
	N	12	12	12	12	12	12	12	

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 9: Organ Weights (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Group	Sex		Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Heart Weight g	Kidney Wt left g	Kidney Wt right g	Liver Weight g
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	0.0249	0.0238	1.692	0.801	0.757	0.788	5.838
		S.D.	0.0037	0.0024	0.084	0.042	0.068	0.075	0.568
		N	12	12	12	12	12	12	12
2	f	Mean	0.0249	0.0242	1.708	0.805	0.742	0.774	6.059
		S.D.	0.0037	0.0029	0.047	0.029	0.041	0.049	0.469
		N	12	12	12	12	12	12	12
3	f	Mean	0.0261	0.0254	1.719	0.858	0.750	0.760	6.158
		S.D.	0.0027	0.0021	0.045	0.195	0.040	0.055	0.317
		N	12	12	12	12	12	12	12
4	f	Mean	0.0254	0.0247	1.771**	0.846	0.768	0.788	6.380*
		S.D.	0.0040	0.0048	0.047	0.043	0.062	0.055	0.618
		N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 9: Organ Weights (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Group	Sex		Lung Weight g	Ovary Wt left g	Ovary Wt right g	Spleen Weight g	Thymus Weight g	Uterus Weight g
			Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	0.9525	0.0436	0.0461	0.428	0.335	0.758
		S.D.	0.0569	0.0056	0.0072	0.049	0.057	0.382
		N	12	12	12	12	12	12
2	f	Mean	1.0118*	0.0459	0.0441	0.415	0.338	0.716
		S.D.	0.0409	0.0088	0.0073	0.035	0.040	0.290
		N	12	12	12	12	12	12
3	f	Mean	1.0730**	0.0444	0.0434	0.444	0.328	0.736
		S.D.	0.0625	0.0058	0.0074	0.041	0.055	0.320
		N	12	12	12	12	12	12
4	f	Mean	1.1854**	0.0441	0.0428	0.474	0.375	0.721
		S.D.	0.0552	0.0062	0.0065	0.061	0.078	0.309
		N	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 10: Breeding Females Organ Weights

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 50 relative to Start Date

Group	Sex		Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Heart Weight g	Kidney Wt left g	Kidney Wt right g	Liver Weight g
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	0.0276	0.0261	1.713	0.838	0.863	0.915	10.039
		S.D.	0.0028	0.0035	0.045	0.084	0.060	0.080	1.272
		N	11	11	11	11	11	11	11
2	f	Mean	0.0267	0.0252	1.750	0.829	0.864	0.906	10.428
		S.D.	0.0035	0.0026	0.071	0.053	0.060	0.048	0.758
		N	9	9	9	9	9	9	9
3	f	Mean	0.0299	0.0277	1.731	0.887	1.034	1.000	10.657
		S.D.	0.0045	0.0038	0.034	0.101	0.414	0.243	0.696
		N	11	11	11	11	11	11	11
4	f	Mean	0.0290	0.0264	1.710	0.872	0.872	0.906	10.572
		S.D.	0.0040	0.0030	0.047	0.065	0.050	0.045	0.811
		N	10	10	10	10	10	10	10

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 10: Breeding Females Organ Weights (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 50 relative to Start Date

Group	Sex		Lung Weight g	Ovary Wt left g	Ovary Wt right g	Spleen Weight g	Thymus Weight g	Uterus Weight g
			Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	1.0056	0.0505	0.0509	0.461	0.210	0.776
		S.D.	0.0600	0.0083	0.0073	0.053	0.041	0.173
		N	11	11	11	11	11	11
2	f	Mean	1.0103	0.0498	0.0498	0.498	0.210	0.771
		S.D.	0.0539	0.0068	0.0060	0.064	0.060	0.102
		N	9	9	9	9	9	9
3	f	Mean	1.0787*	0.0504	0.0535	0.530	0.206	0.734
		S.D.	0.0544	0.0047	0.0095	0.081	0.042	0.083
		N	11	11	11	11	11	11
4	f	Mean	1.1904**	0.0493	0.0469	0.513	0.205	0.698
		S.D.	0.0695	0.0080	0.0101	0.062	0.044	0.143
		N	10	10	10	10	10	10

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 11: Organ Weight/Body Weight Ratios

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Generalised Results Group Summary by Parameter Fixed Time
 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
 Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

			Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Brain /Bodywt g/kg	Liver /Bodywt g/kg	Heart /Bodywt g/kg
Group	Sex		Identity	Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	m	Mean	317.33	0.069010	0.067776	3.86096	3.89947	5.94009	33.47449	3.82513
		S.D.	19.21	0.005881	0.008611	0.32690	0.24142	0.36134	1.98356	0.27399
		N	12	12	12	12	12	12	12	12
2	m	Mean	318.79	0.069263	0.067583	3.91137	4.02858	5.87063	33.68053	3.77237
		S.D.	17.03	0.008708	0.010179	0.20867	0.15380	0.29309	2.47320	0.17045
		N	12	12	12	12	12	12	12	12
3	m	Mean	322.98	0.072300	0.070983	4.09084	4.13133*	5.88577	34.59646	3.80738
		S.D.	14.52	0.009354	0.006326	0.21027	0.17722	0.24809	2.75384	0.24799
		N	12	12	12	12	12	12	12	12
4	m	Mean	302.46	0.077473*	0.071546	3.94488	4.08732	6.24026*	34.81849	3.77560
		S.D.	11.28	0.006284	0.007058	0.18278	0.19943	0.26814	3.18642	0.23725
		N	12	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 11: Organ Weight/Body Weight Ratios (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Group	Sex		Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Epidy. /Bodywt g/kg	R.Epidy. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	m	Mean	1.87003	4.40308	1.34544	2.02118	2.01508	5.21691	5.20277
		S.D.	0.15349	0.52872	0.12938	0.28063	0.29845	0.23202	0.27207
		N	12	12	12	12	12	12	12
2	m	Mean	2.00328	4.32456	1.41871	1.94742	1.97641	5.03205	4.98844
		S.D.	0.16805	0.23936	0.24144	0.16476	0.18579	0.43646	0.40823
		N	12	12	12	12	12	12	12
3	m	Mean	1.95887	4.42077	1.27541	2.02730	2.01538	5.08370	5.10569
		S.D.	0.26834	0.17404	0.19103	0.24285	0.23892	0.61543	0.57900
		N	12	12	12	12	12	12	12
4	m	Mean	1.97574	5.12410**	1.37909	1.93322	2.09883	5.18088	5.57838
		S.D.	0.18802	0.44390	0.27125	0.32646	0.22730	1.16864	0.32152
		N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 11: Organ Weight/Body Weight Ratios (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

			Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Brain /Bodywt g/kg	Liver /Bodywt g/kg
Group	Sex		Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	189.84	0.131025	0.125108	3.98282	4.14898	8.94512	30.72818
		S.D.	10.84	0.015175	0.010692	0.22670	0.26065	0.75696	1.93803
		N	12	12	12	12	12	12	12
2	f	Mean	192.02	0.129690	0.125793	3.86533	4.03073	8.90048	31.54287
		S.D.	5.14	0.018843	0.013924	0.14827	0.20529	0.27571	2.09316
		N	12	12	12	12	12	12	12
3	f	Mean	191.53	0.136373	0.133053	3.92050	3.97243	8.98490	32.15493
		S.D.	6.59	0.015156	0.014158	0.25751	0.32696	0.35909	1.38806
		N	12	12	12	12	12	12	12
4	f	Mean	201.14**	0.126701	0.123396	3.81908	3.91638	8.81838	31.70661
		S.D.	8.46	0.021231	0.024891	0.30837	0.24159	0.43986	2.52853
		N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table11: Organ Weight/Body Weight Ratios (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

			Heart /Bodywt g/kg	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg	Uterus /Bodywt g/kg
Group	Sex	Identity	Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	4.22778	2.25070	5.02397	1.76174	0.229889	0.242090	4.04475
		S.D.	0.28397	0.20418	0.27746	0.25259	0.029341	0.028524	2.19824
		N	12	12	12	12	12	12	12
2	f	Mean	4.19380	2.16113	5.27101	1.75985	0.238869	0.229114	3.72836
		S.D.	0.15457	0.16816	0.21649	0.22503	0.043464	0.033842	1.52423
		N	12	12	12	12	12	12	12
3	f	Mean	4.48568	2.32068	5.60746**	1.70605	0.231943	0.226237	3.87185
		S.D.	1.04981	0.21413	0.36298	0.26154	0.029462	0.034928	1.78535
		N	12	12	12	12	12	12	12
4	f	Mean	4.21061	2.35452	5.89873**	1.86395	0.218728	0.212044	3.60606
		S.D.	0.25594	0.25234	0.28695	0.37720	0.025706	0.027722	1.63207
		N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 12: Breeding Females Organ Weight/Body Weight Ratios

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 50 relative to Start Date

Group	Sex		Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Brain /Bodywt g/kg	Liver /Bodywt g/kg
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	227.11	0.121886	0.114946	3.80395	4.02862	7.56285	44.10529
		S.D.	15.35	0.011945	0.014135	0.20891	0.15612	0.37426	3.59779
		N	11	11	11	11	11	11	11
2	f	Mean	231.36	0.115408	0.109241	3.74018	3.91904	7.57864	45.06698
		S.D.	11.33	0.015657	0.012637	0.26328	0.22733	0.45317	2.32493
		N	9	9	9	9	9	9	9
3	f	Mean	238.08	0.125763	0.116527	4.35054	4.21026	7.28851	44.75378
		S.D.	12.59	0.018398	0.014602	1.77122	1.05405	0.40486	1.41855
		N	11	11	11	11	11	11	11
4	f	Mean	230.74	0.125761	0.114718	3.78095	3.92837	7.41610	45.79015
		S.D.	5.54	0.017465	0.015763	0.23377	0.21260	0.31033	2.90120
		N	10	10	10	10	10	10	10

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 12: Breeding Females Organ Weight/Body Weight Ratios (cont'd)

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Generalised Results Group Summary by Parameter Fixed Time

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
 Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 50 relative to Start Date

			Heart /Bodywt g/kg	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg	Uterus /Bodywt g/kg
Group	Sex	Identity	Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	3.69057	2.03129	4.43399	0.92604	0.222666	0.225262	3.44538
		S.D.	0.26957	0.21077	0.20243	0.17651	0.038349	0.035823	0.91407
		N	11	11	11	11	11	11	11
2	f	Mean	3.58267	2.15358	4.37143	0.90003	0.215944	0.214862	3.33648
		S.D.	0.14533	0.27315	0.23336	0.21445	0.033897	0.020959	0.44203
		N	9	9	9	9	9	9	9
3	f	Mean	3.72917	2.22355	4.53611	0.86745	0.211845	0.224187	3.08900
		S.D.	0.38807	0.29569	0.21771	0.16623	0.020463	0.034912	0.38112
		N	11	11	11	11	11	11	11
4	f	Mean	3.77696	2.22735	5.16104**	0.88944	0.213915	0.203160	3.01892
		S.D.	0.22233	0.30130	0.31268	0.19329	0.035883	0.043142	0.57902
		N	10	10	10	10	10	10	10

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;
 n Data not appropriate for statistical analysis;
 n1 This group has only one value;

Arithmetic Mean Values Presented

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/

Table 13: Hematology 1

Generalised Results Group Summary by Parameter Fixed Time

Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 1

		RBC T/L	HB mmol/L	HCT %	MCV fL	MCH fmol	MCHC mmol/L
Males							
1m	Mean	8.347	9.48	49.38	59.18	1.137	19.208
	S.D.	0.356	0.34	2.27	1.88	0.030	0.320
	N	12	12	12	12	12	12
2m	Mean	8.635*	9.80*	51.52*	59.66	1.135	19.025
	S.D.	0.153	0.23	1.62	1.25	0.024	0.314
	N	12	12	12	12	12	12
3m	Mean	8.361	9.52	49.48	59.18	1.138	19.242
	S.D.	0.237	0.31	1.51	0.97	0.020	0.223
	N	12	12	12	12	12	12
4m	Mean	8.478	9.68	50.28	59.30	1.142	19.250
	S.D.	0.276	0.31	1.98	1.35	0.029	0.261
	N	12	12	12	12	12	12
Females							
1f	Mean	8.189	9.57	49.14	60.04	1.169	19.467
	S.D.	0.276	0.30	1.48	1.44	0.034	0.219
	N	12	12	12	12	12	12
2f	Mean	8.269	9.60	49.44	59.79	1.162	19.408
	S.D.	0.213	0.36	2.18	2.06	0.032	0.264
	N	12	12	12	12	12	12
3f	Mean	8.328	9.62	49.30	59.20	1.155	19.517
	S.D.	0.222	0.32	1.75	1.57	0.027	0.225
	N	12	12	12	12	12	12
4f	Mean	8.245	9.53	48.68	59.06	1.156	19.567
	S.D.	0.348	0.27	1.65	1.40	0.028	0.334
	N	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
** 1% significance level;Group 1 Control Clean air Group 2 30 mg/m3
Group 3 100 mg/m3 Group 4 300 mg/m3

Table 14: Hematology 2

Generalised Results Group Summary by Parameter Fixed Time

Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 2

		PLT G/L	PT Seconds	PTT Seconds
Males				
1m	Mean	1183.6	35.58	19.04
	S.D.	116.1	3.08	3.63
	N	12	12	12
2m	Mean	1155.8	35.33	18.73
	S.D.	93.0	2.75	2.69
	N	11	12	12
3m	Mean	1147.7	35.24	18.37
	S.D.	134.6	1.32	2.07
	N	12	12	12
4m	Mean	1109.1	35.75	17.78
	S.D.	95.8	2.44	2.59
	N	11	11	11
Females				
1f	Mean	1142.1	32.96	19.33
	S.D.	76.0	1.82	1.72
	N	10	12	12
2f	Mean	1159.8	32.08	19.22
	S.D.	133.9	2.65	1.74
	N	12	12	12
3f	Mean	1090.5	33.26	18.62
	S.D.	92.7	3.10	1.72
	N	11	12	12
4f	Mean	1078.1	33.45	19.02
	S.D.	63.6	2.39	3.09
	N	11	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 15: Hematology 3

Generalised Results Group Summary by Parameter Fixed Time

Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 3

		WBC G/L	LYMC G/L	SEGC G/L	BANC G/L	EOSC G/L	BASC G/L	MONC G/L
Males								
1m	Mean	10.51	9.382	0.809	0.173	0.100	0.000	0.050
	S.D.	1.21	1.284	0.296	0.083	0.098	0.000	0.064
	N	12	12	12	12	12	12	12
2m	Mean	11.50	10.068	1.003	0.226	0.131	0.000	0.075
	S.D.	1.31	1.366	0.285	0.126	0.078	0.000	0.093
	N	12	12	12	12	12	12	12
3m	Mean	11.83	10.423	0.943	0.226	0.163	0.000	0.083
	S.D.	3.51	3.054	0.399	0.183	0.146	0.000	0.082
	N	12	12	12	12	12	12	12
4m	Mean	10.29	9.160	0.833	0.133	0.136	0.000	0.033
	S.D.	1.85	1.887	0.295	0.129	0.106	0.000	0.051
	N	12	12	12	12	12	12	12
Females								
1f	Mean	8.98	8.082	0.565	0.153	0.127	0.000	0.051
	S.D.	1.55	1.524	0.206	0.099	0.106	0.000	0.058
	N	12	12	12	12	12	12	12
2f	Mean	9.33	8.419	0.618	0.124	0.119	0.000	0.043
	S.D.	1.64	1.566	0.307	0.088	0.093	0.000	0.047
	N	12	12	12	12	12	12	12
3f	Mean	9.15	8.142	0.670	0.136	0.126	0.000	0.078
	S.D.	2.55	2.454	0.316	0.083	0.094	0.000	0.094
	N	12	12	12	12	12	12	12
4f	Mean	10.14	9.011	0.718	0.193	0.119	0.000	0.107
	S.D.	1.37	1.386	0.327	0.104	0.071	0.000	0.046
	N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 16: Hematology 4

Generalised Results Group Summary by Parameter Fixed Time
 Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
 Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 4

		LYM %	SEGM %	BAND %	EOS %	BASO %	MONO %
Males							
1m	Mean	89.1	7.8	1.7	0.9	0.0	0.5
	S.D.	3.5	3.2	0.8	0.9	0.0	0.7
	N	12	12	12	12	12	12
2m	Mean	87.4	8.8	2.0	1.2	0.0	0.7
	S.D.	4.0	2.4	1.1	0.7	0.0	0.8
	N	12	12	12	12	12	12
3m	Mean	88.3	7.9	1.8	1.4	0.0	0.7
	S.D.	3.5	2.4	1.3	1.2	0.0	0.7
	N	12	12	12	12	12	12
4m	Mean	88.7	8.3	1.3	1.3	0.0	0.3
	S.D.	4.5	3.4	1.2	1.1	0.0	0.5
	N	12	12	12	12	12	12
Females							
1f	Mean	89.9	6.3	1.8	1.4	0.0	0.6
	S.D.	3.7	2.3	1.1	1.2	0.0	0.7
	N	12	12	12	12	12	12
2f	Mean	90.3	6.6	1.3	1.3	0.0	0.5
	S.D.	3.3	3.1	0.9	1.0	0.0	0.5
	N	12	12	12	12	12	12
3f	Mean	88.6	7.8	1.5	1.3	0.0	0.8
	S.D.	5.2	4.5	0.9	0.9	0.0	0.9
	N	12	12	12	12	12	12
4f	Mean	88.8	7.1	1.9	1.2	0.0	1.1
	S.D.	4.4	3.3	1.1	0.7	0.0	0.5
	N	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 17: Clinical Chemistry 1

Generalised Results Group Summary by Parameter Fixed Time

Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 1

		AST U/L	ALT U/L	CK U/L	GGT U/L	AP U/L	SDH U/L	CHE kU/L	TBIL umol/L
Males									
1m	Mean	70.9	44.8	121.4	0.7	134.6	3.0	0.161	2.03
	S.D.	7.0	4.2	15.3	1.2	20.8	1.7	0.016	0.38
	N	12	12	12	12	12	12	12	12
2m	Mean	76.1	48.6	128.7	1.0	145.0	1.6	0.174	2.19
	S.D.	13.6	7.6	30.0	1.1	34.8	1.4	0.028	0.49
	N	12	12	12	12	12	12	12	12
3m	Mean	71.3	47.5	126.3	1.8	151.3	0.9**	0.169	2.05
	S.D.	7.2	5.7	31.1	1.6	25.5	0.9	0.019	0.54
	N	12	12	12	12	12	12	12	12
4m	Mean	80.1	48.0	123.1	0.8	160.1	2.1	0.173	1.91
	S.D.	12.9	7.8	35.4	1.2	27.0	2.2	0.017	0.51
	N	12	12	12	12	12	12	12	12
Females									
1f	Mean	68.1	40.6	104.4	0.4	79.0	2.6	0.920	2.45
	S.D.	12.5	8.2	12.1	0.7	10.3	3.3	0.322	0.32
	N	12	12	12	12	12	12	12	12
2f	Mean	69.6	43.5	116.6	1.0	101.3*	2.0	0.785	2.71
	S.D.	9.4	6.6	26.1	1.2	17.3	3.1	0.156	0.61
	N	12	12	12	12	12	12	12	12
3f	Mean	70.1	41.5	107.3	1.3	97.1	3.2	0.790	2.39
	S.D.	9.4	6.4	33.5	1.1	12.6	4.2	0.280	0.55
	N	12	12	12	12	12	12	12	12
4f	Mean	75.3	44.5	120.8	1.3	103.2**	1.8	0.788	2.22
	S.D.	9.7	9.1	52.9	1.2	29.8	3.0	0.203	0.44
	N	12	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;

Group 1 Control Clean air
 Group 3 100 mg/m3

Group 2 30 mg/m3
 Group 4 300 mg/m3

Table 18: Clinical Chemistry 2

Generalised Results Group Summary by Parameter Fixed Time
 Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
 Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test
 Day: 28 relative to Start Date
 Clinical Chemistry 2

		TP g/L	ALB g/L	GLB g/L	A/G	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L
Males								
1m	Mean	61.61	34.26	27.35	1.253	5.552	1.608	0.548
	S.D.	2.32	1.27	1.13	0.026	0.586	0.216	0.203
	N	12	12	12	12	12	12	12
2m	Mean	63.88*	35.23	28.65	1.230	5.559	1.758	0.523
	S.D.	1.70	0.94	1.18	0.053	0.754	0.242	0.166
	N	12	12	12	12	12	12	12
3m	Mean	63.60	35.15	28.45	1.239	5.523	1.799	0.644
	S.D.	2.28	1.16	1.72	0.072	0.750	0.290	0.258
	N	12	12	12	12	12	12	12
4m	Mean	62.10	34.75	27.35	1.277	5.826	1.643	0.455
	S.D.	1.79	0.81	1.60	0.082	1.107	0.286	0.127
	N	12	12	12	12	12	12	12
Females								
1f	Mean	63.73	36.85	26.88	1.377	5.212	2.092	0.557
	S.D.	2.16	1.38	1.71	0.106	0.673	0.397	0.144
	N	12	12	12	12	12	12	12
2f	Mean	63.34	36.25	27.09	1.342	5.111	2.111	0.553
	S.D.	1.13	1.03	1.25	0.091	0.575	0.275	0.128
	N	12	12	12	12	12	12	12
3f	Mean	63.78	36.66	27.12	1.354	5.016	2.266	0.594
	S.D.	2.33	1.15	1.48	0.061	0.677	0.307	0.152
	N	12	12	12	12	12	12	12
4f	Mean	62.62	36.08	26.53	1.361	4.646	2.230	0.645
	S.D.	2.69	1.85	1.14	0.057	0.611	0.299	0.174
	N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 19: Clinical Chemistry 3

Generalised Results Group Summary by Parameter Fixed Time
 Study: 08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
 Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test
 Day: 28 relative to Start Date
 Clinical Chemistry 3

		CREA umol/L	UREA mmol/L	Na mmol/L	K mmol/L	Ca mmol/L	P04 mmol/L	Cl mmol/L
Males								
1m	Mean	56.56	5.718	141.56	4.020	2.614	2.113	99.8
	S.D.	4.17	0.707	2.05	0.141	0.081	0.100	0.9
	N	12	12	12	12	12	12	12
2m	Mean	58.13	5.952	141.68	3.990	2.681*	2.159	99.7
	S.D.	3.86	0.831	2.03	0.229	0.054	0.116	0.9
	N	12	12	12	12	12	12	12
3m	Mean	55.85	6.063	141.81	4.041	2.682*	2.114	99.8
	S.D.	4.21	0.860	1.80	0.242	0.054	0.112	1.4
	N	12	12	12	12	12	12	12
4m	Mean	59.30	6.270	141.94	4.203	2.643	2.138	99.8
	S.D.	3.66	0.935	1.69	0.266	0.051	0.130	0.9
	N	12	12	12	12	12	12	12
Females								
1f	Mean	59.19	6.308	140.28	4.069	2.647	1.649	100.8
	S.D.	5.45	0.905	1.81	0.330	0.054	0.147	0.9
	N	12	12	12	12	12	12	12
2f	Mean	58.57	6.466	140.47	4.037	2.660	1.676	101.1
	S.D.	7.16	1.240	1.09	0.238	0.038	0.131	0.8
	N	12	12	12	12	12	12	12
3f	Mean	57.33	6.453	141.06	4.054	2.656	1.743	100.7
	S.D.	3.98	0.714	1.72	0.263	0.039	0.168	1.2
	N	12	12	12	12	12	12	12
4f	Mean	61.28	6.374	140.94	4.167	2.646	1.808*	101.2
	S.D.	3.37	1.292	1.47	0.146	0.033	0.143	0.9
	N	12	12	12	12	12	12	12

Statistics Test: Dunnett Test: * 5% significance level;
 ** 1% significance level;

Group 1 Control Clean air Group 2 30 mg/m3
 Group 3 100 mg/m3 Group 4 300 mg/m3

Table 20: Histopathological Findings

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC		THC	THC	THC	
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
CEREBRUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
CEREBELLUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
PITUITARY		(12)			(12)	(12)			(12)
No abnormality detected		11			12	12			12
		(92%)			(100%)	(100%)			(100%)
Focal craniopharyngeal structures		1			0	0			0
		(8%)			(0%)	(0%)			(0%)
EYES		(12)			(12)	(12)			(12)
No abnormality detected		3			4	5			2
		(25%)			(33%)	(42%)			(17%)
Retrobulbar haemorrhage		9			8	7			10
		(75%)			(67%)	(58%)			(83%)
Intra-ocular haemorrhage		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Retrobulbar mononuclear cell infiltration		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
HARDERIAN GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		8			9	11			9
		(67%)			(75%)	(92%)			(75%)
Haemorrhage		4			1	0			1
		(33%)			(8%)	(0%)			(8%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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Date:14-JAN-2009 Time:09:59

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
HARDERIAN GLANDS		(12)			(12)	(12)			(12)
Necrosis		0			0	1			2
		(0%)			(0%)	(8%)			(17%)
Atrophy		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Yellow-brown pigment deposit(s)		0			2	0			0
		(0%)			(17%)	(0%)			(0%)
LACRIMAL GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		10			12	11			11
		(83%)			(100%)	(92%)			(92%)
Harderian gland change(s)		1			0	1			0
		(8%)			(0%)	(8%)			(0%)
Mononuclear cell infiltration		1			0	0			1
		(8%)			(0%)	(0%)			(8%)
NASAL and PARANASAL CAVITIES		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		3	5	4	6	3	8	6	11**
		(25%)	(42%)	(33%)	(50%)	(25%)	(67%)	(50%)	(92%)
Epithelial erosion(s)		1	0	0	0	0	0	0	0
		(8%)	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)	(0%)
Mucosal inflammatory cell infiltration		9	7	7	5	8	4	5	0**
		(75%)	(58%)	(58%)	(42%)	(67%)	(33%)	(42%)	(0%)
Mucous (goblet) cell hyperplasia		3	3	3	4	4	3	1	1
		(25%)	(25%)	(25%)	(33%)	(33%)	(25%)	(8%)	(8%)
Mucosal psammoma bodies		1	2	1	0	2	0	1	0
		(8%)	(17%)	(8%)	(0%)	(17%)	(0%)	(8%)	(0%)
LARYNX		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		10	10	10	11	8	8	10	10
		(83%)	(83%)	(83%)	(92%)	(67%)	(67%)	(83%)	(83%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LARYNX		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Submucosal mononuclear/inflammatory cell infiltration		1 (8%)	2 (17%)	2 (17%)	1 (8%)	1 (8%)	2 (17%)	1 (8%)	1 (8%)
Submucosal foreign-body granuloma		1 (8%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)	2 (17%)	0 (0%)	1 (8%)
Dilatation of the submucosal glands		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
TRACHEA		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		12 (100%)	12 (100%)	11 (92%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)
Submucosal inflammatory cell infiltration		0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LUNGS		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		7 (58%)	7 (58%)	8 (67%)	0** (0%)	11 (92%)	10 (83%)	10 (83%)	0*** (0%)
Accumulation of alveolar macrophages (alveolar histiocytosis)		2 (17%)	4 (33%)	2 (17%)	12*** (100%)	1 (8%)	0 (0%)	2 (17%)	12*** (100%)
Bronchiole-alveolar hyperplasia (bronchiolar type)		0 (0%)	0 (0%)	0 (0%)	12*** (100%)	0 (0%)	0 (0%)	0 (0%)	12*** (100%)
Interstitial mononuclear/inflammatory cell infiltration		1 (8%)	2 (17%)	2 (17%)	5 (42%)	0 (0%)	2 (17%)	1 (8%)	6* (50%)
Alveolar inflammatory cell infiltration		0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bronchial mucous (goblet) cell hyperplasia		0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)
Foreign-body granuloma		1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Osseous metaplasia		1 (8%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LUNGS		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Alveolar haemorrhage		2 (17%)	2 (17%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Alveolar dilatation		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Passive congestion		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Congestion		0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LUNG ASSOCIATED LYMPH NODES		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		12 (100%)	12 (100%)	11 (92%)	12 (100%)	12 (100%)	10 (83%)	12 (100%)	12 (100%)
Lymphoid hyperplasia		0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)
THYROID		(12)			(12)	(12)			(12)
No abnormality detected		11 (92%)			10 (83%)	10 (83%)			10 (83%)
Mononuclear cell infiltration		1 (8%)			1 (8%)	0 (0%)			0 (0%)
Ectopic thymic tissue		1 (8%)			1 (8%)	2 (17%)			2 (17%)
PARATHYROIDIS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
Unilateral section		1 (8%)			3 (25%)	4 (33%)			2 (17%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
HEART		(12)			(12)	(12)			(12)
No abnormality detected		4 (33%)			5 (42%)	9 (75%)			8 (67%)
Myocardial mononuclear cell infiltration		8 (67%)			7 (58%)	3 (25%)			4 (33%)
Myocardial degeneration		0 (0%)			1 (8%)	0 (0%)			0 (0%)
AORTA		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
SALIVARY GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	11 (92%)			12 (100%)
Mononuclear cell infiltration		0 (0%)			0 (0%)	1 (8%)			0 (0%)
MANDIBULAR LYMPH NODES		(12)			(12)	(12)			(12)
No abnormality detected		10 (83%)			10 (83%)	10 (83%)			12 (100%)
Lymphoid hyperplasia		2 (17%)			1 (8%)	2 (17%)			0 (0%)
Congestion		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Unilateral section		3 (25%)			1 (8%)	0 (0%)			3 (25%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC	Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
TONGUE		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	11 (92%)			12 (100%)
Intra-muscular foreign-body granuloma		0 (0%)			0 (0%)	1 (8%)			0 (0%)
PHARYNX (LARYNGO-)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)
ESOPHAGUS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
FORESTOMACH		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
GLANDULAR STOMACH		(12)			(12)	(12)			(12)
No abnormality detected		10 (83%)			11 (92%)	11 (92%)			11 (92%)
Mucosal inflammatory cell infiltration		2 (17%)			1 (8%)	1 (8%)			1 (8%)
LIVER		(12)			(12)	(12)			(12)
No abnormality detected		1 (8%)			3 (25%)	2 (17%)			1 (8%)
Hepatocellular necrosis		0 (0%)			1 (8%)	2 (17%)			2 (17%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LIVER		(12)			(12)	(12)			(12)
Microgranuloma(s)		11 (92%)			9 (75%)	9 (75%)			11 (92%)
Perivascular mononuclear cell infiltration		2 (17%)			1 (8%)	1 (8%)			1 (8%)
PANCREAS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			8 (67%)	11 (92%)			10 (83%)
Islet-cell hyperplasia		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Acinar-cell atrophy		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Mononuclear cell infiltration		0 (0%)			2 (17%)	1 (8%)			2 (17%)
MESENTERY		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
MESENTERIAL LYMPH NODES		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
DUODENUM		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
JEJUNUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
ILEUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
CAECUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
COLON		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
RECTUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
KIDNEYS		(12)			(12)	(12)			(12)
No abnormality detected		6			7	8			10
		(50%)			(58%)	(67%)			(83%)
Hydronephrosis		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Dilatation of the renal pelvis		0			1	2			0
		(0%)			(8%)	(17%)			(0%)
Basophilic tubule(s)		5			5	1			0
		(42%)			(42%)	(8%)			(0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
KIDNEYS		(12)			(12)	(12)			(12)
Tubular dilatation with eosinophilic casts		0 (0%)			1 (8%)	1 (8%)			0 (0%)
Interstitial mononuclear cell infiltration		2 (17%)			0 (0%)	0 (0%)			2 (17%)
Tubular mineralisation		0 (0%)			0 (0%)	2 (17%)			0 (0%)
URINARY BLADDER		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
ADRENALS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
TESTES		(12)			(12)				
No abnormality detected		10 (83%)			9 (75%)				
Degeneration of spermatids/spermatocytes		2 (17%)			1 (8%)				
Depletion of spermatids/spermatocytes		2 (17%)			2 (17%)				
Sertoli-cell vacuolation		1 (8%)			1 (8%)				
Sloughing of germ cells into the lumen		0 (0%)			1 (8%)				
Spermatid retention		1 (8%)			1 (8%)				
Tubular atrophy		1 (8%)			0 (0%)				

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC	Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
TESTES		(12)			(12)				
Tubular dilatation		0 (0%)			1 (8%)				
EPIDIDYMIDES		(12)			(12)				
No abnormality detected		8 (67%)			6 (50%)				
Aspermia		0 (0%)			1 (8%)				
Sloughing of germ cells into the lumen		2 (17%)			0 (0%)				
Interstitial mononuclear cell infiltration		2 (17%)			5 (42%)				
PROSTATE		(12)			(12)				
No abnormality detected		9 (75%)			8 (67%)				
Non-suppurative inflammation		1 (8%)			1 (8%)				
Mononuclear/inflammatory cell infiltration		2 (17%)			3 (25%)				
SEMINAL VESICLES		(12)			(12)				
No abnormality detected		12 (100%)			12 (100%)				
COAGULATING GLANDS		(12)			(12)				
No abnormality detected		12 (100%)			12 (100%)				

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC	Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
OVARIES						(12)			(12)
No abnormality detected						12 (100%)			12 (100%)
UTERUS						(12)			(12)
No abnormality detected						9 (75%)			9 (75%)
Dilatation of the uterine horn(s)						3 (25%)			3 (25%)
VAGINA						(12)			(12)
No abnormality detected						12 (100%)			11 (92%)
Squamous cyst						0 (0%)			1 (8%)
FALLOPIAN TUBES						(12)			(12)
No abnormality detected						12 (100%)			12 (100%)
MAMMARY GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
SKIN		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
STERNUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
FEMUR		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
JOINT (KNEE)		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
SKELETAL MUSCLE		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
SPINAL CORD		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
NERVUS OPTICUS		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
Unilateral section		0			1	0			0
		(0%)			(8%)	(0%)			(0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 20: Histopathological Findings (cont'd)

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FRAUNHOFER INSTITUTE OF
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STUDY : 02G08016

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC	Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
NERVE-PERIPHERAL		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
THYMUS		(12)			(12)	(12)			(12)
No abnormality detected		11 (92%)			10 (83%)	9 (75%)			12 (100%)
Haemorrhage		0 (0%)			2 (17%)	1 (8%)			0 (0%)
Congestion		1 (8%)			0 (0%)	2 (17%)			0 (0%)
SPLEEN		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
HAEMATOP./LYMPHORET.TISSUE		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
BONE MARROW (FEMUR)		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			11 (92%)	12 (100%)			12 (100%)
Fibrosis		0 (0%)			1 (8%)	0 (0%)			0 (0%)
BONE MARROW (STERNUM)		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Listing Complete ***

Table 20a: Histopathological Findings Breeding Females

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Date:12-JAN-2009 Time:14:21

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings - Nasal Cavity - Breeding Females, Groups 1 and 4

LESIONS	TREATMENT	INCIDENCE OF	
		Females	
		Clean Air	300 mg/m ³ THC
	ANIMAL TOTALS	(24)	(24)
NASAL and PARANASAL CAVITIES		(12)	(12)
No abnormality detected		11 (92%)	4** (33%)
Mucosal mononuclear/inflammatory cell infiltration		1 (8%)	7* (58%)
Mucosal mucous (goblet) cell hyperplasia		0 (0%)	1 (8%)
Mucosal psammoma bodies		0 (0%)	1 (8%)
Dilatation of the submucosal glands		0 (0%)	1 (8%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Listing Complete ***

Table 21: Histopathological Findings (with score expansion)

Page: 1

Date:14-JAN-2009 Time:08:47

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC	Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
CEREBRUM		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
CEREBELLUM		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)
PITUITARY		(12)			(12)	(12)			(12)
No abnormality detected		11 (92%)			12 (100%)	12 (100%)			12 (100%)
Craniopharyngeal structures (within pars nervosa) moderate		1 (8%)			0 (0%)	0 (0%)			0 (0%)
Score Expanded Totals		1 (8%)			0 (0%)	0 (0%)			0 (0%)
EYES		(12)			(12)	(12)			(12)
No abnormality detected		3 (25%)			4 (33%)	5 (42%)			2 (17%)
Retrobulbar haemorrhage slight		6 (50%)			6 (50%)	5 (42%)			9 (75%)
moderate		2 (17%)			0 (0%)	1 (8%)			1 (8%)
severe		1 (8%)			2 (17%)	1 (8%)			0 (0%)
Score Expanded Totals		9 (75%)			8 (67%)	7 (58%)			10 (83%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
EYES		(12)			(12)	(12)			(12)
Intra-ocular haemorrhage									
slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Retrobulbar mononuclear cell infiltration									
slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
HARDERIAN GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		8			9	11			9
		(67%)			(75%)	(92%)			(75%)
Haemorrhage									
slight		4			1	0			1
		(33%)			(8%)	(0%)			(8%)
Score Expanded Totals		4			1	0			1
		(33%)			(8%)	(0%)			(8%)
Necrosis									
slight		0			0	1			2
		(0%)			(0%)	(8%)			(17%)
Score Expanded Totals		0			0	1			2
		(0%)			(0%)	(8%)			(17%)
Atrophy									
slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Yellow-brown pigment deposit(s)									
slight		0			2	0			0
		(0%)			(17%)	(0%)			(0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
HARDERIAN GLANDS		(12)			(12)	(12)			(12)
Yellow-brown pigment deposit(s)									
Score Expanded Totals		0 (0%)			2 (17%)	0 (0%)			0 (0%)
LACRIMAL GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		10 (83%)			12 (100%)	11 (92%)			11 (92%)
Harderian gland change(s)									
very slight		1 (8%)			0 (0%)	1 (8%)			0 (0%)
Score Expanded Totals		1 (8%)			0 (0%)	1 (8%)			0 (0%)
Mononuclear cell infiltration									
very slight		1 (8%)			0 (0%)	0 (0%)			0 (0%)
slight		0 (0%)			0 (0%)	0 (0%)			1 (8%)
Score Expanded Totals		1 (8%)			0 (0%)	0 (0%)			1 (8%)
NASAL and PARANASAL CAVITIES		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		3 (25%)	5 (42%)	4 (33%)	6 (50%)	3 (25%)	8 (67%)	6 (50%)	11** (92%)
Epithelial erosion(s)									
slight		1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mucosal inflammatory cell infiltration									
very slight		2 (17%)	4 (33%)	3 (25%)	2 (17%)	5 (42%)	1 (8%)	4 (33%)	0* (0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
NASAL and PARANASAL CAVITIES		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Mucosal inflammatory cell infiltration									
slight		7	3	4	3	3	3	1	0
		(58%)	(25%)	(33%)	(25%)	(25%)	(25%)	(8%)	(0%)
Score Expanded Totals		9	7	7	5	8	4	5	0**
		(75%)	(58%)	(58%)	(42%)	(67%)	(33%)	(42%)	(0%)
Mucous (goblet) cell hyperplasia									
very slight		2	2	3	1	3	3	1	1
		(17%)	(17%)	(25%)	(8%)	(25%)	(25%)	(8%)	(8%)
slight		1	1	0	3	1	0	0	0
		(8%)	(8%)	(0%)	(25%)	(8%)	(0%)	(0%)	(0%)
Score Expanded Totals		3	3	3	4	4	3	1	1
		(25%)	(25%)	(25%)	(33%)	(33%)	(25%)	(8%)	(8%)
Mucosal psammoma bodies									
very slight		1	2	1	0	1	0	1	0
		(8%)	(17%)	(8%)	(0%)	(8%)	(0%)	(8%)	(0%)
slight		0	0	0	0	1	0	0	0
		(0%)	(0%)	(0%)	(0%)	(8%)	(0%)	(0%)	(0%)
Score Expanded Totals		1	2	1	0	2	0	1	0
		(8%)	(17%)	(8%)	(0%)	(17%)	(0%)	(8%)	(0%)
LARYNX		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		10	10	10	11	8	8	10	10
		(83%)	(83%)	(83%)	(92%)	(67%)	(67%)	(83%)	(83%)
Submucosal mononuclear/inflammatory cell infiltration									
very slight		1	2	2	1	0	2	1	1
		(8%)	(17%)	(17%)	(8%)	(0%)	(17%)	(8%)	(8%)
slight		0	0	0	0	1	0	0	0
		(0%)	(0%)	(0%)	(0%)	(8%)	(0%)	(0%)	(0%)
Score Expanded Totals		1	2	2	1	1	2	1	1
		(8%)	(17%)	(17%)	(8%)	(8%)	(17%)	(8%)	(8%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LARYNX		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Submucosal foreign-body granuloma									
very slight		0	0	0	0	1	1	0	1
		(0%)	(0%)	(0%)	(0%)	(8%)	(8%)	(0%)	(8%)
slight		1	0	0	0	2	1	0	0
		(8%)	(0%)	(0%)	(0%)	(17%)	(8%)	(0%)	(0%)
Score Expanded Totals		1	0	0	0	3	2	0	1
		(8%)	(0%)	(0%)	(0%)	(25%)	(17%)	(0%)	(8%)
Dilatation of the submucosal glands									
slight		0	0	0	0	0	0	1	0
		(0%)	(0%)	(0%)	(0%)	(0%)	(0%)	(8%)	(0%)
Score Expanded Totals		0	0	0	0	0	0	1	0
		(0%)	(0%)	(0%)	(0%)	(0%)	(0%)	(8%)	(0%)
TRACHEA		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		12	12	11	12	12	12	12	12
		(100%)	(100%)	(92%)	(100%)	(100%)	(100%)	(100%)	(100%)
Submucosal inflammatory cell infiltration									
very slight		0	0	1	0	0	0	0	0
		(0%)	(0%)	(8%)	(0%)	(0%)	(0%)	(0%)	(0%)
Score Expanded Totals		0	0	1	0	0	0	0	0
		(0%)	(0%)	(8%)	(0%)	(0%)	(0%)	(0%)	(0%)
LUNGS		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		7	7	8	0**	11	10	10	0***
		(58%)	(58%)	(67%)	(0%)	(92%)	(83%)	(83%)	(0%)
Accumulation of alveolar macrophages (alveolar									
histiocytosis)									
very slight		1	3	1	3	1	0	2	6
		(8%)	(25%)	(8%)	(25%)	(8%)	(0%)	(17%)	(50%)
slight		1	1	1	9**	0	0	0	6*
		(8%)	(8%)	(8%)	(75%)	(0%)	(0%)	(0%)	(50%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LUNGS		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Accumulation of alveolar macrophages (alveolar histiocytosis)									
Score Expanded Totals		2 (17%)	4 (33%)	2 (17%)	12*** (100%)	1 (8%)	0 (0%)	2 (17%)	12*** (100%)
Bronchiolo-alveolar hyperplasia (bronchiolar type)									
very slight		0 (0%)	0 (0%)	0 (0%)	3 (25%)	0 (0%)	0 (0%)	0 (0%)	6* (50%)
slight		0 (0%)	0 (0%)	0 (0%)	9*** (75%)	0 (0%)	0 (0%)	0 (0%)	6* (50%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	12*** (100%)	0 (0%)	0 (0%)	0 (0%)	12*** (100%)
Interstitial mononuclear/inflammatory cell infiltration									
very slight		1 (8%)	0 (0%)	2 (17%)	5 (42%)	0 (0%)	2 (17%)	0 (0%)	5* (42%)
slight		0 (0%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	1 (8%)
Score Expanded Totals		1 (8%)	2 (17%)	2 (17%)	5 (42%)	0 (0%)	2 (17%)	1 (8%)	6* (50%)
Alveolar inflammatory cell infiltration									
very slight		0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bronchial mucous (goblet) cell hyperplasia									
very slight		0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	3 (25%)
Foreign-body granuloma									
very slight		1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LUNGS		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Osseous metaplasia very slight		1 (8%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (8%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alveolar haemorrhage very slight		2 (17%)	2 (17%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Score Expanded Totals		2 (17%)	2 (17%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Alveolar dilatation moderate		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Passive congestion slight		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)
Congestion slight		0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LUNG ASSOCIATED LYMPH NODES		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		12 (100%)	12 (100%)	11 (92%)	12 (100%)	12 (100%)	10 (83%)	12 (100%)	12 (100%)
Lymphoid hyperplasia slight		0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	2 (17%)	0 (0%)	0 (0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LUNG ASSOCIATED LYMPH NODES		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
Lymphoid hyperplasia									
Score Expanded Totals		0	0	1	0	0	2	0	0
		(0%)	(0%)	(8%)	(0%)	(0%)	(17%)	(0%)	(0%)
THYROID		(12)			(12)	(12)			(12)
No abnormality detected		11			10	10			10
		(92%)			(83%)	(83%)			(83%)
Mononuclear cell infiltration									
very slight		1			1	0			0
		(8%)			(8%)	(0%)			(0%)
Score Expanded Totals		1			1	0			0
		(8%)			(8%)	(0%)			(0%)
Ectopic thymic tissue		1			1	2			2
		(8%)			(8%)	(17%)			(17%)
PARATHYROID		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
Unilateral section		1			3	4			2
		(8%)			(25%)	(33%)			(17%)
HEART		(12)			(12)	(12)			(12)
No abnormality detected		4			5	9			8
		(33%)			(42%)	(75%)			(67%)
Myocardial mononuclear cell infiltration									
very slight		7			7	3			3
		(58%)			(58%)	(25%)			(25%)
slight		1			0	0			1
		(8%)			(0%)	(0%)			(8%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
HEART		(12)			(12)	(12)			(12)
Myocardial mononuclear cell infiltration									
Score Expanded Totals		8			7	3			4
		(67%)			(58%)	(25%)			(33%)
Myocardial degeneration									
very slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
AORTA		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
SALIVARY GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		12			12	11			12
		(100%)			(100%)	(92%)			(100%)
Mononuclear cell infiltration									
very slight		0			0	1			0
		(0%)			(0%)	(8%)			(0%)
Score Expanded Totals		0			0	1			0
		(0%)			(0%)	(8%)			(0%)
MANDIBULAR LYMPH NODES		(12)			(12)	(12)			(12)
No abnormality detected		10			10	10			12
		(83%)			(83%)	(83%)			(100%)
Lymphoid hyperplasia									
slight		1			1	2			0
		(8%)			(8%)	(17%)			(0%)
moderate		1			0	0			0
		(8%)			(0%)	(0%)			(0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
MANDIBULAR LYMPH NODES		(12)			(12)	(12)			(12)
Lymphoid hyperplasia									
Score Expanded Totals		2 (17%)			1 (8%)	2 (17%)			0 (0%)
Congestion									
slight		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Score Expanded Totals		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Unilateral section		3 (25%)			1 (8%)	0 (0%)			3 (25%)
TONGUE		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	11 (92%)			12 (100%)
Intra-muscular foreign-body granuloma									
slight		0 (0%)			0 (0%)	1 (8%)			0 (0%)
Score Expanded Totals		0 (0%)			0 (0%)	1 (8%)			0 (0%)
PHARYNX (LARYNGO-)		(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)
No abnormality detected		12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)	12 (100%)
ESOPHAGUS		(12)			(12)	(12)			(12)
No abnormality detected		12 (100%)			12 (100%)	12 (100%)			12 (100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
FORESTOMACH		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
GLANDULAR STOMACH		(12)			(12)	(12)			(12)
No abnormality detected		10			11	11			11
		(83%)			(92%)	(92%)			(92%)
Mucosal inflammatory cell infiltration very slight		2			1	1			1
		(17%)			(8%)	(8%)			(8%)
Score Expanded Totals		2			1	1			1
		(17%)			(8%)	(8%)			(8%)
LIVER		(12)			(12)	(12)			(12)
No abnormality detected		1			3	2			1
		(8%)			(25%)	(17%)			(8%)
Hepatocellular necrosis slight		0			1	2			2
		(0%)			(8%)	(17%)			(17%)
Score Expanded Totals		0			1	2			2
		(0%)			(8%)	(17%)			(17%)
Microgranuloma(s) very slight		6			5	7			8
		(50%)			(42%)	(58%)			(67%)
slight		5			4	2			3
		(42%)			(33%)	(17%)			(25%)
Score Expanded Totals		11			9	9			11
		(92%)			(75%)	(75%)			(92%)
Perivascular mononuclear cell infiltration very slight		2			1	1			1
		(17%)			(8%)	(8%)			(8%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
LIVER		(12)			(12)	(12)			(12)
Perivascular mononuclear cell infiltration									
Score Expanded Totals		2			1	1			1
		(17%)			(8%)	(8%)			(8%)
PANCREAS		(12)			(12)	(12)			(12)
No abnormality detected		12			8	11			10
		(100%)			(67%)	(92%)			(83%)
Islet-cell hyperplasia									
slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Acinar-cell atrophy									
slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Mononuclear cell infiltration									
very slight		0			1	1			1
		(0%)			(8%)	(8%)			(8%)
slight		0			1	0			1
		(0%)			(8%)	(0%)			(8%)
Score Expanded Totals		0			2	1			2
		(0%)			(17%)	(8%)			(17%)
MESENTERY		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)

Significance of difference in a pairwise Fisher's test between control and 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

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Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
MESENTERIAL LYMPH NODES		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
DUODENUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
JEJUNUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
ILEUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
CAECUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
COLON		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
RECTUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

		INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
LESIONS	TREATMENT	Clean	30	100	300	Clean	30	100	300
		Air	mg/m3 THC	mg/m3 THC	mg/m3 THC	Air	mg/m3 THC	mg/m3 THC	mg/m3 THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
KIDNEYS		(12)			(12)	(12)			(12)
No abnormality detected		6 (50%)			7 (58%)	8 (67%)			10 (83%)
Hydronephrosis slight		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Score Expanded Totals		0 (0%)			1 (8%)	0 (0%)			0 (0%)
Dilatation of the renal pelvis slight		0 (0%)			1 (8%)	2 (17%)			0 (0%)
Score Expanded Totals		0 (0%)			1 (8%)	2 (17%)			0 (0%)
Basophilic tubule(s) very slight		5 (42%)			5 (42%)	1 (8%)			0 (0%)
Score Expanded Totals		5 (42%)			5 (42%)	1 (8%)			0 (0%)
Tubular dilatation with eosinophilic casts very slight		0 (0%)			1 (8%)	1 (8%)			0 (0%)
Score Expanded Totals		0 (0%)			1 (8%)	1 (8%)			0 (0%)
Interstitial mononuclear cell infiltration very slight		2 (17%)			0 (0%)	0 (0%)			2 (17%)
Score Expanded Totals		2 (17%)			0 (0%)	0 (0%)			2 (17%)
Tubular mineralisation very slight		0 (0%)			0 (0%)	2 (17%)			0 (0%)
Score Expanded Totals		0 (0%)			0 (0%)	2 (17%)			0 (0%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
URINARY BLADDER		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
ADRENALS		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
TESTES		(12)			(12)				
No abnormality detected		10			9				
		(83%)			(75%)				
Degeneration of spermatids/spermatocytes									
slight		2			0				
		(17%)			(0%)				
severe		0			1				
		(0%)			(8%)				
Score Expanded Totals		2			1				
		(17%)			(8%)				
Depletion of spermatids/spermatocytes									
slight		2			1				
		(17%)			(8%)				
severe		0			1				
		(0%)			(8%)				
Score Expanded Totals		2			2				
		(17%)			(17%)				
Sertoli-cell vacuolation									
slight		1			0				
		(8%)			(0%)				
moderate		0			1				
		(0%)			(8%)				
Score Expanded Totals		1			1				
		(8%)			(8%)				

Significance of difference in a pairwise Fisher's test between control and 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

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Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
TESTES		(12)			(12)				
Sloughing of germ cells into the lumen									
very slight		0			1				
		(0%)			(8%)				
Score Expanded Totals		0			1				
		(0%)			(8%)				
Spermatid retention									
very slight		0			1				
		(0%)			(8%)				
slight		1			0				
		(8%)			(0%)				
Score Expanded Totals		1			1				
		(8%)			(8%)				
Tubular atrophy									
slight		1			0				
		(8%)			(0%)				
Score Expanded Totals		1			0				
		(8%)			(0%)				
Tubular dilatation									
slight		0			1				
		(0%)			(8%)				
Score Expanded Totals		0			1				
		(0%)			(8%)				
EPIDIDYMITIDES		(12)			(12)				
No abnormality detected		8			6				
		(67%)			(50%)				
Aspermia		0			1				
		(0%)			(8%)				
Sloughing of germ cells into the lumen									
very slight		2			0				
		(17%)			(0%)				

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC	Clean Air	30 mg/m3 THC	100 mg/m3 THC	300 mg/m3 THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
EPIDIDYMITIS		(12)			(12)				
Sloughing of germ cells into the lumen									
Score Expanded Totals		2 (17%)			0 (0%)				
Interstitial mononuclear cell infiltration very slight		2 (17%)			5 (42%)				
Score Expanded Totals		2 (17%)			5 (42%)				
PROSTATE		(12)			(12)				
No abnormality detected		9 (75%)			8 (67%)				
Non-suppurative inflammation moderate		1 (8%)			1 (8%)				
Score Expanded Totals		1 (8%)			1 (8%)				
Mononuclear/inflammatory cell infiltration very slight		1 (8%)			1 (8%)				
slight		1 (8%)			2 (17%)				
Score Expanded Totals		2 (17%)			3 (25%)				
SEMINAL VESICLES		(12)			(12)				
No abnormality detected		12 (100%)			12 (100%)				

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC	Clean Air	30 mg/m ³ THC	100 mg/m ³ THC	300 mg/m ³ THC
	ANIMAL TOTALS	(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
COAGULATING GLANDS		(12)			(12)				
No abnormality detected		12 (100%)			12 (100%)				
OVARIES						(12)			(12)
No abnormality detected						12 (100%)			12 (100%)
UTERUS						(12)			(12)
No abnormality detected						9 (75%)			9 (75%)
Dilatation of the uterine horn(s) slight						2 (17%)			1 (8%)
moderate						1 (8%)			2 (17%)
Score Expanded Totals						3 (25%)			3 (25%)
VAGINA						(12)			(12)
No abnormality detected						12 (100%)			11 (92%)
Squamous cyst						0 (0%)			1 (8%)
FALLOPIAN TUBES						(12)			(12)
No abnormality detected						12 (100%)			12 (100%)

Significance of difference in a pairwise Fisher's test between control and 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

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Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
MAMMARY GLANDS		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
SKIN		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
STERNUM		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
FEMUR		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
JOINT (KNEE)		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
SKELETAL MUSCLE		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
SPINAL CORD		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)

Significance of difference in a pairwise Fisher's test between control and 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

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Table 21: Histopathological Findings (with score expansion; cont'd)

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Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
NERVUS OPTICUS		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
Unilateral section		(100%)			(100%)	(100%)			(100%)
		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
NERVE-PERIPHERAL		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
THYMUS		(12)			(12)	(12)			(12)
No abnormality detected		11			10	9			12
		(92%)			(83%)	(75%)			(100%)
Haemorrhage									
very slight		0			2	0			0
		(0%)			(17%)	(0%)			(0%)
slight		0			0	1			0
		(0%)			(0%)	(8%)			(0%)
Score Expanded Totals		0			2	1			0
		(0%)			(17%)	(8%)			(0%)
Congestion									
very slight		1			0	0			0
		(8%)			(0%)	(0%)			(0%)
slight		0			0	2			0
		(0%)			(0%)	(17%)			(0%)
Score Expanded Totals		1			0	2			0
		(8%)			(0%)	(17%)			(0%)
SPLEEN		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Continued

Table 21: Histopathological Findings (with score expansion; cont'd)

Page: 21

Date:14-JAN-2009 Time:08:47

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean	30	100	300	Clean	30	100	300
		Air	mg/m3	mg/m3	mg/m3	Air	mg/m3	mg/m3	mg/m3
		THC	THC	THC	THC	THC	THC	THC	THC
ANIMAL TOTALS		(12)	(12)	(12)	(12)	(24)	(24)	(24)	(24)
HAEMATOP./LYMPHORET.TISSUE		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)
BONE MARROW (FEMUR)		(12)			(12)	(12)			(12)
No abnormality detected		12			11	12			12
		(100%)			(92%)	(100%)			(100%)
Fibrosis									
slight		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
Score Expanded Totals		0			1	0			0
		(0%)			(8%)	(0%)			(0%)
BONE MARROW (STERNUM)		(12)			(12)	(12)			(12)
No abnormality detected		12			12	12			12
		(100%)			(100%)	(100%)			(100%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Listing Complete ***

Table 21a: Histopathological Findings Breeding Females (with score expansion)

Page: 1

Date:12-JAN-2009 Time:14:19

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02G08016

Summary of Histopathological Findings (with score expansion) - Nasal Cavity - Breeding Females, Groups 1 and 4

LESIONS	TREATMENT	INCIDENCE OF	
		Females	
		Clean Air	300 mg/m3 THC
	ANIMAL TOTALS	(24)	(24)
NASAL and PARANASAL CAVITIES		(12)	(12)
No abnormality detected		11 (92%)	4** (33%)
Mucosal mononuclear/inflammatory cell infiltration very slight		1 (8%)	5 (42%)
slight		0 (0%)	2 (17%)
Score Expanded Totals		1 (8%)	7* (58%)
Mucosal mucous (goblet) cell hyperplasia very slight		0 (0%)	1 (8%)
Score Expanded Totals		0 (0%)	1 (8%)
Mucosal psammoma bodies very slight		0 (0%)	1 (8%)
Score Expanded Totals		0 (0%)	1 (8%)
Dilatation of the submucosal glands slight		0 (0%)	1 (8%)
Score Expanded Totals		0 (0%)	1 (8%)

Significance of difference in a pairwise Fisher's test between control and 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

*** Listing Complete ***

Table 22: Sperm Evaluation

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF SPERM EVALUATIONS

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
SPERM COUNT (millions)	MEAN	38.125 d	32.250	27.125	24.542
	S.D.	24.142	18.625	9.7843	10.343
	N	12	12	12	12
	p value	0.221			
PERCENT ABNORMAL SPERM	MEAN	4.0 d	2.8	3.5	2.8
	S.D.	1.83	0.81	2.37	0.81
	N	12	12	12	12
	p value	0.211			
PERCENT MOTILITY	MEAN	49 d	53	58	51
	S.D.	19.6	18.9	21.2	19.2
	N	12	12	12	12
	p value	0.703			

Statistical key: d=Dunnett test

Table 23: Cohabitation Data

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF COHABITATION DATA

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
Females paired with males	N	12	12	12	12
Total number mated	N	12 f	11	12	12
female mating index	%	100.0	91.7	100.0	100.0
	p value		1.000	1.000	1.000
pregnant	N	11 f	9	11	11
female fertility index	%	91.7	81.8	91.7	91.7
	p value		1.000	1.000	1.000
Females with defined day 0 of Gestation	N	10	10	11	10
No. of days until Mating	MEAN	2.8 d	2.5	2.5	3.6
	S.D.	1.69	1.90	1.29	1.51
	p value	0.394			
Day 1 to 4	N	8 f	9	10	7
	%	80.0	90.0	90.9	70.0
	p value		1.000	1.000	1.000
Day 5 to 8	N	2 f	1	1	3
	%	20.0	10.0	9.1	30.0
	p value		1.000	1.000	1.000
Day 9 to 14	N	0 f	0	0	0
	%	0.0	0.0	0.0	0.0
	p value				

Statistical key: d=Dunnett test f=Fishers exact test

Table 24: Gestation Body Weights

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF GESTATION BODY WEIGHTS (GRAMS)

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m ³	100 mg/m ³	300 mg/m ³
DAY 0	MEAN	187 d	194	198**	197**
	S.D.	7.6	5.3	7.6	3.6
	N	9	8	10	9
	p-value	0.003	0.101	0.002	0.006
DAY 7	MEAN	208 d	212	216	213
	S.D.	8.7	8.1	9.3	6.3
	N	9	8	10	9
	p-value	0.174			
DAY 14	MEAN	230 d	233	237	232
	S.D.	10.5	10.6	9.4	4.6
	N	9	8	10	9
	p-value	0.464			
DAY 21	MEAN	287 d	291	294	284
	S.D.	15.8	15.5	10.3	18.3
	N	9	8	10	8
	p-value	0.468			

Statistical key: d=Dunnett test ** = p<0.01

Table 25: Gestation Body Weight Gain

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF GESTATION BODY WEIGHT GAIN (GRAMS)

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m ³	100 mg/m ³	300 mg/m ³
DAYS 0 TO 7	MEAN	21 d	18	18	16
	S.D.	5.0	5.1	4.1	3.8
	N	9	8	10	9
	p value	0.196			
DAYS 7 TO 14	MEAN	23 d	21	21	19
	S.D.	3.5	4.4	4.3	3.9
	N	9	8	10	9
	p value	0.318			
DAYS 14 TO 21	MEAN	56 d	58	57	51
	S.D.	7.4	9.7	4.9	14.0
	N	9	8	10	8
	p value	0.449			
DAYS 0 TO 21	MEAN	99 d	98	96	87
	S.D.	9.1	13.7	7.0	16.6
	N	9	8	10	8
	p value	0.149			

Statistical key: d=Dunnett test

Table 26: Gestation Food Consumption

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF GESTATION FOOD CONSUMPTION (GRAMS/ANIMAL/DAY)

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
DAYS 0 TO 7	MEAN	15 d	15	15	14*
	S.D.	1.0	1.2	0.6	0.9
	N	9	8	10	9
	p value	0.032	0.999	0.982	0.029
DAYS 7 TO 14	MEAN	17 d	17	17	16*
	S.D.	1.1	1.2	0.6	0.9
	N	9	8	10	9
	p value	0.026	1.000	0.881	0.021
DAYS 14 TO 21	MEAN	20 d	20	20	19
	S.D.	1.6	1.7	0.6	1.3
	N	9	8	10	9
	p value	0.197			
DAYS 0 TO 21	MEAN	18 d	17	17	16*
	S.D.	1.2	1.2	0.5	1.0
	N	9	8	10	9
	p value	0.043	0.946	0.816	0.024

Statistical key: d=Dunnett test * = p<0.05

Table 27: Gestation Water Consumption

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

		MEAN MATERNAL FLUID CONSUMPTION DURING GESTATION		SUMMARY	
		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m ³	100 mg/m ³	300 mg/m ³
MATERNAL WATER CONSUMPTION	GRAMS/ANIMAL/DAY				
DAYS 0 TO 7	MEAN	24 d	24	28	26
	S.D.	1.7	2.5	7.2	4.2
	N	9	8	10	9
	p value	0.163			
DAYS 7 TO 14	MEAN	27 d	27	27	29
	S.D.	3.0	2.4	11.6	3.3
	N	9	8	10	9
	p value	0.927			
DAYS 14 TO 21	MEAN	34 d	33	37	35
	S.D.	4.4	3.0	7.9	2.7
	N	9	8	10	9
	p value	0.325			

Statistical key: d=Dunnett test

Table 28: Maternal Postpartum Body Weights

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.					
SUMMARY OF MATERNAL POSTPARTUM BODY WEIGHTS (GRAMS)					
		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
DAY 0	MEAN	214 d	213	223	217
	S.D.	12.1	11.3	12.7	11.0
	N	11	9	11	10
	p value	0.194			
DAY 4	MEAN	232 d	235	240	233
	S.D.	14.1	12.0	13.0	5.7
	N	10	9	11	10
	p value	0.429			
Statistical key:		d=Dunnett test			

Table 29: Maternal Postpartum Body Weight Gain

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.					
SUMMARY OF MATERNAL POSTPARTUM BODY WEIGHT GAIN (GRAMS)					
		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
DAYS 0 TO 4	MEAN	18 d	21	17	16
	S.D.	9.2	7.3	9.1	7.2
	N	10	9	11	10
	p value	0.480			
Statistical key: d=Dunnett test					

Table 30: Maternal Postpartum Food Consumption

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.					
SUMMARY OF MATERNAL POSTPARTUM FOOD CONSUMPTION (GRAMS/ANIMAL/DAY)					
		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
DAYS 0 TO 4	MEAN	25 d	25	26	24
	S.D.	3.8	2.8	2.7	2.6
	N	10	9	11	10
	p value	0.809			
Statistical key: d=Dunnett test					

Table 31: Maternal Postpartum Water Consumption

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.					
MEAN MATERNAL FLUID CONSUMPTION DURING LACTATION				SUMMARY	
		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
MATERNAL WATER CONSUMPTION		GRAMS/ANIMAL/DAY			
DAYS 0 TO 4		MEAN	38.4 d	38.9	41.2
		S.D.	5.07	3.07	8.74
		N	10	9	11
		p value	0.698		
Statistical key: d=Dunnett test					

Table 32: Summary of Delivery and Litter Data

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF DELIVERY AND LITTER DATA

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
Females on Study	N	12	12	12	12
Females Mated	N	12 f	11	12	12
Mating Index	%	100.0	91.7	100.0	100.0
	p value		1.000	1.000	1.000
Females Pregnant	N	11 f	9	11	11
Female Fertility Index	%	91.7	81.8	91.7	91.7
	p value		1.000	1.000	1.000
Females with Liveborn	N	11 f	9	11	10 §
Gestation Index	%	100.0	100.0	100.0	90.9
	p value		1.000	1.000	1.000
Females Completing Delivery	N	11 f	9	11	10
	%	91.7	75.0	91.7	83.3
	p value		1.000	1.000	1.000
with Stillborn Pups	N	1 f	1	0	0
	%	9.1	11.1	0.0	0.0
	p value		1.000	1.000	1.000
with all Stillborn	N	0 f	0	0	0
	%	0.0	0.0	0.0	0.0
	p value				
Litters with Liveborn, but no Pups Alive					
day 4	N	1 f	0	0	0
	%	9.1	0.0	0.0	0.0
	p value		1.000	1.000	1.000
Duration of Gestation	MEAN	22.6 d	22.1	22.1	22.4
	S.D.	0.53	0.35	0.32	0.73
	N	9	8	10	9
	p value	0.159			

Statistical key: d=Dunnett test f=Fishers exact test

§ Animal no. 4207 was declared as non pregnant and was therefore killed at the last day of exposure, but was found pregnant with 12 implantation sites (see 16.4.1)

Table 32: Summary of Delivery and Litter Data (cont'd)

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF DELIVERY AND LITTER DATA

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
Litters with Liveborn Pups	N	11	9	11	10
Pups Delivered	TOTAL	108	95	113	90
	MEAN	9.8 d	10.6	10.3	9.0
	S.D.	1.33	1.13	1.49	2.21
	p value	0.168			
Liveborn Live Birth Index	TOTAL	107 f	93	113	90
	%	99.1	97.9	100.0	100.0
	p value		1.000	1.000	1.000
Stillborn	TOTAL	1 f	2	0	0
	%	0.9	2.1	0.0	0.0
	p value		1.000	1.000	1.000
Pups Dying, Missing, and/or Cannibalized day 0	TOTAL	7 f	0*	0*	0*
	%	6.5	0.0	0.0	0.0
	p value		0.047	0.017	0.049
days 1-4	TOTAL	1 f	0	3	0
	%	0.9	0.0	2.7	0.0
	p value		1.000	1.000	1.000
Pups Surviving 4 days Viability Index	TOTAL	99 f	93*	110	90*
	%	92.5	100.0	97.3	100.0
	p value		0.023	0.381	0.025

Statistical key: d=Dunnett test f=Fishers exact test * = p<0.05

Table 32: Summary of Delivery and Litter Data (cont'd)

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF DELIVERY AND LITTER DATA

		Clean	Low	Medium	High
		Air	Dose	Dose	Dose
		Control	30 mg/m3	100 mg/m3	300 mg/m3
Implantation Sites per Litter	TOTAL	118	100	126	98
	MEAN	10.7 d	11.1	11.5	9.8
	S.D.	1.01	1.54	1.37	1.62
	p value	0.060			
Corpora Lutea	TOTAL	129	108	127	109
	MEAN	11.7 d	12.0	11.5	10.9
	S.D.	1.62	1.00	1.44	1.20
	p value	0.337			
Live Pups/Litter day 0	MEAN	9.7 d	10.3	10.3	9.0
	S.D.	1.49	1.22	1.49	2.21
	N	11	9	11	10
	p value	0.256			
day 1	MEAN	9.1 d	10.3	10.2	9.0
	S.D.	3.24	1.22	1.47	2.21
	N	11	9	11	10
	p value	0.399			
day 2	MEAN	9.0 d	10.3	10.0	9.0
	S.D.	3.26	1.22	1.48	2.21
	N	11	9	11	10
	p value	0.429			
day 3	MEAN	9.0 d	10.3	10.0	9.0
	S.D.	3.26	1.22	1.48	2.21
	N	11	9	11	10
	p value	0.429			
day 4	MEAN	9.0 d	10.3	10.0	9.0
	S.D.	3.26	1.22	1.48	2.21
	N	11	9	11	10
	p value	0.429			
Sex Ratio day 0	Male Pups:Total Pups				
	TOTAL	59 f	52	49	47
	%	55.1	55.9	43.4	52.2
	p value		1.000	0.316	1.000
day 4	N	54 f	52	46	47
	%	54.5	55.9	41.8	52.2
	p value		1.000	0.218	1.000

Statistical key: d=Dunnett test f=Fishers exact test

Table 32: Summary of Delivery and Litter Data (cont'd)

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SUMMARY OF DELIVERY AND LITTER DATA

		Clean	Low	Medium	High	
		Air	Dose	Dose	Dose	
		Control	30 mg/m3	100 mg/m3	300 mg/m3	
Pup Weight/Litter (grams)	day 0	MEAN	5.8 d	5.8	5.6	5.7
		S.D.	0.67	0.45	0.37	0.52
		N	11	9	11	10
		p value	0.767			
day 4		MEAN	9.8 d	9.5	9.3	9.9
		S.D.	1.21	0.80	0.77	0.85
		N	10	9	11	10
		p value	0.387			

Statistical key: d=Dunnett test

**Table 33: Red Blood Cell Formation and Micronucleus Induction, Bone Marrow,
28 Days of Exposure to Roofing Asphalt Fume Condensate (RAFC)**

Group	Treatment group	Concentration	PCE per 500 RBC	PCE/NCE	MN per 2000 PCE	% MN in PCE
N			5 ♂ + 5 ♀	5 ♂ + 5 ♀	5 ♂ + 5 ♀	5 ♂ + 5 ♀
1	Negative control, clean air	-	♂ 250 ♀ 247	♂ 1.00 ♀ 0.98	♂ 1.0 ♀ 1.0	♂ 0.05 ♀ 0.05
2	Test item, RAFC	30 mg/m ³ THC	♂ 252 ♀ 247	♂ 1.02 ♀ 0.98	♂ 0.6 ♀ 1.8	♂ 0.03 ♀ 0.09
3	Test item, RAFC	100 mg/m ³ THC	♂ 250 ♀ 247	♂ 1.00 ♀ 0.98	♂ 1.4 ♀ 0.6	♂ 0.07 ♀ 0.03
4	Test item, RAFC	300 mg/m ³ THC	♂ 253 ♀ 252	♂ 1.03 ♀ 1.01	♂ 1.4 ♀ 1.4	♂ 0.07 ♀ 0.07
5	Positive control, CP	60 mg/kg b.w., p.o.	♂ 248 ♀ 251	♂ 0.99 ♀ 1.01*	♂ 15.0** ♀ 12.8**	♂ 0.75 ♀ 0.64

PCE:

polychromatic erythrocyte

RBC: red blood cell

NCE: normochromatic erythrocyte

MN: micronuclei

* : $P < 0.05$ Mann-Whitney U-Test** : $P < 0.01$ Mann-Whitney U-Test

Appendix A

Number Size Distributions (measured not under GLP - conditions)

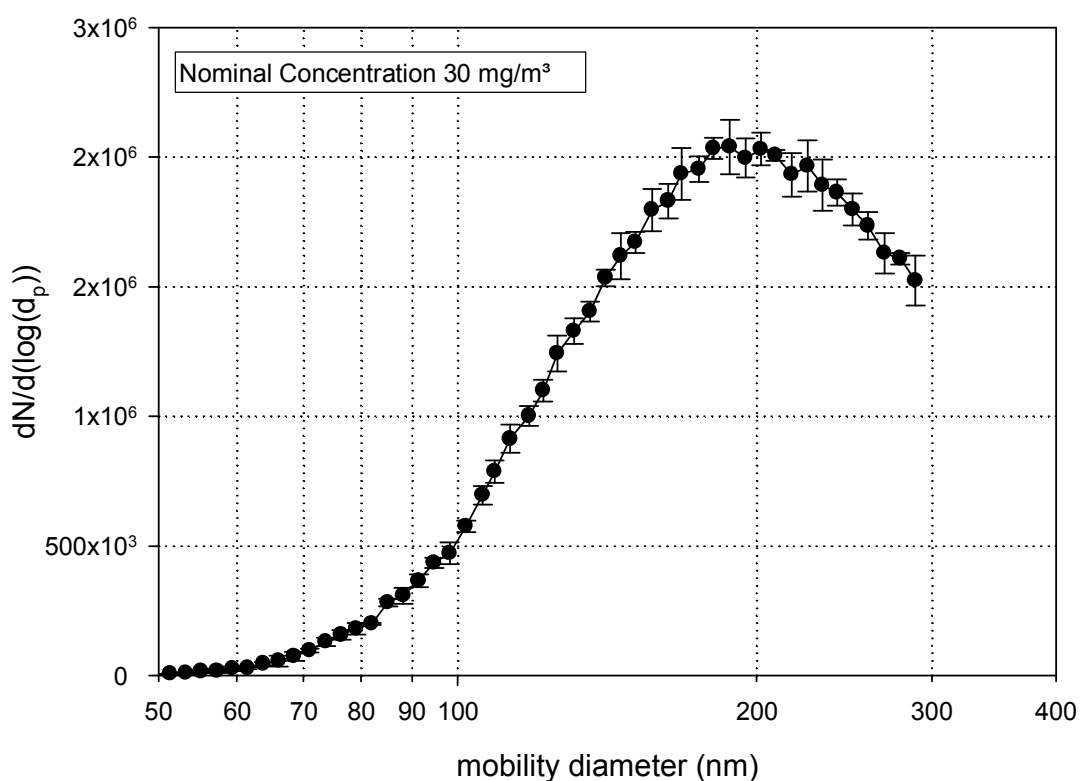


Figure 1 : Number Size Distribution Group 2 (30 mg/m³ THC)

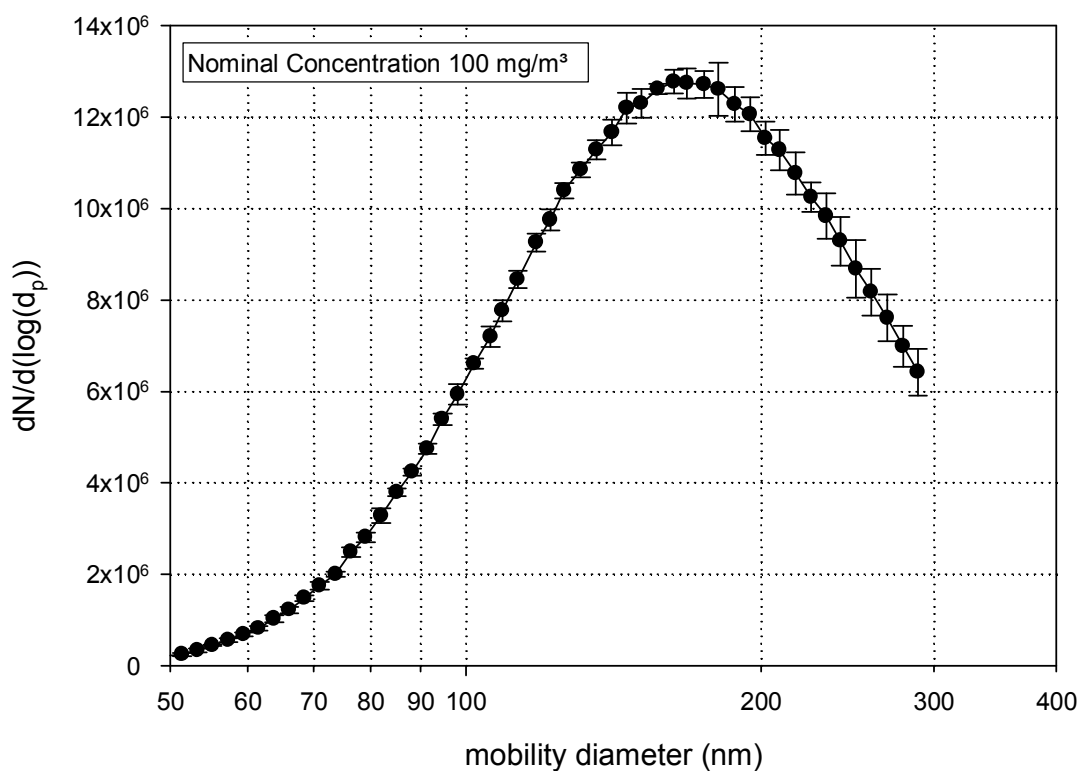
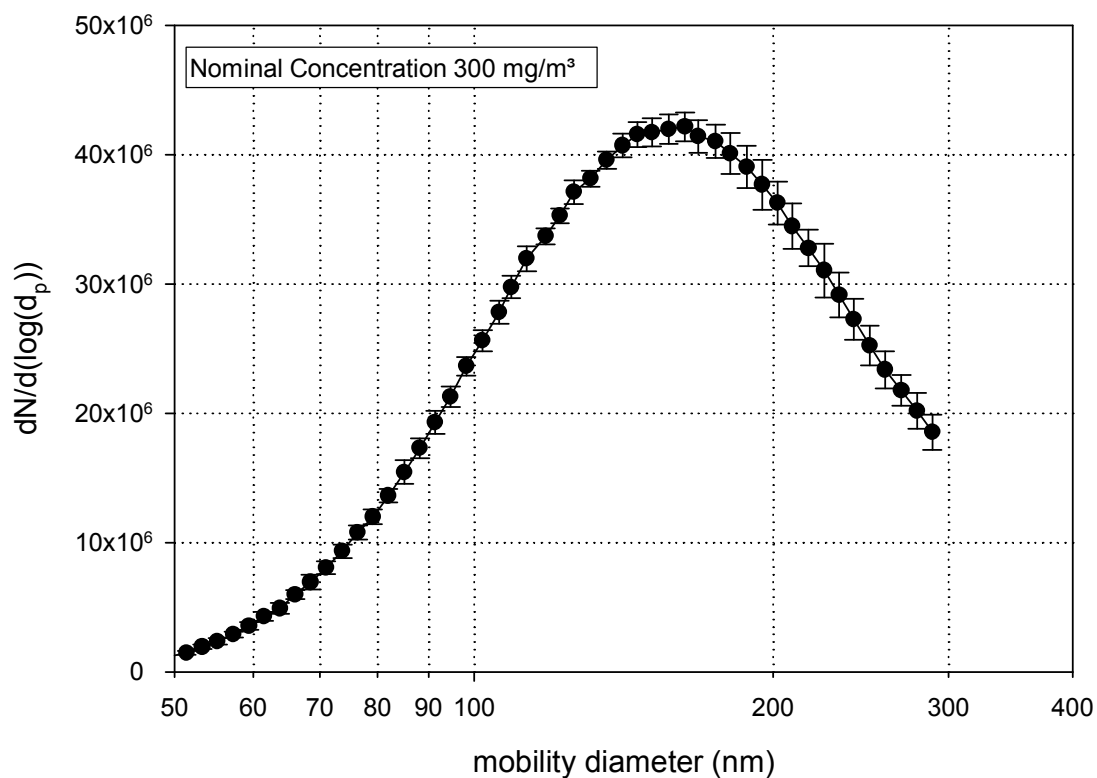


Figure 2 : Number Size Distribution Group 3 (100 mg/m³ THC)**Figure 3 : Number Size Distribution Group 4 (300 mg/m³ THC)**

Appendix B

Clinical Observations Individual Data

RTA001 01/02

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date																													
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4		
1	m	1101	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		1102	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		1103	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		1104	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		1105	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		1106	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		1107	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		1108	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		1109	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		1110	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		1111	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		1112	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
1	m	1101	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1102	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1103	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1104	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1105	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1106	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1107	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1108	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1109	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1110	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1111	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1112	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date																												
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	
2	m	2101	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		2102	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		2103	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		2104	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		2105	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		2106	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		2107	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		2108	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		2109	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		2110	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		2111	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		2112	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date		
Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
2	m	2101	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2102	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2103	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2104	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2105	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2106	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2107	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2108	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2109	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2110	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2111	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2112	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date																														
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4			
3	m	3101	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3102	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3103	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3104	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	
		3105	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	
		3106	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	
		3107	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3108	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3109	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3110	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3111	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		3112	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
3	m	3101	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3102	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3103	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3104	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3105	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3106	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3107	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3108	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3109	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3110	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3111	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3112	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date																												
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	
4	m	4101	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4102	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4103	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4104	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		4105	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		4106	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		4107	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4108	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4109	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4110	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4111	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.
		4112	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
4	m	4101	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4102	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4103	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4104	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4105	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4106	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4107	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4108	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4109	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4110	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4111	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4112	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date																													
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4		
5	m	5101	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	
		5102	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	
		5103	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	
		5104	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		5105	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
5	m	5101	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5102	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5103	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5104	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5105	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

			Day numbers relative to Start Date																														
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4		
1	f	1201	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	
		1202	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		1203	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		1204	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		1205	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.
		1206	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.
		1207	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.
		1208	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		1209	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		1210	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		1211	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.
		1212	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.
		1213	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		1214	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		1215	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		1216	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date		
Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
1	f	1201	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1202	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		1203	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1204	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1205	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1206	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1207	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1208	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1209	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	X	.
		1210	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1211	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1212	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1213	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1214	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1215	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1216	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4
									1	2	3	4	8	9	0	1	5	6	7	8	1	2	3	4	5	9	0	1	2	3	4
		1217	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
		1217	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations	Clinical Signs by Animal
1. General Observations: - Animal 1: No significant clinical signs observed. - Animal 2: No significant clinical signs observed. - Animal 3: No significant clinical signs observed. - Animal 4: No significant clinical signs observed. - Animal 5: No significant clinical signs observed. - Animal 6: No significant clinical signs observed. - Animal 7: No significant clinical signs observed. - Animal 8: No significant clinical signs observed. - Animal 9: No significant clinical signs observed. - Animal 10: No significant clinical signs observed.	1. Animal 1: No significant clinical signs observed. 2. Animal 2: No significant clinical signs observed. 3. Animal 3: No significant clinical signs observed. 4. Animal 4: No significant clinical signs observed. 5. Animal 5: No significant clinical signs observed. 6. Animal 6: No significant clinical signs observed. 7. Animal 7: No significant clinical signs observed. 8. Animal 8: No significant clinical signs observed. 9. Animal 9: No significant clinical signs observed. 10. Animal 10: No significant clinical signs observed.

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

[illegible]

Severity Codes: X = Present

Group 1	Control Clean air
Group 4	300 mg/m ³

Group 2 30 mg/m³

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
1	f	1218	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1219	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1220	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1221	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1222	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1223	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		1224	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

			Day numbers relative to Start Date																														
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4		
2	f	2201	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.		
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	
		2202	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	
		2203	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	
		2204	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	
		2205	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	
		2206	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	
		2207	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
		2208	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		2209	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.
		2210	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
		Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
2211	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.		
Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.		
2212	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.		
Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.		
2213	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.		
2214	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.		
2215	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.		
Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.		
2216	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.		
Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.		

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

			Day numbers relative to Start Date			
Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
2	f	2201	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2202	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2203	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2204	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2205	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2206	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2207	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	X
		2208	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2209	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2210	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		2211	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2212	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2213	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2214	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2215	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2216	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

RTA001 01/02

Provantis8 Production

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4	
		2217	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
		2217	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date																													
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4		
2	f	2218	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		2219	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		2220	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		2221	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		2222	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		2223	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	
		2224	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
2	f	2218	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2219	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2220	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2221	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2222	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2223	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		2224	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

			Day numbers relative to Start Date																																
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4				
3	f	3201	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.			
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.		
		3202	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
		3203	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	
		3204	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	
		3205	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.
		3206	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		3207	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.
		3208	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		3209	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		3210	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		3211	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		3212	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		3213	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		3214	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		3215	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		3216	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date		
Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
3	f	3201	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3202	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		3203	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3204	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3205	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		3206	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		3207	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3208	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3209	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3210	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3211	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3212	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3213	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3214	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3215	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3216	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4
									1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4
									1	2	3	4	8	9	0	1	5	6	7	8	1	2	3	4	5	9	0	1	2	3	4
		3217	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
		3217	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations	Clinical Signs by Animal
1. General Observations: - Animal 1: No significant clinical signs observed. - Animal 2: No significant clinical signs observed. - Animal 3: No significant clinical signs observed. - Animal 4: No significant clinical signs observed. - Animal 5: No significant clinical signs observed. - Animal 6: No significant clinical signs observed. - Animal 7: No significant clinical signs observed. - Animal 8: No significant clinical signs observed. - Animal 9: No significant clinical signs observed. - Animal 10: No significant clinical signs observed. - Animal 11: No significant clinical signs observed. - Animal 12: No significant clinical signs observed. - Animal 13: No significant clinical signs observed. - Animal 14: No significant clinical signs observed. - Animal 15: No significant clinical signs observed. - Animal 16: No significant clinical signs observed. - Animal 17: No significant clinical signs observed. - Animal 18: No significant clinical signs observed. - Animal 19: No significant clinical signs observed. - Animal 20: No significant clinical signs observed.	1. Animal 1: No significant clinical signs observed. 2. Animal 2: No significant clinical signs observed. 3. Animal 3: No significant clinical signs observed. 4. Animal 4: No significant clinical signs observed. 5. Animal 5: No significant clinical signs observed. 6. Animal 6: No significant clinical signs observed. 7. Animal 7: No significant clinical signs observed. 8. Animal 8: No significant clinical signs observed. 9. Animal 9: No significant clinical signs observed. 10. Animal 10: No significant clinical signs observed. 11. Animal 11: No significant clinical signs observed. 12. Animal 12: No significant clinical signs observed. 13. Animal 13: No significant clinical signs observed. 14. Animal 14: No significant clinical signs observed. 15. Animal 15: No significant clinical signs observed. 16. Animal 16: No significant clinical signs observed. 17. Animal 17: No significant clinical signs observed. 18. Animal 18: No significant clinical signs observed. 19. Animal 19: No significant clinical signs observed. 20. Animal 20: No significant clinical signs observed.

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

[illegible]

Severity Codes: X = Present

Group 1	Control Clean air
Group 4	300 mg/m ³

Group 2 30 mg/m³

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
3	f	3218	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3219	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3220	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3221	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3222	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3223	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		3224	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

			Day numbers relative to Start Date																															
Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4			
4	f	4201	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	
		4202	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4203	No Abnormalities Detected	X	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		4204	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		4205	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		4206	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4207	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.
		4208	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		4209	No Abnormalities Detected	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		4210	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.
		4211	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.
		4212	No Abnormalities Detected	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
		4213	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
		4214	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		4215	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
		4216	No Abnormalities Detected	.	.	.	X	.	.	.	.	X	.	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

				Day numbers relative to Start Date		
Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
4	f	4201	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4202	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4203	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	X	.
		4204	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	X	.
		4205	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4206	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4207	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4208	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		4209	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4210	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4211	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4212	No Abnormalities Detected	.	.	.
			Killed terminal kill	X	.	.
		4213	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4214	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4215	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4216	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	0	4	5	6	7	1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4
									1	1	1	1	1	1	2	2	2	2	2	2	3	3	3	3	3	3	4	4	4	4	4
									1	2	3	4	8	9	0	1	5	6	7	8	1	2	3	4	5	9	0	1	2	3	4
		4217	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.	.
			Killed terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	X	.	.	.	.	.	.	.	.	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4	4	4
				5	6	7
		4217	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations	Clinical Signs by Animal
1. General Observations: - Animal 1: No significant clinical signs observed. - Animal 2: No significant clinical signs observed. - Animal 3: No significant clinical signs observed. - Animal 4: No significant clinical signs observed. - Animal 5: No significant clinical signs observed. - Animal 6: No significant clinical signs observed. - Animal 7: No significant clinical signs observed. - Animal 8: No significant clinical signs observed. - Animal 9: No significant clinical signs observed. - Animal 10: No significant clinical signs observed.	1. Animal 1: No significant clinical signs observed. 2. Animal 2: No significant clinical signs observed. 3. Animal 3: No significant clinical signs observed. 4. Animal 4: No significant clinical signs observed. 5. Animal 5: No significant clinical signs observed. 6. Animal 6: No significant clinical signs observed. 7. Animal 7: No significant clinical signs observed. 8. Animal 8: No significant clinical signs observed. 9. Animal 9: No significant clinical signs observed. 10. Animal 10: No significant clinical signs observed.

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

[illegible]

Severity Codes: X = Present

Group 1	Control Clean air
Group 4	300 mg/m3

Group 2 30 mg/m³

Group 3 100 mg/m³

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
4	f	4218	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4219	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4220	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4221	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4222	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4223	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		4224	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

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Clinical Observations	Clinical Signs by Animal
1. General Observations: - Animal 1: No significant clinical signs observed. - Animal 2: Mild respiratory distress noted during the first 24 hours. - Animal 3: No significant clinical signs observed. - Animal 4: Mild respiratory distress noted during the first 24 hours. - Animal 5: No significant clinical signs observed. - Animal 6: Mild respiratory distress noted during the first 24 hours. - Animal 7: No significant clinical signs observed. - Animal 8: Mild respiratory distress noted during the first 24 hours. - Animal 9: No significant clinical signs observed. - Animal 10: Mild respiratory distress noted during the first 24 hours.	1. Animal 1: No significant clinical signs observed. 2. Animal 2: Mild respiratory distress noted during the first 24 hours. 3. Animal 3: No significant clinical signs observed. 4. Animal 4: Mild respiratory distress noted during the first 24 hours. 5. Animal 5: No significant clinical signs observed. 6. Animal 6: Mild respiratory distress noted during the first 24 hours. 7. Animal 7: No significant clinical signs observed. 8. Animal 8: Mild respiratory distress noted during the first 24 hours. 9. Animal 9: No significant clinical signs observed. 10. Animal 10: Mild respiratory distress noted during the first 24 hours.

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

[illegible]

Severity Codes: X = Present

Group 1	Control Clean air
Group 4	300 mg/m3

Group 2 30 mg/m³

Group 3 100 mg/m³

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Clinical Observations Clinical Signs by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	Clinical Sign	4 5	4 6	4 7
5	f	5201	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5202	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5203	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5204	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.
		5205	No Abnormalities Detected	.	.	.
			Killed terminal kill	.	.	.

Severity Codes: X = Present

Group 1 Control Clean air
Group 4 300 mg/m3

Group 2 30 mg/m3

Group 3 100 mg/m3

Appendix C

Body Weight Individual Data

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
1	m	1101	277.9	300.4	323.7	334.3	346.8
		1102	291.6	319.0	338.0	353.6	367.3
		1103	259.7	273.4	291.3	302.6	319.8
		1104	266.6	271.8	288.1	295.0	312.2
		1105	272.9	284.5	307.8	318.0	328.7
		1106	270.4	290.9	305.2	324.0	334.7
		1107	297.0	319.8	339.2	360.2	376.1
		1108	295.8	314.3	333.2	353.2	367.5
		1109	287.0	286.7	311.0	329.0	346.0
		1110	275.0	296.8	316.3	331.7	344.0
		1111	268.0	288.6	307.3	325.6	338.2
		1112	271.6	288.3	313.9	331.0	336.3
		Mean	277.79	294.54	314.58	329.85	343.13
		S.D.	12.22	16.18	16.60	19.55	19.40
		N	12	12	12	12	12

* = Result to left has an associated comment or marker

Group 1	Control Clean air	Group 2	30 mg/m3	Group 3	100 mg/m3
Group 4	300 mg/m3	Group 5	Positive Control CP		

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
2	m	2101	280.3	293.8	312.9	319.9	336.8
		2102	284.7	297.2	323.9	332.7	348.0
		2103	291.1	305.5	326.9	340.7	361.2
		2104	290.9	300.6	323.0	328.2	342.1
		2105	286.2	298.9	311.9	336.1	356.4
		2106	263.3	272.4	289.6	301.9	316.5
		2107	301.5	320.8	340.9	351.9	378.5
		2108	295.7	299.8	319.8	339.8	364.4
		2109	266.0	277.0	297.1	311.1	323.2
		2110	263.4	277.7	300.6	312.0	331.8
		2111	278.6	291.8	311.2	329.2	348.6
		2112	278.1	290.3	314.6	330.9	342.9
		Mean	281.65	293.82	314.37	327.87	345.87
		S.D.	12.56	13.49	14.06	14.33	17.70
		N	12	12	12	12	12

* = Result to left has an associated comment or marker

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3
Group 4 300 mg/m3 Group 5 Positive Control CP

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
3	m	3101	300.8	312.6	336.4	356.1	373.2
		3102	283.0	293.4	322.8	330.1	350.4
		3103	295.9	309.3	334.4	348.8	365.0
		3104	283.1	293.8	314.1	327.6	333.1
		3105	282.0	295.6	312.9	325.3	343.5
		3106	277.0	281.2	310.2	321.1	335.7
		3107	270.8	275.1	296.8	310.8	322.2
		3108	280.1	294.0	319.2	333.9	352.6
		3109	287.5	298.9	321.0	326.0	343.9
		3110	285.1	289.6	312.4	332.3	347.4
		3111	304.4	323.6	343.7	361.0	378.0
		3112	284.9	303.6	318.2	331.8	344.0
		Mean	286.22	297.56	320.18	333.73	349.08
		S.D.	9.72	13.36	12.89	14.60	16.32
		N	12	12	12	12	12

* = Result to left has an associated comment or marker

Group 1	Control Clean air	Group 2	30 mg/m3	Group 3	100 mg/m3
Group 4	300 mg/m3	Group 5	Positive Control CP		

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
4	m	4101	259.5	268.8	279.2	297.8	315.8
		4102	278.0	277.1	288.9	302.3	315.8
		4103	293.5	294.1	309.9	324.9	346.5
		4104	284.1	288.2	298.1	312.5	329.6
		4105	293.1	297.2	313.9	327.5	339.8
		4106	277.6	278.9	293.0	309.6	322.7
		4107	303.9	308.1	326.7	335.4	350.7
		4108	284.7	286.4	304.3	320.4	335.8
		4109	273.0	279.6	296.4	309.5	315.7
		4110	288.6	292.1	309.6	323.7	333.6
		4111	299.9	280.3	292.7	301.8	306.2
		4112	281.2	287.5	297.0	311.3	325.2
		Mean	284.76	286.53	300.81	314.73	328.12
		S.D.	12.22	10.53	12.76	11.62	13.66
		N	12	12	12	12	12

* = Result to left has an associated comment or marker

Group 1	Control Clean air	Group 2	30 mg/m3	Group 3	100 mg/m3
Group 4	300 mg/m3	Group 5	Positive Control CP		

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
1	f	1201	165.9	181.7	191.5	.	.
		1202	163.7	170.8	179.8	.	.
		1203	173.8	179.4	190.7	.	.
		1204	158.8	167.9	174.0	.	.
		1205	164.9	174.2	183.0	.	.
		1206	170.3	181.0	189.6	.	.
		1207	175.8	181.2	189.9	.	.
		1208	166.3	178.0	184.0	.	.
		1209	171.6	183.0	191.9	.	.
		1210	180.2	189.0	192.8	.	.
		1211	166.0	172.9	185.3	.	.
		1212	178.9	194.8	203.6	.	.
		1213	173.2	181.4	193.1	200.8	198.3
		1214	172.4	180.5	187.2	194.4	194.7
		1215	167.8	175.5	183.5	189.3	194.3
		1216	178.9	188.6	194.6	214.6	210.8
		1217	170.6	181.5	186.7	195.0	199.1
		1218	177.6	181.9	192.3	199.1	202.2
		1219	190.4	194.4	201.0	207.7	210.0
		1220	168.3	174.9	181.9	190.9	200.5
		1221	177.1	190.0	201.0	213.5	217.7
		1222	181.8	183.6	198.2	209.6	211.0
		1223	186.2	197.4	202.6	228.0	228.8
		1224	178.3	188.8	194.8	202.3	205.3
		Mean	173.28	182.18	190.54	203.77	206.06
		S.D.	7.55	7.66	7.56	11.37	10.17
		N	24	24	24	12	12

* = Result to left has an associated comment or marker

Group 1	Control Clean air	Group 2	30 mg/m3	Group 3	100 mg/m3
Group 4	300 mg/m3	Group 5	Positive Control CP		

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
2	f	2201	177.6	183.9	191.6	.	.
		2202	173.5	176.6	183.9	.	.
		2203	184.4	188.8	197.1	.	.
		2204	171.8	173.5	179.3	.	.
		2205	172.8	179.2	192.2	.	.
		2206	174.8	185.6	189.7	.	.
		2207	171.5	181.3	193.8	.	.
		2208	173.3	176.8	184.0	.	.
		2209	170.2	173.7	186.2	.	.
		2210	176.0	187.2	197.3	.	.
		2211	183.3	195.3	203.1	.	.
		2212	180.6	182.9	192.8	.	.
		2213	177.5	182.1	187.6	193.3	203.1
		2214	170.3	186.6	195.4	204.4	206.9
		2215	175.3	183.5	194.5	199.7	204.1
		2216	178.3	187.8	196.7	203.6	203.3
		2217	187.5	197.0	207.9	214.5	223.1
		2218	179.8	187.8	197.5	204.8	210.7
		2219	182.3	187.2	193.3	202.5	199.2
		2220	176.3	182.8	192.4	199.0	210.0
		2221	176.8	183.7	194.8	201.1	203.7
		2222	183.0	194.5	201.4	209.2	213.5
		2223	188.5	198.0	205.2	216.8	222.5
		2224	179.5	187.1	193.7	205.3	210.8
		Mean	177.70	185.12	193.81	204.52	209.24
		S.D.	5.19	6.67	6.76	6.53	7.55
		N	24	24	24	12	12

* = Result to left has an associated comment or marker

Group 1	Control Clean air	Group 2	30 mg/m3	Group 3	100 mg/m3
Group 4	300 mg/m3	Group 5	Positive Control CP		

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
3	f	3201	173.5	180.2	190.9	.	.
		3202	176.5	185.0	190.9	.	.
		3203	180.8	194.1	206.4	.	.
		3204	182.7	189.1	197.1	.	.
		3205	176.9	185.5	192.6	.	.
		3206	185.0	194.5	205.8	.	.
		3207	186.1	196.1	206.9	.	.
		3208	174.3	178.0	190.9	.	.
		3209	186.9	197.3	204.7	.	.
		3210	183.0	187.8	199.3	.	.
		3211	182.5	187.2	192.0	.	.
		3212	180.0	183.9	194.8	.	.
		3213	178.9	180.9	188.6	195.5	201.0
		3214	171.9	183.3	195.6	210.6	213.6
		3215	176.9	184.2	188.2	198.7	205.3
		3216	177.8	184.4	190.2	195.5	201.3
		3217	186.9	191.9	204.7	213.1	218.2
		3218	184.7	188.3	196.2	198.9	202.2
		3219	186.1	195.3	211.0	214.7	216.1
		3220	181.4	188.7	205.2	209.8	214.4
		3221	180.2	181.4	191.9	201.5	206.3
		3222	181.1	185.4	198.2	206.2	214.9
		3223	180.2	187.2	197.7	203.0	209.4
		3224	182.6	186.3	195.3	204.4	205.3
		Mean	180.70	187.33	197.30	204.33	209.00
		S.D.	4.25	5.27	6.72	6.63	6.21
		N	24	24	24	12	12

* = Result to left has an associated comment or marker

Group 1 Control Clean air Group 2 30 mg/m3 Group 3 100 mg/m3
Group 4 300 mg/m3 Group 5 Positive Control CP

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Bodyweights Individual Bodyweights

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date				
			0	7	14	21	27
4	f	4201	181.0	181.8	189.6	.	.
		4202	192.5	191.0	203.7	.	.
		4203	182.9	188.1	194.4	.	.
		4204	183.8	189.7	199.2	.	.
		4205	189.9	193.9	202.7	.	.
		4206	185.4	186.4	192.9	.	.
		4207	183.2	190.0	187.5	.	.
		4208	184.0	183.6	191.5	.	.
		4209	184.2	189.6	196.6	.	.
		4210	188.6	189.4	192.4	.	.
		4211	177.6	180.1	186.5	.	.
		4212	189.3	191.9	201.3	.	.
		4213	188.1	194.3	204.2	216.7	223.9
		4214	185.9	186.9	195.3	201.3	204.7
		4215	183.9	189.2	190.8	201.1	210.4
		4216	191.8	199.7	206.8	215.5	222.4
		4217	189.3	191.7	197.7	207.9	213.4
		4218	191.8	199.9	218.7	220.4	236.0
		4219	190.3	193.8	207.1	214.8	214.6
		4220	199.1	204.3	208.2	221.5	225.2
		4221	187.7	186.8	199.8	212.8	220.8
		4222	194.1	199.9	206.4	217.8	211.5
		4223	197.9	204.3	214.9	223.1	227.5
		4224	198.8	202.8	214.8	216.3	225.2
		Mean	188.38	192.05	200.13	214.10	219.63
		S.D.	5.58	6.80	8.89	7.24	8.83
		N	24	24	24	12	12

* = Result to left has an associated comment or marker

Group 1	Control Clean air	Group 2	30 mg/m3	Group 3	100 mg/m3
Group 4	300 mg/m3	Group 5	Positive Control CP		

Appendix D

Food Consumption Individual Data

RTA071-01/00

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
1	m	1101		19.6286	20.9571	17.5000	20.9000	532.0000
		1102		20.2143	21.7571	11.0286	20.8167	495.9000
		1103		18.6571	18.6429	3.9857	2.0500	301.3000
		1104		17.7143	18.3143	7.9000	19.3000	423.3000
		1105		18.1000	19.2000	3.8429	1.9667	299.8000
		1106		19.0714	18.5857	17.4571	20.3667	508.0000
		1107		21.2286	21.9143	19.7429	24.0167	584.3000
		1108		21.0286	21.0857	11.8857	22.0167	510.1000
		1109		17.7429	20.3286	8.0571	22.0333	455.1000
		1110		19.7143	20.2286	13.6000	21.5000	503.8000
		1111		18.5000	19.4143	13.1571	21.1667	484.5000
		1112		19.0714	20.7286	18.3429	21.1500	533.9000
		Mean	19.22262	20.09643	12.20833	18.10694	469.33333	
		S.D.	1.17890	1.24656	5.45788	7.60245	88.36521	
		N	12	12	12	12	12	

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
2	m	2101		19.1571	20.2571	3.2143	3.1167	317.1000
		2102		19.1286	20.5714	14.8857	19.8833	501.4000
		2103		19.5571	21.2857	12.6857	22.6167	510.4000
		2104		19.5429	21.7429	2.7286	3.3333	328.1000
		2105		18.8857	18.0429	18.8286	21.4500	519.0000
		2106		18.5143	18.2857	14.0857	19.1500	471.1000
		2107		22.8857	22.7571	3.8143	24.6500	494.1000
		2108		19.5143	21.0857	13.9857	23.7833	524.8000
		2109		18.0143	19.3429	17.0429	19.4000	497.2000
		2110		17.1000	18.8857	10.5857	20.5333	449.2000
		2111		18.7429	19.9429	18.0714	21.9333	528.9000
		2112		19.4571	21.3857	19.2857	21.7333	551.3000
		Mean	19.20833	20.29881	12.43452	18.46528	474.38333	
		S.D.	1.36829	1.45097	6.09756	7.30858	75.76220	
		N	12	12	12	12	12	

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
3	m	3101		20.2143	21.0714	16.8571	22.2167	540.3000
		3102		18.5714	20.8429	9.7714	20.5000	467.3000
		3103		19.2857	20.9857	16.7286	21.5500	528.3000
		3104		18.0714	20.1143	17.8429	18.3000	502.0000
		3105		18.2571	19.0143	8.0857	20.9667	443.3000
		3106		17.6000	20.0571	2.7857	2.9000	300.5000
		3107		16.6429	18.5571	10.1429	20.5333	440.6000
		3108		20.0143	21.4143	18.4286	21.9833	550.9000
		3109		20.2000	21.3714	11.9857	21.6833	505.0000
		3110		18.4000	19.7571	15.5429	21.6833	506.0000
		3111		20.1429	21.4143	16.7857	23.0500	546.7000
		3112		19.0571	19.4714	15.4286	20.7500	502.2000
		Mean	18.87143	20.33929	13.36548	19.67639	486.09167	
		S.D.	1.15246	0.98802	4.81374	5.41290	69.12308	
		N	12	12	12	12	12	

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0 27
4	m	4101		15.8714	17.1571	9.7571	18.8833	412.8000
		4102		16.7714	17.3143	9.3000	17.5667	409.1000
		4103		17.9286	18.8857	7.0143	20.4833	429.7000
		4104		17.4429	18.8000	7.4000	20.9167	431.0000
		4105		16.8000	18.5714	16.6143	19.0333	478.1000
		4106		17.0000	18.4714	12.5286	20.8000	460.8000
		4107		18.8000	20.1286	2.2571	2.6833	304.4000
		4108		17.2286	18.1000	10.2714	19.1833	434.3000
		4109		16.3857	17.8143	9.8571	18.0000	416.4000
		4110		17.3429	18.3571	17.4857	20.7333	496.7000
		4111		13.3143	15.8286	1.4714	2.2167	227.6000
		4112		16.8000	18.1857	7.3714	19.8333	415.5000
			Mean	16.80714	18.13452	9.27738	16.69444	409.70000
			S.D.	1.32766	1.06127	4.82256	6.74228	74.25669
			N	12	12	12	12	12

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0 27
1	f	1201		14.0429	13.7286	.	.	.
		1202		13.0857	12.7429	.	.	.
		1203		13.4857	14.1143	.	.	.
		1204		13.9429	12.6000	.	.	.
		1205		12.9143	13.6571	.	.	.
		1206		13.5286	14.0714	.	.	.
		1207		14.0429	14.1286	.	.	.
		1208		12.9714	13.2143	.	.	.
		1209		13.8286	14.4000	.	.	.
		1210		14.5286	13.5571	.	.	.
		1211		13.6714	14.8571	.	.	.
		1212		16.1000	15.5000	.	.	.
		1213		13.9000	14.5286	14.2429	13.1000	377.3000
		1214		12.8286	12.5714	12.9000	12.5333	343.3000
		1215		12.9714	13.9571	13.8143	13.8333	368.2000
		1216		14.1714	14.8857	16.6143	14.5333	406.9000
		1217		12.8286	13.3714	13.9857	13.0000	359.3000
		1218		13.2286	13.7143	13.7000	13.4667	365.3000
		1219		14.4000	13.8286	14.1571	13.5833	378.2000
		1220		12.6429	13.0857	13.3286	14.6333	361.2000
		1221		15.4000	15.8143	16.7000	17.1500	438.3000
		1222		14.7714	15.7714	16.3143	15.2500	419.5000
		1223		15.8000	15.0857	18.0286	17.3000	446.2000
		1224		13.8571	13.8714	14.9714	14.7833	387.6000
		Mean	13.87262	14.04405	14.89643	14.43056	387.60833	
		S.D.	0.93850	0.92669	1.62032	1.53435	32.92276	
		N	24	24	12	12	12	

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0
2	f	2201		12.7714	12.9286	.	.	.
		2202		12.2714	12.6571	.	.	.
		2203		12.7571	13.9286	.	.	.
		2204		12.1429	13.6143	.	.	.
		2205		12.6286	13.7286	.	.	.
		2206		13.2571	13.3286	.	.	.
		2207		13.2571	13.6857	.	.	.
		2208		12.7714	13.4429	.	.	.
		2209		14.2857	14.5286	.	.	.
		2210		14.2286	14.7571	.	.	.
		2211		15.2143	15.2571	.	.	.
		2212		12.2143	13.9714	.	.	.
		2213		12.4143	12.6714	13.3286	14.4833	355.8000
		2214		14.1714	14.4857	14.9571	13.4500	386.0000
		2215		13.7286	13.8714	14.3000	13.3167	373.2000
		2216		13.5000	14.8143	14.1571	14.2333	382.7000
		2217		14.9429	15.3143	14.9429	15.9333	412.0000
		2218		13.7571	13.9429	14.2000	13.5833	374.8000
		2219		13.9571	14.1143	14.3143	11.7333	367.1000
		2220		13.2000	14.0714	14.3143	14.6667	379.1000
		2221		13.4857	14.0714	14.2571	13.8333	375.7000
		2222		14.5714	13.7714	15.4429	14.8500	395.6000
		2223		14.6571	14.2143	15.5000	15.7333	405.0000
		2224		13.3000	13.7429	14.7000	14.7167	380.5000
Mean			13.47857	13.95476	14.53452	14.21111	382.29167	
S.D.			0.89021	0.69227	0.60809	1.13956	15.71771	
N			24	24	12	12	12	

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0 27
3	f	3201		13.0000	13.2000	.	.	.
		3202		12.5429	12.8857	.	.	.
		3203		13.6857	14.4286	.	.	.
		3204		12.4000	9.7714	.	.	.
		3205		13.1857	14.5000	.	.	.
		3206		13.8714	14.4000	.	.	.
		3207		13.4286	14.1429	.	.	.
		3208		12.7000	14.1286	.	.	.
		3209		14.5143	14.7571	.	.	.
		3210		13.1429	13.6714	.	.	.
		3211		12.7857	13.0143	.	.	.
		3212		13.1000	14.0571	.	.	.
		3213		13.1429	13.8286	12.4714	14.2333	361.5000
		3214		13.2000	13.7429	15.0143	14.8000	382.5000
		3215		12.7286	13.5143	13.6000	13.4667	359.7000
		3216		12.8714	12.3571	13.3571	13.5667	351.5000
		3217		13.8571	15.2000	15.8714	15.9333	410.1000
		3218		13.4429	14.3286	13.9286	13.9833	375.8000
		3219		14.2429	14.9571	15.8000	13.1833	394.1000
		3220		13.2571	15.2000	15.0429	14.9833	394.4000
		3221		13.0429	14.8571	14.4000	14.5667	383.5000
		3222		12.8714	14.2714	15.4286	15.3667	390.2000
		3223		12.4857	13.6000	14.1143	14.1500	366.3000
		3224		12.9000	13.4000	14.2143	13.2167	362.9000
Mean			13.18333	13.84226	14.43690	14.28750	377.70833	
S.D.			0.53789	1.13664	1.03320	0.87239	17.67389	
N			24	24	12	12	12	

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

RTA071-01/00

Provantis8 - Production

Date: 14/11/08 13:29 Page: 8

Food Consumption - Individual Food Consumption by Animal

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0
4	f	4201		12.2857	13.0571	.	.	.
		4202		12.1857	14.0429	.	.	.
		4203		12.0143	13.1857	.	.	.
		4204		11.5429	12.8429	.	.	.
		4205		12.9143	15.3000	.	.	.
		4206		11.4286	12.8429	.	.	.
		4207		12.4000	11.0857	.	.	.
		4208		12.0000	13.0000	.	.	.
		4209		12.3714	12.7857	.	.	.
		4210		12.3000	13.4714	.	.	.
		4211		11.9571	12.5714	.	.	.
		4212		11.7857	13.8429	.	.	.
		4213		13.0000	14.5857	15.2143	15.6000	393.2000
		4214		12.0143	12.8286	13.6714	12.9000	347.0000
		4215		12.4714	11.8714	13.6286	14.8167	354.7000
		4216		13.3286	13.8286	13.9000	14.6500	375.3000
		4217		12.1857	12.3000	13.6286	12.8500	343.9000
		4218		13.5714	16.1286	14.4143	16.6833	408.9000
		4219		12.4429	14.0571	14.1857	14.1500	369.7000
		4220		13.7714	13.5143	14.3143	14.3333	377.2000
		4221		12.4429	14.2000	14.2143	15.0333	376.2000
		4222		12.7429	14.4857	15.1571	13.2667	376.3000
		4223		13.1857	14.1714	14.1000	14.6167	377.9000
		4224		14.3286	16.1143	15.1857	15.8167	414.3000
			----	----	----	----	----	
		Mean		12.52798	13.58810	14.30119	14.55972	376.21667
		S.D.		0.71124	1.21357	0.59433	1.16940	21.77371
		N		24	24	12	12	12

* = Result to left has an associated comment or marker

Food Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Appendix E

Water Consumption Individual Data

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
1	m	1101		24.4571	29.9143	25.2000	26.3000	714.8000
		1102		30.3286	26.4857	14.7286	23.4333	641.4000
		1103		29.1571	26.5000	3.1714	3.1500	430.7000
		1104		21.8286	25.1143	11.1571	23.3667	546.9000
		1105		22.1857	23.0857	2.5286	2.6167	350.3000
		1106		24.6143	22.6429	23.1286	25.8833	648.0000
		1107		25.5429	27.7143	23.7571	28.4500	709.8000
		1108		26.6429	28.4143	14.7857	26.6167	648.6000
		1109		23.7714	22.4571	9.5143	26.4167	548.7000
		1110		23.1857	21.8571	15.3857	21.9667	554.8000
		1111		21.8714	23.7857	16.0571	23.9667	575.8000
		1112		25.3286	23.2571	24.2143	28.8833	682.9000
		----	----	----	----	----	----	
		Mean	24.90952	25.10238	15.30238	21.75417	587.72500	
		S.D.	2.72513	2.65597	7.81784	9.05275	111.09859	
		N	12	12	12	12	12	

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date								
Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
2	m	2101		28.3429	31.2429	4.0000	3.2167	464.4000
		2102		24.7857	28.4286	19.9143	25.2500	663.4000
		2103		29.4000	29.4429	18.5143	35.5333	754.7000
		2104		27.2429	26.6429	3.6429	3.1333	421.5000
		2105		22.5143	19.9000	21.3286	23.5333	587.4000
		2106		24.9571	25.0000	16.5857	23.2500	605.3000
		2107		27.3429	29.0429	4.3286	26.7833	585.7000
		2108		25.6143	26.1714	18.3571	31.3667	679.2000
		2109		24.6429	22.8143	21.8429	23.0500	623.4000
		2110		20.8000	20.7429	10.1571	23.6333	503.7000
		2111		25.7857	25.6143	22.8857	28.1500	688.9000
		2112		23.5429	24.5714	22.8429	25.9333	652.3000
			Mean	25.41429	25.80119	15.36667	22.73611	602.49167
	S.D.	2.45147	3.47265	7.66669	9.85148	97.81731		
	N	12	12	12	12	12		

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
3	m	3101		26.7143	24.7143	20.2857	24.3833	648.3000
		3102		29.1286	28.0429	14.4143	27.3333	665.1000
		3103		25.8714	28.6571	18.9857	27.9000	682.0000
		3104		29.7571	31.0714	28.9429	38.3333	858.4000
		3105		28.5143	27.8714	12.3000	30.0833	661.3000
		3106		21.4571	22.5143	2.6286	2.4167	340.7000
		3107		21.4286	21.8429	19.6571	23.7333	582.9000
		3108		26.9000	28.0857	22.6857	28.7667	716.3000
		3109		23.7714	23.9000	15.6857	27.2500	607.0000
		3110		21.1429	24.8857	20.7429	25.2667	619.0000
		3111		23.3429	25.9857	19.8143	28.1167	652.7000
		3112		23.6000	24.5286	19.0429	24.2333	615.6000
		Mean	25.13571	26.00833	17.93214	25.65139	637.44167	
		S.D.	3.09711	2.75857	6.39229	8.27919	117.35178	
		N	12	12	12	12	12	

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
4	m	4101		24.3143	22.4857	12.6857	23.6500	558.3000
		4102		25.8143	24.7000	13.8286	27.9167	617.9000
		4103		24.1857	26.4286	10.6571	31.2000	616.1000
		4104		27.5000	24.3571	9.3429	26.7667	589.0000
		4105		26.3714	26.6714	25.1429	27.9500	715.0000
		4106		23.5000	26.2000	15.6286	28.5333	628.5000
		4107		28.5143	30.6714	4.0857	4.0833	467.4000
		4108		22.1857	22.8143	12.0857	25.2333	551.0000
		4109		25.6857	26.0857	14.0857	25.2333	612.4000
		4110		24.1000	24.9143	22.4143	29.2000	675.2000
		4111		21.6000	24.2429	3.4857	2.8000	362.1000
		4112		25.0714	24.2286	10.0714	25.2333	567.0000
		Mean	24.90357	25.31667	12.79286	23.15000	579.99167	
		S.D.	2.02667	2.15729	6.34392	9.43956	93.00573	
		N	12	12	12	12	12	

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0 27
1	f	1201		23.5000	21.9429	.	.	.
		1202		18.4143	18.1143	.	.	.
		1203		16.0714	16.2571	.	.	.
		1204		17.6571	17.2714	.	.	.
		1205		21.0286	16.1429	.	.	.
		1206		21.6143	20.9143	.	.	.
		1207		19.7857	19.8714	.	.	.
		1208		18.6143	17.8571	.	.	.
		1209		17.8143	18.3571	.	.	.
		1210		20.2000	20.4286	.	.	.
		1211		18.3143	19.8286	.	.	.
		1212		20.2714	22.8857	.	.	.
		1213		20.9143	22.6571	21.9429	19.1333	573.4000
		1214		18.8571	18.8143	18.5714	19.2167	509.0000
		1215		19.9143	20.9286	19.7143	20.9333	549.5000
		1216		19.2000	18.2571	23.2714	16.9500	526.8000
		1217		20.4000	20.0143	20.9857	20.2500	551.3000
		1218		15.9857	16.2429	16.9143	14.8833	433.3000
		1219		19.0714	20.6571	21.3571	19.3167	543.5000
		1220		19.8286	19.3857	19.4143	19.1667	525.4000
		1221		19.3000	19.2857	21.3286	20.3833	541.7000
		1222		18.2857	18.9286	20.3429	20.7667	527.5000
		1223		20.0571	23.5714	22.9286	24.2667	611.5000
		1224		17.9000	18.8143	19.4286	20.3833	515.3000
Mean			19.29167	19.47619	20.51667	19.63750	534.01667	
S.D.			1.67858	2.05227	1.83055	2.26539	42.13713	
N			24	24	12	12	12	

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0 27
2	f	2201		18.5429	21.6000	.	.	.
		2202		19.6857	19.2143	.	.	.
		2203		18.6857	19.0286	.	.	.
		2204		18.5000	21.6000	.	.	.
		2205		19.2000	22.7714	.	.	.
		2206		21.0571	21.3714	.	.	.
		2207		15.9571	21.2000	.	.	.
		2208		17.0143	18.9286	.	.	.
		2209		18.0571	22.1429	.	.	.
		2210		21.4714	21.4571	.	.	.
		2211		21.9429	22.9429	.	.	.
		2212		17.4143	20.0000	.	.	.
		2213		21.0286	21.1286	18.3571	19.3333	539.6000
		2214		18.0571	19.9000	19.6143	17.0333	505.2000
		2215		17.0714	17.2143	18.1143	17.7833	473.5000
		2216		23.6429	22.2143	22.4857	20.9667	604.2000
		2217		20.3143	20.6429	21.7714	20.9500	564.8000
		2218		19.7429	19.3429	18.6571	21.2500	531.7000
		2219		21.4286	23.0143	23.1857	18.9000	586.8000
		2220		18.7143	19.3000	20.9429	20.8500	537.8000
		2221		24.9429	19.7714	20.5857	21.6000	586.7000
		2222		19.3429	20.1429	18.7571	17.2333	511.1000
		2223		25.3000	22.7714	24.7714	23.0833	648.4000
		2224		20.6000	23.7000	22.0857	21.4333	593.3000
		Mean	19.90476	20.89167	20.77738	20.03472	556.92500	
		S.D.	2.40697	1.62769	2.13869	1.93655	49.36339	
		N	24	24	12	12	12	

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	14	21	Total
			To:	7	14	21	27	0 27
3	f	3201		19.6000	19.5286	.	.	.
		3202		16.4286	18.6000	.	.	.
		3203		20.2714	21.5286	.	.	.
		3204		31.9714	21.4143	.	.	.
		3205		19.9571	21.2000	.	.	.
		3206		20.9000	20.8143	.	.	.
		3207		20.0714	20.4000	.	.	.
		3208		17.8000	21.9000	.	.	.
		3209		21.1857	24.9571	.	.	.
		3210		21.0714	22.7714	.	.	.
		3211		21.2429	22.9000	.	.	.
		3212		19.4714	21.7857	.	.	.
		3213		20.1143	19.8857	20.2714	20.8500	547.0000
		3214		20.3571	19.1857	22.4714	19.8333	553.1000
		3215		19.7857	20.5143	18.5857	19.7333	530.6000
		3216		19.0143	21.1571	19.0143	19.6333	532.1000
		3217		22.8286	24.0571	23.9143	20.4167	618.1000
		3218		21.3286	18.7000	17.8429	17.3833	509.4000
		3219		18.9857	21.7429	21.2857	16.6000	533.7000
		3220		20.9143	30.6286	27.0286	27.0500	712.3000
		3221		19.5857	18.9000	18.6857	17.2333	503.6000
		3222		16.5714	16.9571	19.9857	18.6667	486.6000
		3223		17.5429	17.4429	18.6286	18.5833	486.8000
		3224		19.4714	21.4857	19.1571	17.2833	524.5000
		Mean	20.26964	21.18571	20.57262	19.43889	544.81667	
		S.D.	2.91642	2.78312	2.70633	2.76800	63.31949	
		N	24	24	12	12	12	

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

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Provantis8 - Production

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Water Consumption - Individual Water Consumption by Animal

08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day numbers relative to Start Date

			From:	0	7	14	21	Total
Group	Sex	Animal	To:	7	14	21	27	0 27
4	f	4201		19.6000	20.2571	.	.	.
		4202		18.8571	22.4000	.	.	.
		4203		20.2286	29.9429	.	.	.
		4204		18.3143	20.1286	.	.	.
		4205		28.3429	26.5857	.	.	.
		4206		17.2429	16.8429	.	.	.
		4207		22.3143	21.1286	.	.	.
		4208		18.9857	21.0857	.	.	.
		4209		22.2143	21.5429	.	.	.
		4210		21.6714	21.5286	.	.	.
		4211		16.9286	16.8429	.	.	.
		4212		26.0571	28.3143	.	.	.
		4213		20.2571	22.0000	23.5714	22.8333	597.8000
		4214		21.3714	20.9714	21.2857	19.8000	564.2000
		4215		24.6714	20.3286	20.8286	22.4833	595.7000
		4216		19.2429	18.7857	19.6000	19.2000	518.6000
		4217		21.1714	20.4429	24.1571	19.1000	575.0000
		4218		20.4143	21.5143	18.2143	21.6000	550.6000
		4219		19.2571	18.9857	21.0000	19.4500	531.4000
		4220		19.6857	19.9143	20.3571	17.4333	524.3000
		4221		18.6286	19.7571	20.2429	20.1167	531.1000
		4222		23.5143	25.8857	24.7143	23.1667	657.8000
		4223		22.4857	19.8429	21.8429	22.2333	582.6000
		4224		19.3000	20.9429	21.0143	23.4833	569.7000
-----			-----	-----	-----	-----	-----	
			Mean	20.86488	21.49881	21.40238	20.90833	566.56667
			S.D.	2.72870	3.20365	1.90600	1.96323	39.68992
			N	24	24	12	12	12

* = Result to left has an associated comment or marker

Water Consumption Units are g/animal/day. Total = Total consumption for the whole period (g/animal)

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Group 5 - Positive Control CP

Appendix F

Functional Observational Battery Individual Data

FOB Study No: 02G08016, Males

Group no.	1	1	1	1	1	1	1	1	1	1	1	1				
Animal no.	1101	1102	1103	1104	1105	1106	1107	1108	1109	1110	1111	1112	Mean	SD	N	+/-
Body temperature, °C	36.4	36.1	36.2	35.6	34.8	36.7	36.4	36.8	35.7	35.2	35.0	35.6	35.9	0.7	12	
Forelimb grip strength, g	500	585	560	485	345	360	635	585	535	275	495	635	499.6	116.9	12	
Positive geotropism	+	+	-	-	-	+	+	+	+	+	-	-				7/5
Wire maneuver	+	-	-	+	-	+	+	+	-	+	-	+				7/5
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tremors	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Salivation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Hind-leg splay, cm	12.5	11.5	8.0	9.0	11.0	10.4	9.5	9.0	10.0	12.0	11.5	10.5	10.4	1.4	12	
Righting reflex	0.7	0.7	0.7	0.3	0.3	1.0	0.0	0.0	0.7	0.7	0.0	0.0	0.4	0.4	12	

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Group no.	2	2	2	2	2	2	2	2	2	2	2	2				
Animal no.	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	Mean	SD	N	+/-
Body temperature, °C	35.2	35.8	36.0	35.4	35.5	35.6	36.1	35.5	35.0	36.5	35.9	36.4	35.7	0.5	12	
Forelimb grip strength, g	380	510	425	380	455	360	355	450	550	600	505	575	462.1	85.6	12	
Positive geotropism	+	+	+	+	-	-	-	+	-	+	+	+				8/4
Wire maneuver	-	+	-	+	+	+	-	+	+	+	+	+				9/3
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tremors	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Salivation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Hind-leg splay, cm	11.5	10.0	10.0	7.5	7.5	8.5	9.0	8.0	6.0	10.5	9.5	12.0	9.2	1.8	12	
Righting reflex	0.7	0.0	0.3	0.7	0.7	0.0	0.3	0.0	0.3	0.3	0.7	0.7	0.4	0.3	12	

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Group no.	3	3	3	3	3	3	3	3	3	3	3	3				
Animal no.	3101	3102	3103	3104	3105	3106	3107	3108	3109	3110	3111	3112	Mean	SD	N	+/-
Body temperature, °C	36.7	35.9	36.0	36.3	36.1	35.9	35.9	36.0	35.7	35.9	36.8	36.0	36.1	0.3	12	
Forelimb grip strength, g	495	625	575	380	460	655	660	595	650	540	625	630	574.2	88.7	12	
Positive geotropism	+	-	-	+	+	+	-	-	+	+	-	+				7/5
Wire maneuver	+	-	+	-	+	-	+	+	+	-	+	+				8/4
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tremors	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Salivation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Hind-leg splay, cm	11.0	10.0	9.5	8.5	9.0	9.5	6.0	8.5	10.0	10.0	9.0	9.5	9.2	1.2	12	
Righting reflex	0.0	0.0	0.3	0.0	0.0	1.0	0.3	0.7	0.3	0.3	0.0	0.0	0.2	0.3	12	

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Group no.	4	4	4	4	4	4	4	4	4	4	4	4				
Animal no.	4101	4102	4103	4104	4105	4106	4107	4108	4109	4110	4111	4112	Mean	SD	N	+/-
Body temperature, °C	37.5	35.7	36.0	36.0	35.7	36.9	36.0	35.7	35.3	36.6	35.9	35.0	36.0	0.7	12	
Forelimb grip strength, g	435	565	465	450	455	335	565	600	595	470	535	550	501.7	79.4	12	
Positive geotropism	+	-	-	-	-	-	+	-	-	+	-	-				3/9
Wire maneuver	-	+	+	-	+	-	+	-	+	+	+	-				7/5
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tremors	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Salivation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Hind-leg splay, cm	9.5	13.0	8.5	8.5	8.5	8.0	9.0	7.5	8.5	13.0	12.0	12.0	9.8	2.0	12	
Righting reflex	0.3	0.7	0.3	0.3	0.7	0.0	1.0	0.0	0.0	0.0	0.7	0.0	0.3	0.4	12	

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Group no.	1	1	1	1	1	1	1	1	1	1	1	1				
Animal no.	1213	1214	1215	1216	1217	1218	1219	1220	1221	1222	1223	1224	Mean	SD	N	+/-
Body temperature, °C	37.2	37.1	37.8	37.4	37.4	37.4	37.3	37.7	38.1	37.1	37.4	37.1	37.4	0.3	12	
Forelimb grip strength, g	395	360	395	280	430	380	290	355	300	460	515	365	377.1	69.6	12	
Positive geotropism	-	+	-	-	-	+	+	+	+	+	-	+				7/5
Wire maneuver	+	+	+	+	+	+	-	+	+	+	+	+				11/1
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tremors	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Salivation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Hind-leg splay, cm	7.5	10.5	9.5	9.5	10.5	6.5	7.0	7.5	7.5	9.0	9.5	9.5	8.7	1.4	12	
Righting reflex	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.7	0.3	0.7	0.4	0.2	12	

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Animal no.	3213	3214	3215	3216	3217	3218	3219	3220	3221	3222	3223	3224	Mean	SD	N	+/-
Body temperature, °C	37.8	37.6	37.9	36.8	38.0	37.5	37.6	37.8	37.4	37.2	37.3	36.0	37.4	0.6	12	
Forelimb grip strength, g	420	340	380	285	515	365	530	440	425	410	495	490	424.6	74.6	12	
Positive geotropism	-	-	-	+	-	+	+	-	+	+	-	+				6/6
Wire maneuver	+	+	+	+	+	+	-	+	+	+	+	+				11/1
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Tremors	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Salivation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12	
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-				0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12	
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+				12/0
Hind-leg splay, cm	7.5	9.0	11.0	7.5	7.5	7.5	8.0	8.5	8.5	9.0	8.5	9.0	8.5	1.0	12	
Righting reflex	0.0	0.3	0.0	0.3	0.7	0.0	0.0	0.3	0.3	0.7	0.3	0.3	0.3	0.2	12	

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Group no.	4	4	4	4	4	4	4	4	4	4	4	4				
Animal no.	4213	4214	4215	4216	4217	4218	4219	4220	4221	4222	4223	4224	Mean	SD	N	+/-

Body temperature, °C	37.6	37.1	37.2	37.8	37.1	37.6	38.0	36.7	37.5	37.2	37.2	37.4	37.4	0.4	12
Forelimb grip strength, g	360	395	420	390	470	310	580	515	395	535	400	540	442.5	83.6	12
Positive geotropism	-	-	-	-	+	+	+	-	+	-	+	+			6/6
Wire maneuver	+	+	+	+	+	+	+	+	+	+	+	+			12/0
Stereotypy	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12
Toe pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12
Tail pinch	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12
Tremors	-	-	-	-	-	-	-	-	-	-	-	-			0/12
Extensor thrust	+	+	+	+	+	+	+	+	+	+	+	+			12/0
Limb rotation	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12
Activity	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12
Salivation	-	-	-	-	-	-	-	-	-	-	-	-			0/12
Startle response	+	+	+	+	+	+	+	+	+	+	+	+			12/0
Respiration	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12
Urination	3	3	3	3	3	3	3	3	3	3	3	3	3.0	0.0	12
Mouth breathing	-	-	-	-	-	-	-	-	-	-	-	-			0/12
Convulsions	-	-	-	-	-	-	-	-	-	-	-	-			0/12
Pineal response	+	+	+	+	+	+	+	+	+	+	+	+			12/0
Piloerection	-	-	-	-	-	-	-	-	-	-	-	-			0/12
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12
Lacrimation	-	-	-	-	-	-	-	-	-	-	-	-			0/12
Impaired gait	0	0	0	0	0	0	0	0	0	0	0	0	0.0	0.0	12
Pupil response	+	+	+	+	+	+	+	+	+	+	+	+			12/0
Hind-leg splay, cm	11.0	9.0	10.0	10.0	10.0	6.5	9.5	8.5	7.5	6.0	7.5	8.0	8.6	1.6	12
Righting reflex	0.0	0.0	0.0	0.3	0.3	0.7	0.3	0.3	1.0	0.0	0.7	0.0	0.3	0.3	12

Appendix G

Organ Weights Individual Data

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Epid. left g	Epid. right g	Heart Weight g	Kidney Wt left g
1	m	1101	28	0.022	0.022	1.99	0.59	0.62	1.29	1.31
		1102	28	0.021	0.023	1.86	0.75	0.72	1.23	1.19
		1103	28	0.022	0.021	1.83	0.59	0.57	1.29	1.08
		1104	28	0.023	0.023	1.84	0.52	0.52	0.99	1.12
		1105	28	0.020	0.019	1.95	0.78	0.80	1.15	1.09
		1106	28	0.022	0.022	1.86	0.79	0.79	1.18	1.21
		1107	28	0.024	0.024	1.92	0.64	0.68	1.42	1.21
		1108	28	0.022	0.028	1.86	0.60	0.59	1.20	1.59
		1109	28	0.022	0.019	1.86	0.67	0.68	1.28	1.30
		1110	28	0.020	0.018	1.84	0.52	0.51	1.19	1.16
		1111	28	0.020	0.017	1.90	0.59	0.54	1.12	1.16
		1112	28	0.024	0.022	1.84	0.65	0.65	1.22	1.29
2	m	2101	28	0.026	0.029	1.90	0.56	0.59	1.14	1.18
		2102	28	0.024	0.022	1.82	0.62	0.66	1.21	1.16
		2103	28	0.022	0.024	1.88	0.61	0.64	1.28	1.36
		2104	28	0.025	0.023	1.79	0.52	0.52	1.25	1.34
		2105	28	0.020	0.021	1.92	0.67	0.68	1.18	1.25
		2106	28	0.019	0.019	1.84	0.66	0.65	1.02	1.11
		2107	28	0.026	0.022	1.95	0.70	0.69	1.31	1.41
		2108	28	0.025	0.021	1.88	0.66	0.63	1.27	1.39
		2109	28	0.020	0.020	1.90	0.65	0.68	1.21	1.20
		2110	28	0.021	0.019	1.85	0.58	0.54	1.12	1.16
		2111	28	0.020	0.021	1.85	0.59	0.68	1.19	1.16
		2112	28	0.017	0.017	1.83	0.62	0.59	1.25	1.25
3	m	3101	28	0.027	0.026	1.90	0.61	0.62	1.24	1.52
		3102	28	0.025	0.022	1.87	0.80	0.80	1.21	1.30
		3103	28	0.023	0.020	1.94	0.60	0.60	1.23	1.37
		3104	28	0.024	0.019	1.83	0.63	0.64	1.20	1.26
		3105	28	0.022	0.022	1.84	0.59	0.59	1.06	1.30
		3106	28	0.019	0.024	1.89	0.65	0.64	1.26	1.19
		3107	28	0.023	0.023	1.94	0.69	0.66	1.30	1.33
		3108	28	0.029	0.025	1.87	0.66	0.62	1.23	1.25
		3109	28	0.025	0.023	1.84	0.53	0.53	1.16	1.39

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Epid. left g	Epid. right g	Heart Weight g	Kidney Wt left g
3	m	3110	28	0.018	0.025	1.93	0.72	0.74	1.28	1.33
		3111	28	0.022	0.025	1.97	0.69	0.73	1.36	1.34
		3112	28	0.023	0.021	1.96	0.67	0.63	1.21	1.27
4	m	4101	28	0.022	0.019	1.91	0.31	0.62	0.96	1.14
		4102	28	0.024	0.021	1.86	0.51	0.53	1.04	1.06
		4103	28	0.021	0.019	1.85	0.62	0.63	1.33	1.21
		4104	28	0.025	0.021	1.94	0.57	0.57	1.12	1.14
		4105	28	0.024	0.023	1.87	0.57	0.55	1.15	1.26
		4106	28	0.021	0.021	1.88	0.57	0.61	1.06	1.12
		4107	28	0.022	0.027	1.91	0.66	0.76	1.27	1.25
		4108	28	0.026	0.022	1.85	0.60	0.62	1.12	1.21
		4109	28	0.024	0.022	1.84	0.74	0.75	1.21	1.17
		4110	28	0.027	0.026	1.94	0.66	0.73	1.21	1.33
		4111	28	0.022	0.019	1.93	0.61	0.62	1.10	1.25
		4112	28	0.023	0.020	1.84	0.61	0.63	1.15	1.18

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Kidney Wt right g	Liver Weight g	Lung Weight g	Spleen Weight g	Testis Wt left g	Testis Wt right g	Thymus Weight g
1	m	1101	28	1.35	11.51	1.868	0.64	1.61	1.63	0.45
		1102	28	1.19	11.53	1.367	0.69	1.72	1.71	0.56
		1103	28	1.14	10.23	1.222	0.57	1.49	1.38	0.42
		1104	28	1.13	10.11	1.163	0.50	1.50	1.58	0.38
		1105	28	1.12	9.36	1.269	0.53	1.63	1.61	0.44
		1106	28	1.31	9.87	1.395	0.55	1.65	1.63	0.42
		1107	28	1.23	10.75	1.758	0.66	1.63	1.65	0.44
		1108	28	1.44	11.58	1.321	0.69	1.73	1.74	0.40
		1109	28	1.27	11.31	1.366	0.54	1.76	1.77	0.41
		1110	28	1.24	10.56	1.326	0.59	1.71	1.67	0.42
		1111	28	1.14	10.83	1.363	0.65	1.67	1.69	0.40
		1112	28	1.28	9.71	1.372	0.52	1.74	1.73	0.38
2	m	2101	28	1.27	11.28	1.460	0.74	1.38	1.44	0.38
		2102	28	1.20	9.64	1.327	0.58	1.59	1.53	0.40
		2103	28	1.33	12.30	1.533	0.68	1.79	1.69	0.57
		2104	28	1.36	11.12	1.443	0.60	1.33	1.34	0.51
		2105	28	1.33	11.29	1.411	0.65	1.55	1.59	0.44
		2106	28	1.14	9.20	1.280	0.59	1.59	1.64	0.53
		2107	28	1.44	11.52	1.477	0.72	1.87	1.77	0.49
		2108	28	1.34	10.79	1.417	0.62	1.67	1.63	0.43
		2109	28	1.24	9.28	1.254	0.55	1.73	1.69	0.48
		2110	28	1.21	10.22	1.250	0.64	1.54	1.64	0.47
		2111	28	1.25	10.58	1.323	0.69	1.60	1.52	0.38
		2112	28	1.30	11.65	1.359	0.60	1.60	1.57	0.33
3	m	3101	28	1.48	12.66	1.583	0.65	1.66	1.74	0.50
		3102	28	1.29	10.55	1.409	0.67	1.75	1.70	0.37
		3103	28	1.35	12.90	1.519	0.63	1.60	1.63	0.53
		3104	28	1.24	11.91	1.430	0.85	1.75	1.79	0.42
		3105	28	1.30	11.08	1.370	0.58	1.68	1.66	0.39
		3106	28	1.19	9.00	1.273	0.57	1.59	1.63	0.43
		3107	28	1.30	10.41	1.380	0.61	1.59	1.63	0.39
		3108	28	1.34	11.98	1.485	0.55	1.86	1.85	0.47
		3109	28	1.43	10.86	1.361	0.61	1.08	1.13	0.32

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Kidney Wt right g	Liver Weight g	Lung Weight g	Spleen Weight g	Testis Wt left g	Testis Wt right g	Thymus Weight g
3	m	3110	28	1.34	10.16	1.367	0.58	1.69	1.67	0.42
		3111	28	1.39	11.56	1.499	0.69	1.73	1.66	0.32
		3112	28	1.36	11.11	1.458	0.59	1.70	1.67	0.38
4	m	4101	28	1.21	11.06	1.426	0.62	0.44	1.84	0.51
		4102	28	1.12	10.64	1.690	0.57	1.60	1.56	0.42
		4103	28	1.23	11.36	1.798	0.61	1.70	1.75	0.49
		4104	28	1.14	12.19	1.722	0.61	1.65	1.65	0.32
		4105	28	1.27	11.18	1.518	0.67	1.80	1.76	0.41
		4106	28	1.17	11.10	1.490	0.59	1.53	1.56	0.51
		4107	28	1.29	10.61	1.557	0.59	1.76	1.80	0.47
		4108	28	1.31	10.49	1.450	0.52	1.70	1.65	0.43
		4109	28	1.23	9.32	1.507	0.56	1.62	1.68	0.24
		4110	28	1.31	9.99	1.707	0.60	1.69	1.64	0.37
		4111	28	1.32	8.88	1.330	0.69	1.75	1.71	0.44
		4112	28	1.23	9.48	1.404	0.53	1.62	1.63	0.39

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Heart Weight g	Kidney Wt left g	Kidney Wt right g	Liver Weight g
1	f	1201	41	0.028	0.029	1.75	0.86	1.00	1.00	8.20
		1202	45	0.025	0.021	1.68	0.77	0.83	0.90	10.23
		1203	43	0.027	0.025	1.79	0.83	0.82	0.90	10.33
		1204	43	0.024	0.027	1.69	0.75	0.81	0.81	7.75
		1205	42	0.025	0.022	1.68	0.83	0.80	0.83	9.24
		1206	41	0.025	0.024	1.72	1.01	0.83	0.93	10.68
		1207	41	0.028	0.024	1.69	0.80	0.91	0.93	9.30
		1208	44	0.031	0.033	1.77	0.83	0.87	0.98	10.46
		1209	46	0.028	0.026	1.68	0.94	0.86	0.90	9.46
		1210	44	0.033	0.030	1.69	0.79	0.89	0.91	11.02
		1211	43	0.029	0.026	1.67	0.75	0.86	0.87	9.25
		1212	42	0.029	0.029	1.78	0.92	1.01	1.11	12.71
		1213	28	0.022	0.023	1.74	0.85	0.79	0.80	5.71
		1214	28	0.023	0.020	1.74	0.73	0.67	0.69	5.29
		1215	28	0.024	0.024	1.71	0.82	0.72	0.70	5.34
		1216	28	0.026	0.024	1.76	0.82	0.80	0.82	6.84
		1217	28	0.024	0.020	1.66	0.78	0.70	0.80	5.69
		1218	28	0.022	0.023	1.64	0.78	0.72	0.78	5.35
		1219	28	0.026	0.027	1.76	0.81	0.86	0.91	6.10
		1220	28	0.026	0.025	1.68	0.84	0.68	0.70	5.61
		1221	28	0.026	0.028	1.46	0.83	0.84	0.87	5.95
		1222	28	0.025	0.024	1.76	0.75	0.74	0.81	5.46
		1223	28	0.035	0.025	1.68	0.85	0.85	0.87	7.03
		1224	28	0.020	0.022	1.71	0.75	0.71	0.71	5.69
2	f	2201	43	0.025	0.023	1.85	0.81	0.79	0.82	10.83
		2202	42	0.024	0.026	1.64	0.81	0.81	0.86	10.00
		2203	43	0.027	0.024	1.71	0.82	0.88	0.89	10.64
		2204	43	0.024	0.023	1.70	0.82	0.74	0.78	7.27
		2205	41	0.023	0.023	1.76	0.84	0.88	0.92	10.21
		2206	42	0.025	0.021	1.79	0.86	0.88	0.80	7.72
		2207	47	0.028	0.022	1.85	0.86	0.78	0.88	9.69
		2208	43	0.032	0.030	1.71	0.77	0.94	0.91	10.35
		2209	41	0.025	0.025	1.73	0.81	0.82	0.84	7.94

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Heart Weight g	Kidney Wt left g	Kidney Wt right g	Liver Weight g
2	f	2210	45	0.031	0.026	1.78	0.85	0.90	0.95	11.24
		2211	41	0.028	0.028	1.76	0.94	0.94	0.97	11.66
		2212	41	0.022	0.025	1.69	0.76	0.86	0.95	9.23
		2213	28	0.017	0.020	1.66	0.80	0.68	0.71	5.88
		2214	28	0.031	0.025	1.66	0.76	0.73	0.79	6.49
		2215	28	0.022	0.020	1.60	0.81	0.73	0.74	5.80
		2216	28	0.024	0.024	1.76	0.83	0.76	0.81	6.37
		2217	28	0.026	0.027	1.70	0.78	0.76	0.79	6.55
		2218	28	0.022	0.020	1.75	0.83	0.77	0.81	5.28
		2219	28	0.024	0.025	1.73	0.77	0.70	0.78	5.39
		2220	28	0.023	0.023	1.72	0.78	0.73	0.74	5.59
		2221	28	0.027	0.026	1.71	0.79	0.75	0.73	6.16
		2222	28	0.027	0.025	1.72	0.84	0.79	0.79	6.44
		2223	28	0.029	0.027	1.74	0.82	0.82	0.88	6.66
		2224	28	0.027	0.028	1.75	0.85	0.69	0.72	6.10
3	f	3201	42	0.024	0.028	1.72	0.85	0.86	0.89	9.93
		3202	45	0.032	0.027	1.75	0.87	0.92	0.93	10.45
		3203	42	0.023	0.024	1.71	1.10	0.96	0.97	11.83
		3204	41	0.032	0.027	1.67	1.06	2.27	1.72	10.92
		3205	45	0.036	0.029	1.70	0.88	0.91	0.94	10.61
		3206	45	0.033	0.038	1.74	0.85	1.03	1.02	11.71
		3207	44	0.036	0.029	1.72	0.80	0.92	0.92	11.11
		3208	41	0.026	0.026	1.72	0.83	0.90	0.91	9.89
		3209	43	0.024	0.024	1.76	0.85	0.92	0.91	8.81
		3210	42	0.027	0.024	1.75	0.80	0.82	0.96	9.81
		3211	42	0.031	0.027	1.79	0.90	0.88	0.87	10.22
		3212	42	0.029	0.026	1.77	0.82	0.90	0.87	10.75
		3213	28	0.028	0.027	1.70	0.74	0.82	0.87	6.28
		3214	28	0.028	0.023	1.72	0.81	0.80	0.82	6.37
		3215	28	0.026	0.026	1.69	0.89	0.73	0.75	5.66
		3216	28	0.025	0.028	1.71	0.81	0.70	0.65	5.76
		3217	28	0.029	0.024	1.72	0.76	0.77	0.79	6.44
		3218	28	0.022	0.026	1.65	1.46	0.69	0.73	6.14

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Adrenal Wt left g	Adrenal Wt right g	Brain Weight g	Heart Weight g	Kidney Wt left g	Kidney Wt right g	Liver Weight g
3	f	3219	28	0.022	0.024	1.73	0.82	0.72	0.74	6.34
		3220	28	0.023	0.021	1.81	0.75	0.74	0.77	6.58
		3221	28	0.030	0.025	1.74	0.84	0.76	0.75	5.91
		3222	28	0.027	0.027	1.65	0.76	0.75	0.72	6.35
		3223	28	0.025	0.026	1.77	0.84	0.73	0.79	5.70
		3224	28	0.028	0.028	1.74	0.81	0.79	0.74	6.36
4	f	4201	44	0.025	0.022	1.77	0.91	0.85	0.92	10.97
		4202	44	0.027	0.027	1.73	0.86	0.83	0.89	10.36
		4203	46	0.037	0.026	1.65	0.86	0.93	0.99	11.96
		4204	46	0.024	0.029	1.77	0.84	0.98	0.97	10.00
		4205	41	0.032	0.031	1.77	0.91	0.93	0.93	9.15
		4206	44	0.027	0.024	1.65	0.91	0.84	0.86	10.14
		4207	42	0.040	0.035	1.67	0.83	0.86	0.83	10.97
		4208	45	0.030	0.032	1.75	0.83	0.84	0.88	9.30
		4209	43	0.030	0.025	1.71	0.81	0.82	0.85	9.78
		4210	42	0.032	0.028	1.67	0.85	0.89	0.89	11.47
		4211	43	0.032	0.028	1.67	0.82	0.86	0.92	10.72
		4212	45	0.026	0.023	1.73	1.03	0.88	0.89	11.02
		4213	28	0.026	0.029	1.76	0.85	0.78	0.79	6.23
		4214	28	0.026	0.021	1.70	0.84	0.76	0.74	5.95
		4215	28	0.031	0.029	1.77	0.82	0.67	0.69	6.03
		4216	28	0.027	0.026	1.78	0.84	0.80	0.86	7.76
		4217	28	0.023	0.024	1.86	0.78	0.79	0.79	6.18
		4218	28	0.024	0.018	1.73	0.87	0.82	0.84	7.39
		4219	28	0.022	0.023	1.76	0.82	0.75	0.80	5.87
		4220	28	0.021	0.019	1.82	0.84	0.70	0.78	6.12
		4221	28	0.022	0.021	1.77	0.84	0.78	0.78	6.60
		4222	28	0.027	0.027	1.81	0.96	0.82	0.84	6.24
		4223	28	0.022	0.025	1.79	0.83	0.67	0.70	5.68
		4224	28	0.034	0.035	1.70	0.86	0.87	0.84	6.51

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Lung Weight g	Ovary Wt left g	Ovary Wt right g	Spleen Weight g	Thymus Weight g	Uterus Weight g
1	f	1201	41	0.999	0.047	0.043	0.46	0.25	1.08
		1202	45	0.936	0.050	0.055	0.47	0.19	0.78
		1203	43	1.005	0.056	0.053	0.42	0.20	0.78
		1204	43	0.938	0.059	0.054	0.45	0.24	1.20
		1205	42	1.009	0.031	0.053	0.39	0.24	0.76
		1206	41	1.082	0.050	0.044	0.45	0.22	0.75
		1207	41	0.912	0.052	0.055	0.42	0.19	0.82
		1208	44	1.029	0.059	0.067	0.48	0.17	0.66
		1209	46	1.073	0.043	0.047	0.56	0.26	0.79
		1210	44	1.011	0.056	0.046	0.46	0.16	0.55
		1211	43	0.982	0.045	0.041	0.42	0.16	0.57
		1212	42	1.085	0.054	0.045	0.55	0.28	0.88
		1213	28	0.937	0.037	0.037	0.37	0.30	0.63
		1214	28	0.881	0.042	0.041	0.39	0.31	1.80
		1215	28	0.900	0.038	0.040	0.38	0.32	0.58
		1216	28	1.004	0.041	0.049	0.48	0.45	1.16
		1217	28	0.918	0.047	0.049	0.45	0.33	0.52
		1218	28	0.917	0.044	0.044	0.38	0.32	0.55
		1219	28	1.025	0.052	0.047	0.46	0.25	0.61
		1220	28	0.952	0.039	0.043	0.40	0.32	0.96
		1221	28	0.884	0.042	0.045	0.38	0.36	0.49
		1222	28	1.019	0.056	0.053	0.47	0.28	0.59
		1223	28	1.042	0.041	0.064	0.51	0.43	0.65
		1224	28	0.951	0.044	0.041	0.46	0.35	0.56
2	f	2201	43	0.974	0.041	0.051	0.58	0.19	0.76
		2202	42	0.923	0.061	0.048	0.50	0.18	0.82
		2203	43	1.016	0.055	0.051	0.44	0.28	0.69
		2204	43	1.085	0.038	0.045	0.43	0.26	0.99
		2205	41	0.991	0.047	0.052	0.44	0.17	0.93
		2206	42	1.072	0.046	0.039	0.42	0.32	1.20
		2207	47	0.999	0.052	0.041	0.56	0.22	0.75
		2208	43	1.054	0.057	0.040	0.48	0.19	0.80
		2209	41	1.001	0.047	0.055	0.42	0.26	0.74

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Lung Weight g	Ovary Wt left g	Ovary Wt right g	Spleen Weight g	Thymus Weight g	Uterus Weight g
2	f	2210	45	1.090	0.046	0.057	0.47	0.22	0.72
		2211	41	1.074	0.043	0.057	0.59	0.32	0.88
		2212	41	0.972	0.046	0.051	0.42	0.12	0.59
		2213	28	1.005	0.037	0.042	0.42	0.33	0.59
		2214	28	0.999	0.056	0.037	0.45	0.43	0.49
		2215	28	1.009	0.048	0.040	0.41	0.35	0.56
		2216	28	1.065	0.038	0.038	0.40	0.38	0.57
		2217	28	0.970	0.046	0.053	0.46	0.34	0.58
		2218	28	0.995	0.037	0.032	0.35	0.36	0.67
		2219	28	0.954	0.040	0.042	0.37	0.33	0.48
		2220	28	1.046	0.048	0.044	0.44	0.33	1.07
		2221	28	1.033	0.051	0.043	0.44	0.30	1.49
		2222	28	1.076	0.055	0.052	0.40	0.30	0.77
		2223	28	1.037	0.061	0.057	0.45	0.32	0.69
		2224	28	0.952	0.034	0.049	0.39	0.28	0.63
3	f	3201	42	1.023	0.042	0.050	0.44	0.21	0.73
		3202	45	1.153	0.052	0.054	0.47	0.20	0.81
		3203	42	1.107	0.053	0.048	0.70	0.31	0.80
		3204	41	1.086	0.050	0.055	0.58	0.16	0.84
		3205	45	0.981	0.051	0.057	0.55	0.20	0.59
		3206	45	1.154	0.043	0.068	0.52	0.15	0.60
		3207	44	1.064	0.053	0.068	0.52	0.19	0.71
		3208	41	1.063	0.053	0.047	0.58	0.24	0.80
		3209	43	1.191	0.053	0.043	0.42	0.32	0.70
		3210	42	1.040	0.046	0.045	0.44	0.21	0.71
		3211	42	1.064	0.054	0.059	0.59	0.21	0.70
		3212	42	1.131	0.057	0.037	0.44	0.19	0.78
		3213	28	1.056	0.046	0.034	0.44	0.30	0.61
		3214	28	1.081	0.055	0.059	0.41	0.39	0.93
		3215	28	1.066	0.050	0.043	0.40	0.25	0.69
		3216	28	0.980	0.041	0.036	0.45	0.22	1.55
		3217	28	1.085	0.051	0.052	0.50	0.36	0.54
		3218	28	1.245	0.038	0.041	0.49	0.41	0.54

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Lung Weight g	Ovary Wt left g	Ovary Wt right g	Spleen Weight g	Thymus Weight g	Uterus Weight g
3	f	3219	28	1.018	0.043	0.041	0.43	0.37	0.53
		3220	28	1.069	0.043	0.042	0.49	0.30	0.52
		3221	28	1.079	0.044	0.047	0.41	0.33	0.55
		3222	28	1.052	0.048	0.049	0.41	0.35	0.65
		3223	28	1.090	0.037	0.034	0.40	0.31	0.57
		3224	28	1.055	0.037	0.043	0.50	0.34	1.15
4	f	4201	44	1.355	0.040	0.056	0.51	0.24	0.72
		4202	44	1.171	0.060	0.040	0.52	0.16	0.92
		4203	46	1.231	0.036	0.054	0.54	0.16	0.60
		4204	46	1.172	0.050	0.059	0.62	0.21	0.66
		4205	41	1.228	0.041	0.055	0.50	0.39	0.65
		4206	44	1.138	0.054	0.039	0.52	0.31	0.52
		4207	42	1.206	0.053	0.063	0.52	0.16	21.73
		4208	45	1.222	0.053	0.036	0.57	0.21	0.54
		4209	43	1.148	0.044	0.040	0.39	0.20	0.79
		4210	42	1.153	0.060	0.034	0.52	0.19	0.71
		4211	43	1.108	0.045	0.060	0.48	0.19	0.60
		4212	45	1.206	0.051	0.051	0.46	0.18	0.92
		4213	28	1.189	0.052	0.044	0.45	0.43	0.60
		4214	28	1.198	0.035	0.033	0.46	0.33	0.53
		4215	28	1.184	0.039	0.034	0.40	0.44	1.56
		4216	28	1.094	0.050	0.048	0.57	0.54	1.05
		4217	28	1.098	0.041	0.039	0.43	0.36	0.53
		4218	28	1.272	0.050	0.041	0.59	0.41	0.49
		4219	28	1.129	0.038	0.049	0.45	0.32	0.59
		4220	28	1.200	0.054	0.050	0.42	0.30	0.65
		4221	28	1.217	0.045	0.041	0.54	0.33	0.87
		4222	28	1.171	0.043	0.035	0.44	0.26	0.60
		4223	28	1.242	0.038	0.048	0.49	0.44	0.61
		4224	28	1.231	0.044	0.051	0.45	0.34	0.57

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

Appendix H

Organ Weight Ratios / Body Weight

Individual Data

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Heart /Bodywt g/kg
1	m	1101	28	322.0	0.06832	0.06832	4.0683	4.1925	35.7453	4.0062
		1102	28	339.0	0.06195	0.06785	3.5103	3.5103	34.0118	3.6283
		1103	28	290.2	0.07581	0.07236	3.7216	3.9283	35.2516	4.4452
		1104	28	283.0	0.08127	0.08127	3.9576	3.9929	35.7244	3.4982
		1105	28	302.7	0.06607	0.06277	3.6009	3.7000	30.9217	3.7991
		1106	28	319.7	0.06881	0.06881	3.7848	4.0976	30.8727	3.6910
		1107	28	345.6	0.06944	0.06944	3.5012	3.5590	31.1053	4.1088
		1108	28	340.5	0.06461	0.08223	4.6696	4.2291	34.0088	3.5242
		1109	28	324.5	0.06780	0.05855	4.0062	3.9137	34.8536	3.9445
		1110	28	313.8	0.06373	0.05736	3.6966	3.9516	33.6520	3.7922
		1111	28	312.0	0.06410	0.05449	3.7179	3.6538	34.7115	3.5897
2	m	2101	28	314.9	0.07621	0.06986	4.0965	4.0648	30.8352	3.8742
		2102	28	305.2	0.08519	0.09502	3.8663	4.1612	36.9594	3.7353
		2103	28	317.8	0.07552	0.06923	3.6501	3.7760	30.3335	3.8074
		2104	28	326.1	0.06746	0.07360	4.1705	4.0785	37.7185	3.9252
		2105	28	316.4	0.07901	0.07269	4.2351	4.2984	35.1454	3.9507
		2106	28	325.2	0.06150	0.06458	3.8438	4.0898	34.7171	3.6285
		2107	28	293.3	0.06478	0.06478	3.7845	3.8868	31.3672	3.4777
		2108	28	354.1	0.07343	0.06213	3.9819	4.0666	32.5332	3.6995
		2109	28	337.4	0.07410	0.06224	4.1197	3.9715	31.9798	3.7641
		2110	28	297.0	0.06734	0.06734	4.0404	4.1751	31.2458	4.0741
		2111	28	307.7	0.06825	0.06175	3.7699	3.9324	33.2142	3.6399
3	m	3101	28	326.8	0.06120	0.06426	3.5496	3.8250	32.3745	3.6414
		3102	28	318.5	0.05338	0.05338	3.9246	4.0816	36.5777	3.9246
		3103	28	343.3	0.07865	0.07574	4.4276	4.3111	36.8774	3.6120
		3104	28	318.1	0.07859	0.06916	4.0868	4.0553	33.1657	3.8038
		3105	28	337.4	0.06817	0.05928	4.0605	4.0012	38.2336	3.6455
		3106	28	310.2	0.07737	0.06125	4.0619	3.9974	38.3946	3.8685
		3107	28	317.8	0.06923	0.06923	4.0906	4.0906	34.8647	3.3354
		3108	28	308.6	0.06157	0.07777	3.8561	3.8561	29.1640	4.0830
		3109	28	301.7	0.07623	0.07623	4.4084	4.3089	34.5045	4.3089
		3110	28	324.4	0.08940	0.07707	3.8533	4.1307	36.9297	3.7916
		3111	28	319.5	0.07825	0.07199	4.3505	4.4757	33.9906	3.6307

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Heart /Bodywt g/kg
3	m	3110	28	323.6	0.05562	0.07726	4.1100	4.1409	31.3968	3.9555
		3111	28	351.3	0.06262	0.07116	3.8144	3.9567	32.9063	3.8713
		3112	28	319.9	0.07190	0.06565	3.9700	4.2513	34.7296	3.7824
4	m	4101	28	287.2	0.07660	0.06616	3.9694	4.2131	38.5097	3.3426
		4102	28	288.1	0.08330	0.07289	3.6793	3.8875	36.9316	3.6099
		4103	28	316.9	0.06627	0.05996	3.8182	3.8814	35.8473	4.1969
		4104	28	301.2	0.08300	0.06972	3.7849	3.7849	40.4714	3.7185
		4105	28	310.5	0.07729	0.07407	4.0580	4.0902	36.0064	3.7037
		4106	28	295.8	0.07099	0.07099	3.7863	3.9554	37.5254	3.5835
		4107	28	318.9	0.06899	0.08467	3.9197	4.0452	33.2706	3.9824
		4108	28	311.2	0.08355	0.07069	3.8882	4.2095	33.7082	3.5990
		4109	28	296.3	0.08100	0.07425	3.9487	4.1512	31.4546	4.0837
		4110	28	313.2	0.08621	0.08301	4.2465	4.1826	31.8966	3.8633
		4111	28	291.1	0.07558	0.06527	4.2941	4.5345	30.5050	3.7788
		4112	28	299.1	0.07690	0.06687	3.9452	4.1123	31.6951	3.8449

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Epidy. /Bodywt g/kg	R.Epidy. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
1	m	1101	28	1.9876	5.8012	1.3975	1.8323	1.9255	5.0000	5.0621
		1102	28	2.0354	4.0324	1.6519	2.2124	2.1239	5.0737	5.0442
		1103	28	1.9642	4.2109	1.4473	2.0331	1.9642	5.1344	4.7553
		1104	28	1.7668	4.1095	1.3428	1.8375	1.8375	5.3004	5.5830
		1105	28	1.7509	4.1923	1.4536	2.5768	2.6429	5.3849	5.3188
		1106	28	1.7204	4.3635	1.3137	2.4711	2.4711	5.1611	5.0985
		1107	28	1.9097	5.0868	1.2731	1.8519	1.9676	4.7164	4.7743
		1108	28	2.0264	3.8796	1.1747	1.7621	1.7327	5.0808	5.1101
		1109	28	1.6641	4.2096	1.2635	2.0647	2.0955	5.4237	5.4545
		1110	28	1.8802	4.2256	1.3384	1.6571	1.6252	5.4493	5.3219
		1111	28	2.0833	4.3686	1.2821	1.8910	1.7308	5.3526	5.4167
		1112	28	1.6513	4.3569	1.2067	2.0641	2.0641	5.5256	5.4938
2	m	2101	28	2.4246	4.7837	1.2451	1.8349	1.9332	4.5216	4.7182
		2102	28	1.8250	4.1756	1.2587	1.9509	2.0768	5.0031	4.8143
		2103	28	2.0852	4.7010	1.7479	1.8706	1.9626	5.4891	5.1825
		2104	28	1.8963	4.5607	1.6119	1.6435	1.6435	4.2035	4.2351
		2105	28	1.9988	4.3389	1.3530	2.0603	2.0910	4.7663	4.8893
		2106	28	2.0116	4.3641	1.8070	2.2503	2.2162	5.4211	5.5915
		2107	28	2.0333	4.1711	1.3838	1.9768	1.9486	5.2810	4.9986
		2108	28	1.8376	4.1998	1.2745	1.9561	1.8672	4.9496	4.8311
		2109	28	1.8519	4.2222	1.6162	2.1886	2.2896	5.8249	5.6902
		2110	28	2.0799	4.0624	1.5275	1.8850	1.7550	5.0049	5.3299
		2111	28	2.1114	4.0483	1.1628	1.8054	2.0808	4.8960	4.6512
		2112	28	1.8838	4.2669	1.0361	1.9466	1.8524	5.0235	4.9294
3	m	3101	28	1.8934	4.6111	1.4565	1.7769	1.8060	4.8354	5.0685
		3102	28	2.1063	4.4294	1.1632	2.5149	2.5149	5.5014	5.3442
		3103	28	1.8672	4.5021	1.5708	1.7783	1.7783	4.7421	4.8311
		3104	28	2.7402	4.6099	1.3540	2.0309	2.0632	5.6415	5.7705
		3105	28	1.8250	4.3109	1.2272	1.8565	1.8565	5.2863	5.2234
		3106	28	1.8471	4.1251	1.3934	2.1063	2.0739	5.1523	5.2819
		3107	28	2.0219	4.5741	1.2927	2.2870	2.1876	5.2701	5.4027
		3108	28	1.6954	4.5777	1.4488	2.0345	1.9112	5.7337	5.7028
		3109	28	1.9092	4.2598	1.0016	1.6588	1.6588	3.3803	3.5368

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Epidy. /Bodywt g/kg	R.Epidy. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
3	m	3110	28	1.7923	4.2244	1.2979	2.2250	2.2868	5.2225	5.1607
		3111	28	1.9641	4.2670	0.9109	1.9641	2.0780	4.9246	4.7253
		3112	28	1.8443	4.5577	1.1879	2.0944	1.9694	5.3142	5.2204
4	m	4101	28	2.1588	4.9652	1.7758	1.0794	2.1588	1.5320	6.4067
		4102	28	1.9785	5.8660	1.4578	1.7702	1.8396	5.5536	5.4148
		4103	28	1.9249	5.6737	1.5462	1.9565	1.9880	5.3645	5.5222
		4104	28	2.0252	5.7171	1.0624	1.8924	1.8924	5.4781	5.4781
		4105	28	2.1578	4.8889	1.3205	1.8357	1.7713	5.7971	5.6683
		4106	28	1.9946	5.0372	1.7241	1.9270	2.0622	5.1724	5.2738
		4107	28	1.8501	4.8824	1.4738	2.0696	2.3832	5.5190	5.6444
		4108	28	1.6710	4.6594	1.3817	1.9280	1.9923	5.4627	5.3021
		4109	28	1.8900	5.0861	0.8100	2.4975	2.5312	5.4674	5.6699
		4110	28	1.9157	5.4502	1.1814	2.1073	2.3308	5.3959	5.2363
		4111	28	2.3703	4.5689	1.5115	2.0955	2.1299	6.0117	5.8743
		4112	28	1.7720	4.6941	1.3039	2.0395	2.1063	5.4162	5.4497

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Heart /Bodywt g/kg
1	f	1201	41	217.0	0.12903	0.13364	4.6083	4.6083	37.7880	3.9631
		1202	45	213.0	0.11737	0.09859	3.8967	4.2254	48.0282	3.6150
		1203	43	232.1	0.11633	0.10771	3.5330	3.8776	44.5067	3.5760
		1204	43	204.0	0.11765	0.13235	3.9706	3.9706	37.9902	3.6765
		1205	42	217.4	0.11500	0.10120	3.6799	3.8178	42.5023	3.8178
		1206	41	240.1	0.10412	0.09996	3.4569	3.8734	44.4815	4.2066
		1207	41	222.2	0.12601	0.10801	4.0954	4.1854	41.8542	3.6004
		1208	44	241.7	0.12826	0.13653	3.5995	4.0546	43.2768	3.4340
		1209	46	225.8	0.12400	0.11515	3.8087	3.9858	41.8955	4.1630
		1210	44	221.0	0.14932	0.13575	4.0271	4.1176	49.8643	3.5747
		1211	43	221.7	0.13081	0.11728	3.8791	3.9242	41.7230	3.3829
		1212	42	259.2	0.11188	0.11188	3.8966	4.2824	49.0355	3.5494
		1213	28	182.1	0.12081	0.12630	4.3383	4.3932	31.3564	4.6678
		1214	28	177.2	0.12980	0.11287	3.7810	3.8939	29.8533	4.1196
		1215	28	177.9	0.13491	0.13491	4.0472	3.9348	30.0169	4.6093
		1216	28	196.1	0.13259	0.12239	4.0796	4.1815	34.8802	4.1815
		1217	28	184.4	0.13015	0.10846	3.7961	4.3384	30.8568	4.2299
		1218	28	188.9	0.11646	0.12176	3.8115	4.1292	28.3219	4.1292
		1219	28	194.7	0.13354	0.13867	4.4171	4.6739	31.3303	4.1602
		1220	28	177.6	0.14640	0.14077	3.8288	3.9414	31.5878	4.7297
		1221	28	205.1	0.12677	0.13652	4.0956	4.2418	29.0102	4.0468
		1222	28	191.1	0.13082	0.12559	3.8723	4.2386	28.5714	3.9246
		1223	28	211.0	0.16588	0.11848	4.0284	4.1232	33.3175	4.0284
		1224	28	192.0	0.10417	0.11458	3.6979	3.6979	29.6354	3.9063
2	f	2201	43	226.4	0.11042	0.10159	3.4894	3.6219	47.8357	3.5777
		2202	42	225.4	0.10648	0.11535	3.5936	3.8154	44.3656	3.5936
		2203	43	246.5	0.10953	0.09736	3.5700	3.6105	43.1643	3.3266
		2204	43	205.3	0.11690	0.11203	3.6045	3.7993	35.4116	3.9942
		2205	41	229.6	0.10017	0.10017	3.8328	4.0070	44.4686	3.6585
		2206	42	212.3	0.11776	0.09892	4.1451	3.7683	36.3636	4.0509
		2207	47	226.3	0.12373	0.09722	3.4468	3.8886	42.8193	3.8003
		2208	43	218.2	0.14665	0.13749	4.3080	4.1705	47.4335	3.5289
		2209	41	209.9	0.11910	0.11910	3.9066	4.0019	37.8275	3.8590

Group 1 - Control Clean air Group 2 - 30 mg/m3
Group 3 - 100 mg/m3 Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Heart /Bodywt g/kg
2	f	2210	45	235.7	0.13152	0.11031	3.8184	4.0305	47.6877	3.6063
		2211	41	252.1	0.11107	0.11107	3.7287	3.8477	46.2515	3.7287
		2212	41	222.0	0.09910	0.11261	3.8739	4.2793	41.5766	3.4234
		2213	28	186.8	0.09101	0.10707	3.6403	3.8009	31.4775	4.2827
		2214	28	187.3	0.16551	0.13348	3.8975	4.2178	34.6503	4.0577
		2215	28	189.1	0.11634	0.10576	3.8604	3.9133	30.6716	4.2834
		2216	28	192.8	0.12448	0.12448	3.9419	4.2012	33.0394	4.3050
		2217	28	201.0	0.12935	0.13433	3.7811	3.9303	32.5871	3.8806
		2218	28	192.8	0.11411	0.10373	3.9938	4.2012	27.3859	4.3050
		2219	28	184.8	0.12987	0.13528	3.7879	4.2208	29.1667	4.1667
		2220	28	192.2	0.11967	0.11967	3.7981	3.8502	29.0843	4.0583
		2221	28	189.6	0.14241	0.13713	3.9557	3.8502	32.4895	4.1667
		2222	28	195.7	0.13797	0.12775	4.0368	4.0368	32.9075	4.2923
		2223	28	200.9	0.14435	0.13440	4.0816	4.3803	33.1508	4.0816
		2224	28	191.2	0.14121	0.14644	3.6088	3.7657	31.9038	4.4456
3	f	3201	42	223.0	0.10762	0.12556	3.8565	3.9910	44.5291	3.8117
		3202	45	239.1	0.13384	0.11292	3.8478	3.8896	43.7056	3.6386
		3203	42	260.0	0.08846	0.09231	3.6923	3.7308	45.5000	4.2308
		3204	41	234.7	0.13634	0.11504	9.6719	7.3285	46.5275	4.5164
		3205	45	228.4	0.15762	0.12697	3.9842	4.1156	46.4536	3.8529
		3206	45	251.9	0.13100	0.15085	4.0889	4.0492	46.4867	3.3744
		3207	44	256.3	0.14046	0.11315	3.5895	3.5895	43.3476	3.1213
		3208	41	229.4	0.11334	0.11334	3.9233	3.9669	43.1125	3.6181
		3209	43	231.5	0.10367	0.10367	3.9741	3.9309	38.0562	3.6717
		3210	42	225.6	0.11968	0.10638	3.6348	4.2553	43.4840	3.5461
		3211	42	235.8	0.13147	0.11450	3.7320	3.6896	43.3418	3.8168
		3212	42	234.7	0.12356	0.11078	3.8347	3.7069	45.8032	3.4938
		3213	28	181.2	0.15453	0.14901	4.5254	4.8013	34.6578	4.0839
		3214	28	193.3	0.14485	0.11899	4.1386	4.2421	32.9540	4.1904
		3215	28	185.0	0.14054	0.14054	3.9459	4.0541	30.5946	4.8108
		3216	28	182.2	0.13721	0.15368	3.8419	3.5675	31.6136	4.4457
		3217	28	201.5	0.14392	0.11911	3.8213	3.9206	31.9603	3.7717
		3218	28	190.1	0.11573	0.13677	3.6297	3.8401	32.2988	7.6802

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Terminal Bweight g	L.Adren. /Bodywt g/kg	R.Adren. /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Heart /Bodywt g/kg
3	f	3219	28	199.8	0.11011	0.12012	3.6036	3.7037	31.7317	4.1041
		3220	28	195.3	0.11777	0.10753	3.7890	3.9427	33.6918	3.8402
		3221	28	191.1	0.15699	0.13082	3.9770	3.9246	30.9262	4.3956
		3222	28	198.5	0.13602	0.13602	3.7783	3.6272	31.9899	3.8287
		3223	28	191.0	0.13089	0.13613	3.8220	4.1361	29.8429	4.3979
4	f	3224	28	189.3	0.14791	0.14791	4.1733	3.9091	33.5975	4.2789
		4201	44	233.0	0.10730	0.09442	3.6481	3.9485	47.0815	3.9056
		4202	44	231.7	0.11653	0.11653	3.5822	3.8412	44.7130	3.7117
		4203	46	234.5	0.15778	0.11087	3.9659	4.2217	51.0021	3.6674
		4204	46	226.5	0.10596	0.12804	4.3267	4.2826	44.1501	3.7086
		4205	41	239.7	0.13350	0.12933	3.8798	3.8798	38.1727	3.7964
		4206	44	232.0	0.11638	0.10345	3.6207	3.7069	43.7069	3.9224
		4207	42	242.7	0.16481	0.14421	3.5435	3.4199	45.1998	3.4199
		4208	45	218.7	0.13717	0.14632	3.8409	4.0238	42.5240	3.7952
		4209	43	231.3	0.12970	0.10808	3.5452	3.6749	42.2827	3.5019
		4210	42	231.3	0.13835	0.12105	3.8478	3.8478	49.5893	3.6749
		4211	43	228.4	0.14011	0.12259	3.7653	4.0280	46.9352	3.5902
		4212	45	240.0	0.10833	0.09583	3.6667	3.7083	45.9167	4.2917
		4213	28	200.4	0.12974	0.14471	3.8922	3.9421	31.0878	4.2415
		4214	28	186.9	0.13911	0.11236	4.0663	3.9593	31.8352	4.4944
		4215	28	191.0	0.16230	0.15183	3.5079	3.6126	31.5707	4.2932
		4216	28	205.9	0.13113	0.12627	3.8854	4.1768	37.6882	4.0797
		4217	28	195.0	0.11795	0.12308	4.0513	4.0513	31.6923	4.0000
		4218	28	218.1	0.11004	0.08253	3.7597	3.8514	33.8835	3.9890
		4219	28	199.0	0.11055	0.11558	3.7688	4.0201	29.4975	4.1206
		4220	28	208.5	0.10072	0.09113	3.3573	3.7410	29.3525	4.0288
		4221	28	199.6	0.11022	0.10521	3.9078	3.9078	33.0661	4.2084
		4222	28	196.8	0.13720	0.13720	4.1667	4.2683	31.7073	4.8780
		4223	28	206.0	0.10680	0.12136	3.2524	3.3981	27.5728	4.0291
		4224	28	206.5	0.16465	0.16949	4.2131	4.0678	31.5254	4.1646

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg	Uterus /Bodywt g/kg
1	f	1201	41	2.1198	4.6037	1.1521	0.21659	0.19816	4.9770
		1202	45	2.2066	4.3944	0.8920	0.23474	0.25822	3.6620
		1203	43	1.8096	4.3300	0.8617	0.24128	0.22835	3.3606
		1204	43	2.2059	4.5980	1.1765	0.28922	0.26471	5.8824
		1205	42	1.7939	4.6412	1.1040	0.14259	0.24379	3.4959
		1206	41	1.8742	4.5065	0.9163	0.20825	0.18326	3.1237
		1207	41	1.8902	4.1044	0.8551	0.23402	0.24752	3.6904
		1208	44	1.9859	4.2573	0.7034	0.24410	0.27720	2.7307
		1209	46	2.4801	4.7520	1.1515	0.19043	0.20815	3.4987
		1210	44	2.0814	4.5747	0.7240	0.25339	0.20814	2.4887
		1211	43	1.8945	4.4294	0.7217	0.20298	0.18493	2.5710
		1212	42	2.1219	4.1860	1.0802	0.20833	0.17361	3.3951
		1213	28	2.0319	5.1455	1.6474	0.20319	0.20319	3.4596
		1214	28	2.2009	4.9718	1.7494	0.23702	0.23138	10.1580
		1215	28	2.1360	5.0590	1.7988	0.21360	0.22485	3.2603
		1216	28	2.4477	5.1198	2.2947	0.20908	0.24987	5.9153
		1217	28	2.4403	4.9783	1.7896	0.25488	0.26573	2.8200
		1218	28	2.0116	4.8544	1.6940	0.23293	0.23293	2.9116
		1219	28	2.3626	5.2645	1.2840	0.26708	0.24140	3.1330
		1220	28	2.2523	5.3604	1.8018	0.21959	0.24212	5.4054
		1221	28	1.8528	4.3101	1.7552	0.20478	0.21941	2.3891
		1222	28	2.4594	5.3323	1.4652	0.29304	0.27734	3.0874
		1223	28	2.4171	4.9384	2.0379	0.19431	0.30332	3.0806
		1224	28	2.3958	4.9531	1.8229	0.22917	0.21354	2.9167
2	f	2201	43	2.5618	4.3021	0.8392	0.18110	0.22527	3.3569
		2202	42	2.2183	4.0949	0.7986	0.27063	0.21295	3.6380
		2203	43	1.7850	4.1217	1.1359	0.22312	0.20690	2.7992
		2204	43	2.0945	5.2849	1.2664	0.18509	0.21919	4.8222
		2205	41	1.9164	4.3162	0.7404	0.20470	0.22648	4.0505
		2206	42	1.9783	5.0495	1.5073	0.21667	0.18370	5.6524
		2207	47	2.4746	4.4145	0.9722	0.22978	0.18118	3.3142
		2208	43	2.1998	4.8304	0.8708	0.26123	0.18332	3.6664
		2209	41	2.0010	4.7689	1.2387	0.22392	0.26203	3.5255

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

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Provantis8 - Production

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg	Uterus /Bodywt g/kg
2	f	2210	45	1.9941	4.6245	0.9334	0.19516	0.24183	3.0547
		2211	41	2.3403	4.2602	1.2693	0.17057	0.22610	3.4907
		2212	41	1.8919	4.3784	0.5405	0.20721	0.22973	2.6577
		2213	28	2.2484	5.3801	1.7666	0.19807	0.22484	3.1585
		2214	28	2.4026	5.3337	2.2958	0.29899	0.19754	2.6161
		2215	28	2.1682	5.3358	1.8509	0.25383	0.21153	2.9614
		2216	28	2.0747	5.5239	1.9710	0.19710	0.19710	2.9564
		2217	28	2.2886	4.8259	1.6915	0.22886	0.26368	2.8856
		2218	28	1.8154	5.1608	1.8672	0.19191	0.16598	3.4751
		2219	28	2.0022	5.1623	1.7857	0.21645	0.22727	2.5974
		2220	28	2.2893	5.4422	1.7170	0.24974	0.22893	5.5671
		2221	28	2.3207	5.4483	1.5823	0.26899	0.22679	7.8586
		2222	28	2.0439	5.4982	1.5330	0.28104	0.26571	3.9346
		2223	28	2.2399	5.1618	1.5928	0.30363	0.28372	3.4345
		2224	28	2.0397	4.9791	1.4644	0.17782	0.25628	3.2950
3	f	3201	42	1.9731	4.5874	0.9417	0.18834	0.22422	3.2735
		3202	45	1.9657	4.8223	0.8365	0.21748	0.22585	3.3877
		3203	42	2.6923	4.2577	1.1923	0.20385	0.18462	3.0769
		3204	41	2.4712	4.6272	0.6817	0.21304	0.23434	3.5790
		3205	45	2.4081	4.2951	0.8757	0.22329	0.24956	2.5832
		3206	45	2.0643	4.5812	0.5955	0.17070	0.26995	2.3819
		3207	44	2.0289	4.1514	0.7413	0.20679	0.26531	2.7702
		3208	41	2.5283	4.6338	1.0462	0.23104	0.20488	3.4874
		3209	43	1.8143	5.1447	1.3823	0.22894	0.18575	3.0238
		3210	42	1.9504	4.6099	0.9309	0.20390	0.19947	3.1472
		3211	42	2.5021	4.5123	0.8906	0.22901	0.25021	2.9686
		3212	42	1.8747	4.8189	0.8095	0.24286	0.15765	3.3234
		3213	28	2.4283	5.8278	1.6556	0.25386	0.18764	3.3664
		3214	28	2.1211	5.5923	2.0176	0.28453	0.30523	4.8112
		3215	28	2.1622	5.7622	1.3514	0.27027	0.23243	3.7297
		3216	28	2.4698	5.3787	1.2075	0.22503	0.19759	8.5071
		3217	28	2.4814	5.3846	1.7866	0.25310	0.25806	2.6799
		3218	28	2.5776	6.5492	2.1568	0.19989	0.21568	2.8406

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

RTA053-02/00

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Generalised Results - Animals by Parameter - Multiple Times

08016 Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity
Screening Test and Mammalian Erythrocyte Micronucleus Test

Group	Sex	Animal	Day Number	Spleen /Bodywt g/kg	Lung /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg	Uterus /Bodywt g/kg
3	f	3219	28	2.1522	5.0951	1.8519	0.21522	0.20521	2.6527
		3220	28	2.5090	5.4736	1.5361	0.22017	0.21505	2.6626
		3221	28	2.1455	5.6463	1.7268	0.23025	0.24594	2.8781
		3222	28	2.0655	5.2997	1.7632	0.24181	0.24685	3.2746
		3223	28	2.0942	5.7068	1.6230	0.19372	0.17801	2.9843
		3224	28	2.6413	5.5732	1.7961	0.19546	0.22715	6.0750
4	f	4201	44	2.1888	5.8155	1.0300	0.17167	0.24034	3.0901
		4202	44	2.2443	5.0539	0.6905	0.25896	0.17264	3.9707
		4203	46	2.3028	5.2495	0.6823	0.15352	0.23028	2.5586
		4204	46	2.7373	5.1744	0.9272	0.22075	0.26049	2.9139
		4205	41	2.0859	5.1231	1.6270	0.17105	0.22945	2.7117
		4206	44	2.2414	4.9052	1.3362	0.23276	0.16810	2.2414
		4207	42	2.1426	4.9691	0.6593	0.21838	0.25958	89.5344
		4208	45	2.6063	5.5876	0.9602	0.24234	0.16461	2.4691
		4209	43	1.6861	4.9633	0.8647	0.19023	0.17294	3.4155
		4210	42	2.2482	4.9849	0.8214	0.25940	0.14700	3.0696
		4211	43	2.1016	4.8511	0.8319	0.19702	0.26270	2.6270
		4212	45	1.9167	5.0250	0.7500	0.21250	0.21250	3.8333
		4213	28	2.2455	5.9331	2.1457	0.25948	0.21956	2.9940
		4214	28	2.4612	6.4098	1.7657	0.18727	0.17657	2.8357
		4215	28	2.0942	6.1990	2.3037	0.20419	0.17801	8.1675
		4216	28	2.7683	5.3133	2.6226	0.24284	0.23312	5.0996
		4217	28	2.2051	5.6308	1.8462	0.21026	0.20000	2.7179
		4218	28	2.7052	5.8322	1.8799	0.22925	0.18799	2.2467
		4219	28	2.2613	5.6734	1.6080	0.19095	0.24623	2.9648
		4220	28	2.0144	5.7554	1.4388	0.25899	0.23981	3.1175
		4221	28	2.7054	6.0972	1.6533	0.22545	0.20541	4.3587
		4222	28	2.2358	5.9502	1.3211	0.21850	0.17785	3.0488
		4223	28	2.3786	6.0291	2.1359	0.18447	0.23301	2.9612
		4224	28	2.1792	5.9613	1.6465	0.21308	0.24697	2.7603

Group 1 - Control Clean air

Group 2 - 30 mg/m3

Group 3 - 100 mg/m3

Group 4 - 300 mg/m3

Appendix J

Hematology Individual Data

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 1

Males		RBC T/L	HB mmol/L	HCT %	MCV fL	MCH fmol	MCHC mmol/L
1m	1101	7.65	8.8	45.6	59.6	1.15	19.30
	1102	8.09	9.2	47.0	58.1	1.14	19.60
	1103	8.55	9.9	52.0	60.8	1.16	19.00
	1104	8.28	9.3	48.3	58.3	1.12	19.30
	1105	8.42	9.6	51.0	60.6	1.14	18.80
	1106	8.24	9.5	48.4	58.7	1.15	19.60
	1107	8.99	9.8	50.6	56.3	1.09	19.40
	1108	8.00	9.2	46.6	58.3	1.15	19.70
	1109	8.14	9.7	51.3	63.0	1.19	18.90
	1110	8.58	9.8	51.4	59.9	1.14	19.10
	1111	8.55	9.2	48.3	56.5	1.08	19.00
	1112	8.67	9.8	52.0	60.0	1.13	18.80
	Mean	8.347	9.48	49.38	59.18	1.137	19.208
	S.D.	0.356	0.34	2.27	1.88	0.030	0.320
	N	12	12	12	12	12	12
2m	2101	8.37	9.7	50.4	60.2	1.16	19.20
	2102	8.61	9.7	50.3	58.4	1.13	19.30
	2103	8.67	10.2	53.2	61.4	1.18	19.20
	2104	8.74	9.7	50.5	57.8	1.11	19.20
	2105	8.66	9.8	51.8	59.8	1.13	18.90
	2106	8.51	9.6	50.1	58.9	1.13	19.20
	2107	8.78	10.0	53.2	60.6	1.14	18.80
	2108	8.83	9.9	53.3	60.4	1.12	18.60
	2109	8.72	10.2	53.3	61.1	1.17	19.10
	2110	8.47	9.6	50.7	59.9	1.13	18.90
	2111	8.45	9.5	48.6	57.5	1.12	19.50
	2112	8.81	9.7	52.8	59.9	1.10	18.40
	Mean	8.635	9.80	51.52	59.66	1.135	19.025
	S.D.	0.153	0.23	1.62	1.25	0.024	0.314
	N	12	12	12	12	12	12
3m	3101	8.49	9.6	49.9	58.8	1.13	19.20
	3102	8.38	9.3	49.3	58.8	1.11	18.90
	3103	8.20	9.5	49.1	59.9	1.16	19.30
	3104	7.93	8.9	46.8	59.0	1.12	19.00
	3105	8.33	9.4	48.3	58.0	1.13	19.50
	3106	7.99	9.1	47.4	59.3	1.14	19.20
	3107	8.47	9.6	50.6	59.7	1.13	19.00
	3108	8.74	9.7	50.1	57.3	1.11	19.40
	3109	8.37	9.6	49.0	58.5	1.15	19.60
	3110	8.44	9.9	50.8	60.2	1.17	19.50
	3111	8.66	10.0	52.2	60.3	1.16	19.20
	3112	8.33	9.6	50.3	60.4	1.15	19.10
	Mean	8.361	9.52	49.48	59.18	1.138	19.242
	S.D.	0.237	0.31	1.51	0.97	0.020	0.223
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 1

Males		RBC T/L	HB mmol/L	HCT %	MCV fL	MCH fmol	MCHC mmol/L
4m	4101	8.25	9.7	49.9	60.5	1.18	19.40
	4102	8.89	9.9	52.4	58.9	1.11	18.90
	4103	8.67	10.0	51.9	59.9	1.15	19.30
	4104	8.51	9.3	47.9	56.3	1.09	19.40
	4105	8.40	9.8	49.9	59.4	1.17	19.60
	4106	8.33	9.4	48.6	58.3	1.13	19.30
	4107	7.89	9.1	46.7	59.2	1.15	19.50
	4108	8.56	9.4	49.7	58.1	1.10	18.90
	4109	8.22	9.7	50.1	60.9	1.18	19.40
	4110	8.78	10.1	53.8	61.3	1.15	18.80
	4111	8.63	9.9	51.1	59.2	1.15	19.40
	4112	8.61	9.8	51.3	59.6	1.14	19.10
	Mean	8.478	9.68	50.28	59.30	1.142	19.250
	S.D.	0.276	0.31	1.98	1.35	0.029	0.261
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 1

Females		RBC T/L	HB mmol/L	HCT %	MCV fL	MCH fmol	MCHC mmol/L
1f	1213	8.19	9.5	49.3	60.2	1.16	19.30
	1214	7.75	9.0	45.8	59.1	1.16	19.70
	1215	8.60	10.0	51.5	59.9	1.16	19.40
	1216	7.98	9.1	48.1	60.3	1.14	18.90
	1217	8.10	9.6	48.9	60.4	1.19	19.60
	1218	8.45	9.7	50.0	59.2	1.15	19.40
	1219	8.18	9.3	47.5	58.1	1.14	19.60
	1220	8.11	9.6	49.2	60.7	1.18	19.50
	1221	8.43	9.8	50.6	60.0	1.16	19.40
	1222	8.59	9.7	49.7	57.9	1.13	19.50
	1223	7.86	9.8	49.7	63.2	1.25	19.70
	1224	8.03	9.7	49.4	61.5	1.21	19.60
	Mean	8.189	9.57	49.14	60.04	1.169	19.467
	S.D.	0.276	0.30	1.48	1.44	0.034	0.219
	N	12	12	12	12	12	12
2f	2213	8.23	9.3	47.4	57.6	1.13	19.60
	2214	8.14	9.9	51.5	63.3	1.22	19.20
	2215	8.15	9.8	50.8	62.3	1.20	19.30
	2216	7.93	9.0	45.9	57.9	1.14	19.60
	2217	8.37	9.5	49.1	58.7	1.14	19.30
	2218	7.99	9.1	47.4	59.3	1.14	19.20
	2219	8.67	9.8	51.0	58.8	1.13	19.20
	2220	8.25	9.8	50.8	61.6	1.19	19.30
	2221	8.43	9.9	50.9	60.4	1.17	19.40
	2222	8.22	9.5	47.3	57.5	1.16	20.10
	2223	8.31	9.4	48.2	58.0	1.13	19.50
	2224	8.54	10.2	53.0	62.1	1.19	19.20
	Mean	8.269	9.60	49.44	59.79	1.162	19.408
	S.D.	0.213	0.36	2.18	2.06	0.032	0.264
	N	12	12	12	12	12	12
3f	3213	8.31	9.4	47.8	57.5	1.13	19.70
	3214	8.29	9.8	50.4	60.8	1.18	19.40
	3215	8.55	9.4	48.3	56.5	1.10	19.50
	3216	8.19	9.3	48.0	58.6	1.14	19.40
	3217	8.59	9.9	51.7	60.2	1.15	19.10
	3218	8.71	10.2	51.3	58.9	1.17	19.90
	3219	8.49	9.9	50.8	59.8	1.17	19.50
	3220	8.15	9.6	48.7	59.8	1.18	19.70
	3221	8.09	9.3	48.0	59.3	1.15	19.40
	3222	8.07	9.1	46.0	57.0	1.13	19.80
	3223	8.42	9.8	50.8	60.3	1.16	19.30
	3224	8.07	9.7	49.8	61.7	1.20	19.50
	Mean	8.328	9.62	49.30	59.20	1.155	19.517
	S.D.	0.222	0.32	1.75	1.57	0.027	0.225
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 1

Females		RBC T/L	HB mmol/L	HCT %	MCV fL	MCH fmol	MCHC mmol/L
4f	4213	8.76	9.9	51.1	58.3	1.13	19.40
	4214	8.60	9.8	51.5	59.9	1.14	19.00
	4215	8.10	9.2	47.4	58.5	1.14	19.40
	4216	7.84	9.4	46.9	59.8	1.20	20.00
	4217	8.80	9.8	50.2	57.0	1.11	19.50
	4218	7.83	9.1	47.4	60.5	1.16	19.20
	4219	8.24	9.5	47.9	58.1	1.15	19.80
	4220	7.82	9.1	46.6	59.6	1.16	19.50
	4221	8.04	9.7	49.1	61.1	1.21	19.80
	4222	8.26	9.6	47.7	57.7	1.16	20.10
	4223	8.46	9.6	48.6	57.4	1.14	19.80
	4224	8.19	9.6	49.8	60.8	1.17	19.30
	Mean	8.245	9.53	48.68	59.06	1.156	19.567
	S.D.	0.348	0.27	1.65	1.40	0.028	0.334
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 2

Males		PLT G/L	PT Seconds	PTT Seconds
1m	1101	1140	33.0	15.2
	1102	1290	35.0	16.2
	1103	1128	33.6	19.4
	1104	1303	35.5	18.3
	1105	1115	39.2	17.7
	1106	1123	38.4	20.6
	1107	1179	36.6	16.6
	1108	1014	39.0	16.5
	1109	1172	37.9	17.9
	1110	1082	37.5	20.8
	1111	1447	31.7	29.0
	1112	1210	29.6	20.3
	Mean	1183.6	35.58	19.04
	S.D.	116.1	3.08	3.63
	N	12	12	12
2m	2101	1166	34.3	16.1
	2102	1211	34.7	18.3
	2103	1213	39.9	17.8
	2104	1148	34.6	16.7
	2105	1195	36.3	16.5
	2106	1201	37.8	19.0
	2107	mc	35.3	15.9
	2108	942	33.3	19.0
	2109	1180	37.1	17.2
	2110	1061	38.4	24.1
	2111	1292	30.5	21.3
	2112	1105	31.7	22.8
	Mean	1155.8	35.33	18.73
	S.D.	93.0	2.75	2.69
	N	11	12	12
3m	3101	1156	34.9	16.8
	3102	1142	34.8	16.2
	3103	1234	32.9	16.7
	3104	1394	35.5	16.4
	3105	1176	34.1	18.2
	3106	1077	35.3	20.5
	3107	885	37.4	15.5
	3108	1197	35.2	18.8
	3109	1037	35.7	18.4
	3110	1270	34.7	20.8
	3111	1208	37.8	20.9
	3112	996	34.6	21.2
	Mean	1147.7	35.24	18.37
	S.D.	134.6	1.32	2.07
	N	12	12	12

mc: micro clotts

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 2

Males		PLT G/L	PT Seconds	PTT Seconds
4m	4101	1181	35.1	15.3
	4102	1265	35.7	16.4
	4103	1159	34.8	17.3
	4104	1024	37.1	15.7
	4105	1123	36.7	16.9
	4106	1005	32.8	19.9
	4107	974	35.1	16.1
	4108	1189	30.8	15.2
	4109	1010	38.7	18.5
	4110	mc	37.4	21.4
	4111	1081	Werte nicht	plausibel
	4112	1189	39.0	22.9
	Mean	1109.1	35.75	17.78
	S.D.	95.8	2.44	2.59
	N	11	11	11

mc: micro clotts

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 2

Females		PLT G/L	PT Seconds	PTT Seconds
1f	1213	1161	33.5	17.5
	1214	1189	33.8	16.6
	1215	1090	32.3	20.3
	1216	1097	34.1	19.2
	1217	1127	32.3	19.6
	1218	mc	31.1	22.0
	1219	1307	34.5	16.7
	1220	1085	32.7	18.6
	1221	1132	31.6	19.4
	1222	mc	37.3	21.1
	1223	1196	31.1	20.9
	1224	1037	31.2	20.0
	Mean	1142.1	32.96	19.33
	S.D.	76.0	1.82	1.72
	N	10	12	12
2f	2213	1247	32.4	17.0
	2214	1095	33.5	17.7
	2215	1090	34.8	20.2
	2216	1111	30.7	18.8
	2217	1184	32.5	17.8
	2218	1077	32.5	20.5
	2219	1405	34.6	17.3
	2220	1238	33.3	18.4
	2221	1350	32.4	18.5
	2222	910	31.8	21.8
	2223	1110	24.5	22.0
	2224	1100	32.0	20.6
	Mean	1159.8	32.08	19.22
	S.D.	133.9	2.65	1.74
	N	12	12	12
3f	3213	1071	30.7	16.7
	3214	1200	38.3	17.0
	3215	1085	33.1	22.0
	3216	1084	32.0	19.2
	3217	1039	30.7	20.5
	3218	mc	34.7	19.2
	3219	1195	36.1	16.3
	3220	1197	37.5	17.0
	3221	893	34.2	18.4
	3222	1120	27.6	18.9
	3223	1000	33.0	20.1
	3224	1111	31.2	18.1
	Mean	1090.5	33.26	18.62
	S.D.	92.7	3.10	1.72
	N	11	12	12

mc: micro clotts

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 2

Females		PLT G/L	PT Seconds	PTT Seconds
4f	4213	978	32.8	17.5
	4214	1138	36.1	19.2
	4215	1072	35.5	21.6
	4216	1098	31.8	15.7
	4217	1211	31.4	18.1
	4218	1051	33.5	21.6
	4219	1115	35.5	15.9
	4220	1005	33.7	17.3
	4221	mc	34.3	16.6
	4222	1048	28.5	25.1
	4223	1083	36.8	16.6
	4224	1060	31.5	23.0
	Mean	1078.1	33.45	19.02
	S.D.	63.6	2.39	3.09
	N	11	12	12

mc: micro clotts

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 3

Males		WBC G/L	LYMC G/L	SEGC G/L	BANC G/L	EOSC G/L	BASC G/L	MONC G/L
1m	1101	11.4	9.69	1.25	0.23	0.23	0.00	0.00
	1102	10.5	9.35	0.74	0.32	0.11	0.00	0.00
	1103	10.1	8.79	1.01	0.20	0.00	0.00	0.10
	1104	11.7	10.65	0.70	0.12	0.23	0.00	0.00
	1105	8.5	7.57	0.43	0.17	0.17	0.00	0.17
	1106	11.4	9.69	1.14	0.23	0.23	0.00	0.11
	1107	11.9	11.31	0.48	0.00	0.12	0.00	0.00
	1108	10.2	8.98	1.02	0.10	0.00	0.00	0.10
	1109	9.8	8.82	0.78	0.20	0.00	0.00	0.00
	1110	8.2	6.89	1.15	0.16	0.00	0.00	0.00
	1111	10.9	10.14	0.55	0.11	0.11	0.00	0.00
	1112	11.5	10.70	0.46	0.23	0.00	0.00	0.12
	Mean	10.51	9.382	0.809	0.173	0.100	0.000	0.050
	S.D.	1.21	1.284	0.296	0.083	0.098	0.000	0.064
	N	12	12	12	12	12	12	12
2m	2101	10.6	9.12	1.06	0.21	0.11	0.00	0.11
	2102	10.8	9.83	0.65	0.11	0.22	0.00	0.00
	2103	13.1	11.00	1.57	0.39	0.13	0.00	0.00
	2104	12.7	11.30	0.89	0.13	0.13	0.00	0.25
	2105	9.8	8.04	1.18	0.29	0.20	0.00	0.10
	2106	12.1	11.37	0.73	0.00	0.00	0.00	0.00
	2107	10.2	8.77	0.92	0.31	0.10	0.00	0.10
	2108	11.8	9.91	1.42	0.35	0.12	0.00	0.00
	2109	11.9	10.00	1.07	0.36	0.24	0.00	0.24
	2110	14.0	12.88	0.98	0.14	0.00	0.00	0.00
	2111	10.3	8.76	0.93	0.31	0.21	0.00	0.10
	2112	10.7	9.84	0.64	0.11	0.11	0.00	0.00
	Mean	11.50	10.068	1.003	0.226	0.131	0.000	0.075
	S.D.	1.31	1.366	0.285	0.126	0.078	0.000	0.093
	N	12	12	12	12	12	12	12
3m	3101	11.5	9.78	1.04	0.46	0.12	0.00	0.12
	3102	8.1	7.21	0.73	0.08	0.08	0.00	0.00
	3103	13.9	12.79	0.70	0.14	0.14	0.00	0.14
	3104	19.2	16.90	1.34	0.38	0.38	0.00	0.19
	3105	9.4	8.93	0.47	0.00	0.00	0.00	0.00
	3106	10.3	9.27	0.62	0.10	0.31	0.00	0.00
	3107	13.6	11.70	1.22	0.41	0.14	0.00	0.14
	3108	17.2	14.96	1.72	0.52	0.00	0.00	0.00
	3109	9.3	8.37	0.56	0.19	0.19	0.00	0.00
	3110	10.5	8.72	1.37	0.32	0.00	0.00	0.11
	3111	10.9	9.16	0.98	0.11	0.44	0.00	0.22
	3112	8.1	7.29	0.57	0.00	0.16	0.00	0.08
	Mean	11.83	10.423	0.943	0.226	0.163	0.000	0.083
	S.D.	3.51	3.054	0.399	0.183	0.146	0.000	0.082
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 3

Males		WBC G/L	LYMC G/L	SEGC G/L	BANC G/L	EOSC G/L	BASC G/L	MONC G/L
4m	4101	12.9	11.87	1.03	0.00	0.00	0.00	0.00
	4102	10.3	9.17	0.82	0.10	0.21	0.00	0.00
	4103	11.5	10.35	0.69	0.23	0.12	0.00	0.12
	4104	9.9	8.02	1.29	0.30	0.30	0.00	0.00
	4105	11.3	10.62	0.68	0.00	0.00	0.00	0.00
	4106	12.6	11.09	0.88	0.38	0.13	0.00	0.13
	4107	9.8	8.43	1.18	0.00	0.20	0.00	0.00
	4108	9.3	7.81	1.12	0.19	0.19	0.00	0.00
	4109	7.4	6.73	0.52	0.07	0.00	0.00	0.07
	4110	7.0	5.74	0.91	0.21	0.07	0.00	0.07
	4111	9.7	9.12	0.29	0.00	0.29	0.00	0.00
	4112	11.8	10.97	0.59	0.12	0.12	0.00	0.00
	Mean	10.29	9.160	0.833	0.133	0.136	0.000	0.033
S.D.		1.85	1.887	0.295	0.129	0.106	0.000	0.051
N		12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 3

Females		WBC G/L	LYMC G/L	SEGC G/L	BANC G/L	EOSC G/L	BASC G/L	MONC G/L
1f	1213	10.7	9.42	0.75	0.32	0.11	0.00	0.11
	1214	8.6	7.65	0.43	0.26	0.09	0.00	0.17
	1215	8.1	7.21	0.65	0.16	0.08	0.00	0.00
	1216	9.1	8.28	0.46	0.18	0.09	0.00	0.09
	1217	8.5	7.99	0.34	0.09	0.09	0.00	0.00
	1218	7.3	6.57	0.44	0.15	0.07	0.00	0.07
	1219	7.6	6.46	0.68	0.15	0.30	0.00	0.00
	1220	7.6	7.22	0.30	0.08	0.00	0.00	0.00
	1221	9.7	9.12	0.49	0.00	0.10	0.00	0.00
	1222	8.3	6.89	1.00	0.25	0.08	0.00	0.08
	1223	12.8	11.90	0.77	0.00	0.13	0.00	0.00
	1224	9.4	8.27	0.47	0.19	0.38	0.00	0.09
	Mean	8.98	8.082	0.565	0.153	0.127	0.000	0.051
	S.D.	1.55	1.524	0.206	0.099	0.106	0.000	0.058
	N	12	12	12	12	12	12	12
2f	2213	9.2	8.10	0.74	0.18	0.18	0.00	0.00
	2214	10.7	9.84	0.64	0.21	0.00	0.00	0.00
	2215	12.8	12.03	0.77	0.00	0.00	0.00	0.00
	2216	9.3	8.46	0.37	0.09	0.28	0.00	0.09
	2217	8.2	7.63	0.33	0.16	0.08	0.00	0.00
	2218	10.3	9.37	0.41	0.21	0.21	0.00	0.10
	2219	10.6	9.22	0.85	0.21	0.21	0.00	0.11
	2220	7.9	7.27	0.47	0.00	0.08	0.00	0.08
	2221	8.8	8.18	0.44	0.18	0.00	0.00	0.00
	2222	8.4	7.48	0.67	0.00	0.17	0.00	0.08
	2223	9.3	7.63	1.40	0.19	0.09	0.00	0.00
	2224	6.4	5.82	0.32	0.06	0.13	0.00	0.06
	Mean	9.33	8.419	0.618	0.124	0.119	0.000	0.043
	S.D.	1.64	1.566	0.307	0.088	0.093	0.000	0.047
	N	12	12	12	12	12	12	12
3f	3213	13.3	11.97	0.80	0.27	0.13	0.00	0.13
	3214	7.4	6.51	0.52	0.22	0.15	0.00	0.00
	3215	8.2	6.97	1.15	0.08	0.00	0.00	0.00
	3216	8.0	7.12	0.56	0.08	0.08	0.00	0.16
	3217	12.0	10.56	0.84	0.24	0.24	0.00	0.12
	3218	14.4	13.25	0.43	0.14	0.29	0.00	0.29
	3219	8.2	7.46	0.41	0.08	0.25	0.00	0.00
	3220	7.3	6.06	1.02	0.15	0.07	0.00	0.00
	3221	7.6	7.07	0.38	0.08	0.08	0.00	0.00
	3222	7.8	7.33	0.31	0.08	0.08	0.00	0.00
	3223	7.0	5.32	1.19	0.21	0.14	0.00	0.14
	3224	8.6	8.08	0.43	0.00	0.00	0.00	0.09
	Mean	9.15	8.142	0.670	0.136	0.126	0.000	0.078
	S.D.	2.55	2.454	0.316	0.083	0.094	0.000	0.094
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 3

Females		WBC G/L	LYMC G/L	SEGC G/L	BANC G/L	EOSC G/L	BASC G/L	MONC G/L
4f	4213	9.7	8.54	0.78	0.29	0.00	0.00	0.10
	4214	11.3	9.83	1.02	0.23	0.11	0.00	0.11
	4215	10.5	9.24	0.74	0.21	0.21	0.00	0.11
	4216	11.1	10.10	0.56	0.11	0.22	0.00	0.11
	4217	9.4	8.08	0.75	0.38	0.09	0.00	0.09
	4218	11.8	10.86	0.59	0.24	0.12	0.00	0.00
	4219	10.3	8.55	1.34	0.21	0.10	0.00	0.10
	4220	9.3	7.44	1.21	0.28	0.19	0.00	0.19
	4221	7.9	7.03	0.40	0.16	0.16	0.00	0.16
	4222	9.5	8.93	0.38	0.00	0.10	0.00	0.10
	4223	12.5	11.63	0.50	0.13	0.13	0.00	0.13
	4224	8.4	7.90	0.34	0.08	0.00	0.00	0.08
	Mean	10.14	9.011	0.718	0.193	0.119	0.000	0.107
	S.D.	1.37	1.386	0.327	0.104	0.071	0.000	0.046
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 4

Male		LYM %	SEGM %	BAND %	EOS %	BASO %	MONO %
1m	1101	85	11	2	2	0	0
	1102	89	7	3	1	0	0
	1103	87	10	2	0	0	1
	1104	91	6	1	2	0	0
	1105	89	5	2	2	0	2
	1106	85	10	2	2	0	1
	1107	95	4	0	1	0	0
	1108	88	10	1	0	0	1
	1109	90	8	2	0	0	0
	1110	84	14	2	0	0	0
	1111	93	5	1	1	0	0
	1112	93	4	2	0	0	1
	Mean	89.1	7.8	1.7	0.9	0.0	0.5
	S.D.	3.5	3.2	0.8	0.9	0.0	0.7
	N	12	12	12	12	12	12
2m	2101	86	10	2	1	0	1
	2102	91	6	1	2	0	0
	2103	84	12	3	1	0	0
	2104	89	7	1	1	0	2
	2105	82	12	3	2	0	1
	2106	94	6	0	0	0	0
	2107	86	9	3	1	0	1
	2108	84	12	3	1	0	0
	2109	84	9	3	2	0	2
	2110	92	7	1	0	0	0
	2111	85	9	3	2	0	1
	2112	92	6	1	1	0	0
	Mean	87.4	8.8	2.0	1.2	0.0	0.7
	S.D.	4.0	2.4	1.1	0.7	0.0	0.8
	N	12	12	12	12	12	12
3m	3101	85	9	4	1	0	1
	3102	89	9	1	1	0	0
	3103	92	5	1	1	0	1
	3104	88	7	2	2	0	1
	3105	95	5	0	0	0	0
	3106	90	6	1	3	0	0
	3107	86	9	3	1	0	1
	3108	87	10	3	0	0	0
	3109	90	6	2	2	0	0
	3110	83	13	3	0	0	1
	3111	84	9	1	4	0	2
	3112	90	7	0	2	0	1
	Mean	88.3	7.9	1.8	1.4	0.0	0.7
	S.D.	3.5	2.4	1.3	1.2	0.0	0.7
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 4

Male		LYM	SEGM	BAND	EOS	BASO	MONO
		%	%	%	%	%	%
4m	4101	92	8	0	0	0	0
	4102	89	8	1	2	0	0
	4103	90	6	2	1	0	1
	4104	81	13	3	3	0	0
	4105	94	6	0	0	0	0
	4106	88	7	3	1	0	1
	4107	86	12	0	2	0	0
	4108	84	12	2	2	0	0
	4109	91	7	1	0	0	1
	4110	82	13	3	1	0	1
	4111	94	3	0	3	0	0
	4112	93	5	1	1	0	0
	Mean	88.7	8.3	1.3	1.3	0.0	0.3
	S.D.	4.5	3.4	1.2	1.1	0.0	0.5
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 4

Female		LYM %	SEGM %	BAND %	EOS %	BASO %	MONO %
1f	1213	88	7	3	1	0	1
	1214	89	5	3	1	0	2
	1215	89	8	2	1	0	0
	1216	91	5	2	1	0	1
	1217	94	4	1	1	0	0
	1218	90	6	2	1	0	1
	1219	85	9	2	4	0	0
	1220	95	4	1	0	0	0
	1221	94	5	0	1	0	0
	1222	83	12	3	1	0	1
	1223	93	6	0	1	0	0
	1224	88	5	2	4	0	1
	Mean	89.9	6.3	1.8	1.4	0.0	0.6
	S.D.	3.7	2.3	1.1	1.2	0.0	0.7
	N	12	12	12	12	12	12
2f	2213	88	8	2	2	0	0
	2214	92	6	2	0	0	0
	2215	94	6	0	0	0	0
	2216	91	4	1	3	0	1
	2217	93	4	2	1	0	0
	2218	91	4	2	2	0	1
	2219	87	8	2	2	0	1
	2220	92	6	0	1	0	1
	2221	93	5	2	0	0	0
	2222	89	8	0	2	0	1
	2223	82	15	2	1	0	0
	2224	91	5	1	2	0	1
	Mean	90.3	6.6	1.3	1.3	0.0	0.5
	S.D.	3.3	3.1	0.9	1.0	0.0	0.5
	N	12	12	12	12	12	12
3f	3213	90	6	2	1	0	1
	3214	88	7	3	2	0	0
	3215	85	14	1	0	0	0
	3216	89	7	1	1	0	2
	3217	88	7	2	2	0	1
	3218	92	3	1	2	0	2
	3219	91	5	1	3	0	0
	3220	83	14	2	1	0	0
	3221	93	5	1	1	0	0
	3222	94	4	1	1	0	0
	3223	76	17	3	2	0	2
	3224	94	5	0	0	0	1
	Mean	88.6	7.8	1.5	1.3	0.0	0.8
	S.D.	5.2	4.5	0.9	0.9	0.0	0.9
	N	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental
Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Hematology 4

Female		LYM %	SEGM %	BAND %	EOS %	BASO %	MONO %
4f	4213	88	8	3	0	0	1
	4214	87	9	2	1	0	1
	4215	88	7	2	2	0	1
	4216	91	5	1	2	0	1
	4217	86	8	4	1	0	1
	4218	92	5	2	1	0	0
	4219	83	13	2	1	0	1
	4220	80	13	3	2	0	2
	4221	89	5	2	2	0	2
	4222	94	4	0	1	0	1
	4223	93	4	1	1	0	1
	4224	94	4	1	0	0	1
	Mean	88.8	7.1	1.9	1.2	0.0	1.1
	S.D.	4.4	3.3	1.1	0.7	0.0	0.5
	N	12	12	12	12	12	12

Appendix K

Clinical Chemistry Individual Data

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 1

Males		AST U/L	ALT U/L	CK U/L	GGT U/L	AP U/L	SDH U/L	CHE kU/L	TBIL umol/L
1m	1101	62	45	119	1	85	1	0.16	2.2
	1102	72	46	121	4	117	1	0.15	2.1
	1103	66	41	105	0	139	1	0.14	2.2
	1104	72	48	120	0	125	3	0.18	1.5
	1105	79	40	130	0	129	4	0.16	2.1
	1106	60	40	157	0	155	4	0.20	2.1
	1107	70	48	138	0	148	4	0.16	2.0
	1108	64	40	102	0	132	5	0.15	1.8
	1109	75	47	110	0	144	3	0.15	2.2
	1110	70	42	128	0	146	1	0.17	1.3
	1111	82	53	116	1	129	6	0.16	2.1
	1112	79	48	111	2	166	3	0.15	2.8
	Mean	70.9	44.8	121.4	0.7	134.6	3.0	0.161	2.03
	S.D.	7.0	4.2	15.3	1.2	20.8	1.7	0.016	0.38
	N	12	12	12	12	12	12	12	12
2m	2101	103	51	112	0	111	0	0.14	3.0
	2102	67	40	127	0	96	1	0.16	2.2
	2103	63	49	128	1	146	0	0.16	2.0
	2104	82	56	124	0	102	3	0.22	2.7
	2105	66	40	109	1	131	2	0.17	1.7
	2106	58	41	132	1	169	3	0.17	2.2
	2107	87	60	169	3	120	4	0.18	1.6
	2108	66	43	102	0	186	3	0.22	1.8
	2109	69	41	206	0	136	2	0.19	1.9
	2110	85	49	114	2	165	0	0.16	3.1
	2111	92	60	114	1	204	0	0.19	1.9
	2112	75	53	107	3	174	1	0.13	2.2
	Mean	76.1	48.6	128.7	1.0	145.0	1.6	0.174	2.19
	S.D.	13.6	7.6	30.0	1.1	34.8	1.4	0.028	0.49
	N	12	12	12	12	12	12	12	12
3m	3101	64	54	100	2	136	1	0.14	3.1
	3102	74	57	125	1	134	0	0.17	1.9
	3103	65	43	141	4	170	0	0.20	2.6
	3104	69	50	125	1	136	1	0.17	2.1
	3105	73	43	107	1	151	1	0.15	2.1
	3106	76	50	107	0	163	1	0.17	2.1
	3107	69	41	158	2	129	1	0.19	1.1
	3108	76	49	89	0	218	1	0.16	1.4
	3109	83	41	107	0	161	2	0.19	2.6
	3110	56	41	99	2	123	0	0.18	1.8
	3111	77	54	179	3	145	0	0.14	2.0
	3112	73	47	178	5	150	3	0.17	1.8
	Mean	71.3	47.5	126.3	1.8	151.3	0.9	0.169	2.05
	S.D.	7.2	5.7	31.1	1.6	25.5	0.9	0.019	0.54
	N	12	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 1

Males		AST	ALT	CK	GGT	AP	SDH	CHE	TBIL
		U/L	U/L	U/L	U/L	U/L	U/L	kU/L	umol/L
4m	4101	71	47	110	2	176	0	0.18	2.6
	4102	83	48	96	1	164	0	0.16	1.7
	4103	95	50	167	0	183	0	0.18	2.0
	4104	98	49	90	0	145	5	0.19	2.5
	4105	75	40	110	0	110	4	0.18	1.8
	4106	85	52	97	0	162	5	0.16	2.6
	4107	92	54	179	0	153	3	0.18	1.8
	4108	54	42	104	3	167	0	0.17	1.2
	4109	68	45	90	0	140	2	0.16	0.9
	4110	69	33	181	0	156	1	0.21	1.9
	4111	85	52	104	1	144	5	0.15	2.0
	4112	86	64	149	3	221	0	0.16	1.9
Mean		80.1	48.0	123.1	0.8	160.1	2.1	0.173	1.91
S.D.		12.9	7.8	35.4	1.2	27.0	2.2	0.017	0.51
N		12	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 1

Females		AST U/L	ALT U/L	CK U/L	GGT U/L	AP U/L	SDH U/L	CHE kU/L	TBIL umol/L
1f	1213	83	55	106	0	70	0	1.17	3.0
	1214	58	40	87	1	89	0	1.11	2.6
	1215	70	38	110	0	82	5	0.50	2.5
	1216	68	34	110	0	81	6	0.78	2.4
	1217	67	34	98	0	68	10	0.99	3.0
	1218	98	56	105	1	70	1	1.05	2.6
	1219	49	36	94	0	73	0	0.89	2.3
	1220	69	36	92	0	73	4	0.63	2.5
	1221	68	47	95	0	70	5	0.91	2.0
	1222	66	31	124	0	82	0	1.69	2.1
	1223	60	36	126	2	102	0	0.59	2.2
	1224	61	44	106	1	88	0	0.73	2.2
	Mean	68.1	40.6	104.4	0.4	79.0	2.6	0.920	2.45
	S.D.	12.5	8.2	12.1	0.7	10.3	3.3	0.322	0.32
	N	12	12	12	12	12	12	12	12
2f	2213	69	42	175	0	106	0	0.92	3.7
	2214	65	41	102	0	84	4	0.72	3.2
	2215	82	57	83	0	77	11	1.07	3.2
	2216	64	42	131	1	98	1	0.75	2.8
	2217	64	37	103	1	92	1	0.55	2.1
	2218	61	36	100	2	111	0	0.68	3.5
	2219	71	50	107	0	99	0	0.96	2.6
	2220	68	38	95	0	87	0	0.74	2.2
	2221	58	39	129	0	87	2	0.60	2.0
	2222	80	50	142	2	126	3	0.88	2.9
	2223	64	40	97	3	118	0	0.88	2.4
	2224	89	50	135	3	131	2	0.67	1.9
	Mean	69.6	43.5	116.6	1.0	101.3	2.0	0.785	2.71
	S.D.	9.4	6.6	26.1	1.2	17.3	3.1	0.156	0.61
	N	12	12	12	12	12	12	12	12
3f	3213	65	40	201	2	88	0	0.72	1.6
	3214	57	35	95	0	84	2	0.49	2.6
	3215	68	35	100	1	122	0	0.53	3.3
	3216	63	33	69	2	89	1	0.85	3.2
	3217	56	39	111	2	94	12	0.66	3.0
	3218	87	46	109	2	74	8	1.00	2.4
	3219	81	52	117	0	101	7	0.56	1.7
	3220	65	51	89	0	105	0	1.05	2.2
	3221	74	40	126	0	104	1	1.44	2.1
	3222	73	47	102	2	106	7	0.95	2.0
	3223	75	36	84	1	94	0	0.57	2.5
	3224	77	44	85	3	104	0	0.66	2.1
	Mean	70.1	41.5	107.3	1.3	97.1	3.2	0.790	2.39
	S.D.	9.4	6.4	33.5	1.1	12.6	4.2	0.280	0.55
	N	12	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 1

Females		AST U/L	ALT U/L	CK U/L	GGT U/L	AP U/L	SDH U/L	CHE kU/L	TBIL umol/L
4f	4213	81	47	161	0	105	1	0.68	1.9
	4214	71	46	96	1	115	0	0.92	2.9
	4215	95	67	97	2	86	2	1.07	2.3
	4216	63	35	108	2	121	1	0.54	2.4
	4217	78	48	104	0	105	11	0.90	2.4
	4218	67	35	93	1	77	2	0.49	2.9
	4219	84	40	113	1	174	2	0.60	1.4
	4220	75	38	110	0	107	0	0.57	2.5
	4221	78	44	278	0	113	0	0.77	1.9
	4222	62	35	89	4	62	0	0.95	1.9
	4223	82	49	97	2	108	1	0.97	2.0
	4224	67	50	103	2	65	1	0.99	2.1
	Mean	75.3	44.5	120.8	1.3	103.2	1.8	0.788	2.22
	S.D.	9.7	9.1	52.9	1.2	29.8	3.0	0.203	0.44
	N	12	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 2

Males		TP g/L	ALB g/L	GLB g/L	A/G	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L
1m	1101	59.6	33.5	26.1	1.28	5.32	2.05	0.90
	1102	61.3	34.6	26.7	1.30	4.81	1.54	0.88
	1103	60.9	33.7	27.2	1.24	5.09	1.38	0.36
	1104	62.1	34.5	27.6	1.25	4.75	1.72	0.51
	1105	59.3	33.0	26.3	1.25	6.10	1.61	0.32
	1106	62.6	34.7	27.9	1.24	5.68	1.49	0.61
	1107	66.6	37.0	29.6	1.25	5.34	1.77	0.62
	1108	60.8	33.5	27.3	1.23	5.17	1.39	0.70
	1109	62.5	34.9	27.6	1.26	5.49	1.87	0.38
	1110	57.5	31.9	25.6	1.25	6.18	1.54	0.35
	1111	63.7	34.8	28.9	1.20	6.07	1.62	0.57
	1112	62.4	35.0	27.4	1.28	6.62	1.31	0.37
	Mean	61.61	34.26	27.35	1.253	5.552	1.608	0.548
	S.D.	2.32	1.27	1.13	0.026	0.586	0.216	0.203
	N	12	12	12	12	12	12	12
2m	2101	64.7	36.3	28.4	1.28	4.20	1.81	0.37
	2102	62.6	35.4	27.2	1.30	5.38	1.67	0.59
	2103	65.4	36.1	29.3	1.23	5.25	1.62	0.58
	2104	61.8	33.2	28.6	1.16	5.70	2.06	0.41
	2105	64.6	35.9	28.7	1.25	4.98	1.95	0.68
	2106	64.6	35.4	29.2	1.21	5.62	1.48	0.43
	2107	61.7	33.8	27.9	1.21	6.98	2.16	0.91
	2108	66.0	35.2	30.8	1.14	6.27	1.90	0.65
	2109	64.6	35.4	29.2	1.21	6.27	1.53	0.51
	2110	61.2	34.5	26.7	1.29	4.68	1.34	0.39
	2111	63.3	35.6	27.7	1.29	5.49	1.77	0.40
	2112	66.0	35.9	30.1	1.19	5.89	1.81	0.36
	Mean	63.88	35.23	28.65	1.230	5.559	1.758	0.523
	S.D.	1.70	0.94	1.18	0.053	0.754	0.242	0.166
	N	12	12	12	12	12	12	12
3m	3101	67.1	36.9	30.2	1.22	5.49	1.95	0.78
	3102	59.0	33.9	25.1	1.35	6.83	1.80	0.44
	3103	63.8	35.2	28.6	1.23	5.36	2.28	1.11
	3104	65.8	33.8	32.0	1.06	6.28	1.42	0.55
	3105	62.5	34.2	28.3	1.21	5.17	1.95	0.58
	3106	60.4	33.7	26.7	1.26	6.53	1.66	0.44
	3107	62.7	35.6	27.1	1.31	4.33	1.96	0.50
	3108	64.8	35.7	29.1	1.23	4.43	1.32	0.25
	3109	65.1	36.2	28.9	1.25	5.55	1.66	0.64
	3110	64.1	35.3	28.8	1.23	5.43	2.03	0.52
	3111	62.9	34.4	28.5	1.21	5.66	2.06	1.03
	3112	65.0	36.9	28.1	1.31	5.21	1.50	0.89
	Mean	63.60	35.15	28.45	1.239	5.523	1.799	0.644
	S.D.	2.28	1.16	1.72	0.072	0.750	0.290	0.258
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 2

Males		TP g/L	ALB g/L	GLB g/L	A/G	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L
4m	4101	64.6	36.1	28.5	1.27	4.39	1.73	0.60
	4102	62.6	35.7	26.9	1.33	4.93	1.75	0.42
	4103	61.0	34.9	26.1	1.34	7.21	1.74	0.45
	4104	65.0	34.8	30.2	1.15	5.14	1.59	0.51
	4105	64.4	35.1	29.3	1.20	4.25	1.84	0.53
	4106	62.3	34.3	28.0	1.23	5.39	1.22	0.32
	4107	60.6	34.6	26.0	1.33	5.96	1.61	0.41
	4108	62.4	34.3	28.1	1.22	6.92	2.29	0.71
	4109	60.5	33.1	27.4	1.21	5.47	1.40	0.30
	4110	61.5	34.0	27.5	1.24	7.25	1.80	0.51
	4111	59.4	34.6	24.8	1.40	7.30	1.32	0.43
	4112	60.9	35.5	25.4	1.40	5.70	1.43	0.27
	Mean	62.10	34.75	27.35	1.277	5.826	1.643	0.455
	S.D.	1.79	0.81	1.60	0.082	1.107	0.286	0.127
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 2

Females		TP g/L	ALB g/L	GLB g/L	A/G	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L
1f	1213	64.0	38.6	25.4	1.52	4.56	1.78	0.36
	1214	65.6	38.4	27.2	1.41	5.59	2.27	0.70
	1215	59.8	36.4	23.4	1.56	3.82	1.83	0.39
	1216	62.2	35.2	27.0	1.30	5.59	1.88	0.44
	1217	66.4	37.9	28.5	1.33	4.93	1.85	0.49
	1218	66.0	39.0	27.0	1.44	4.50	1.93	0.42
	1219	65.2	36.2	29.0	1.25	5.27	2.15	0.64
	1220	64.3	36.4	27.9	1.30	6.22	3.22	0.69
	1221	65.2	36.7	28.5	1.29	5.80	1.88	0.68
	1222	62.5	34.6	27.9	1.24	5.79	2.31	0.45
	1223	63.1	37.0	26.1	1.42	5.38	2.10	0.65
	1224	60.4	35.8	24.6	1.46	5.09	1.90	0.77
	Mean	63.73	36.85	26.88	1.377	5.212	2.092	0.557
	S.D.	2.16	1.38	1.71	0.106	0.673	0.397	0.144
	N	12	12	12	12	12	12	12
2f	2213	64.2	37.2	27.0	1.38	6.09	2.26	0.42
	2214	63.1	37.1	26.0	1.43	4.49	1.55	0.41
	2215	62.8	38.2	24.6	1.55	4.21	1.72	0.53
	2216	61.5	34.9	26.6	1.31	5.59	1.99	0.59
	2217	63.9	35.4	28.5	1.24	4.76	2.36	0.56
	2218	63.0	35.9	27.1	1.32	5.15	2.35	0.69
	2219	61.5	35.4	26.1	1.36	5.91	1.90	0.37
	2220	64.2	36.3	27.9	1.30	4.86	2.33	0.59
	2221	63.4	34.7	28.7	1.21	5.43	2.44	0.57
	2222	65.6	36.7	28.9	1.27	4.56	2.21	0.68
	2223	63.5	36.6	26.9	1.36	5.23	2.10	0.79
	2224	63.4	36.6	26.8	1.37	5.05	2.12	0.43
	Mean	63.34	36.25	27.09	1.342	5.111	2.111	0.553
	S.D.	1.13	1.03	1.25	0.091	0.575	0.275	0.128
	N	12	12	12	12	12	12	12
3f	3213	66.1	39.0	27.1	1.44	5.75	2.26	0.48
	3214	63.5	37.0	26.5	1.40	5.64	1.96	0.69
	3215	62.7	36.9	25.8	1.43	5.56	2.14	0.52
	3216	66.2	37.3	28.9	1.29	5.15	2.66	0.62
	3217	66.3	37.1	29.2	1.27	5.33	2.42	0.90
	3218	64.3	36.4	27.9	1.30	4.29	2.02	0.43
	3219	59.5	34.7	24.8	1.40	4.21	1.79	0.45
	3220	65.0	36.9	28.1	1.31	5.06	2.77	0.68
	3221	62.4	35.6	26.8	1.33	4.57	2.61	0.81
	3222	66.2	37.7	28.5	1.32	4.84	2.17	0.60
	3223	60.3	35.5	24.8	1.43	3.83	2.38	0.45
	3224	62.8	35.8	27.0	1.33	5.96	2.01	0.50
	Mean	63.78	36.66	27.12	1.354	5.016	2.266	0.594
	S.D.	2.33	1.15	1.48	0.061	0.677	0.307	0.152
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 2

Females		TP g/L	ALB g/L	GLB g/L	A/G	GLUC mmol/L	CHOL mmol/L	TRIG mmol/L
4f	4213	64.9	37.9	27.0	1.40	3.99	2.10	0.42
	4214	60.7	35.3	25.4	1.39	4.78	2.17	0.64
	4215	66.3	39.2	27.1	1.45	4.53	1.95	0.48
	4216	61.7	35.1	26.6	1.32	5.61	2.37	0.92
	4217	63.7	36.9	26.8	1.38	3.82	2.32	0.71
	4218	58.0	33.3	24.7	1.35	5.05	1.87	0.68
	4219	61.5	34.8	26.7	1.30	4.41	2.46	0.60
	4220	60.4	34.7	25.7	1.35	4.19	2.09	0.90
	4221	61.8	34.2	27.6	1.24	5.42	2.63	0.72
	4222	60.6	35.6	25.0	1.42	4.24	2.84	0.72
	4223	65.0	37.8	27.2	1.39	4.24	1.96	0.34
	4224	66.8	38.2	28.6	1.34	5.47	2.00	0.61
	Mean	62.62	36.08	26.53	1.361	4.646	2.230	0.645
	S.D.	2.69	1.85	1.14	0.057	0.611	0.299	0.174
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 3

Males		CREA umol/L	UREA mmol/L	Na mmol/L	K mmol/L	Ca mmol/L	P04 mmol/L	Cl mmol/L
1m	1101	49.9	5.03	141.8	4.03	2.65	2.14	100
	1102	53.1	6.96	143.1	4.22	2.66	2.20	101
	1103	53.5	6.53	140.2	4.08	2.58	2.13	100
	1104	51.4	5.30	142.0	3.96	2.65	2.16	99
	1105	59.2	6.47	140.7	3.90	2.54	1.96	101
	1106	59.5	5.01	137.6	4.19	2.63	2.12	101
	1107	59.9	6.12	145.1	4.08	2.64	2.04	99
	1108	58.0	5.07	142.7	4.18	2.66	2.29	99
	1109	52.2	5.73	144.2	3.96	2.70	2.20	100
	1110	61.1	4.81	140.1	3.78	2.40	1.96	98
	1111	60.1	5.50	140.0	4.03	2.67	2.13	100
	1112	60.8	6.08	141.2	3.83	2.59	2.02	100
	Mean	56.56	5.718	141.56	4.020	2.614	2.113	99.8
	S.D.	4.17	0.707	2.05	0.141	0.081	0.100	0.9
	N	12	12	12	12	12	12	12
2m	2101	54.6	6.37	142.8	3.77	2.64	2.01	100
	2102	52.3	5.85	144.2	3.76	2.68	2.32	99
	2103	53.4	5.93	142.8	3.78	2.76	2.22	101
	2104	56.9	4.64	136.9	4.16	2.56	2.19	99
	2105	60.2	5.49	142.4	3.96	2.71	2.29	99
	2106	57.2	4.76	140.4	4.37	2.70	1.97	100
	2107	57.2	6.33	140.0	4.22	2.66	2.19	98
	2108	59.2	5.51	142.8	4.15	2.72	2.20	100
	2109	58.4	5.57	140.9	4.21	2.71	2.21	100
	2110	58.9	7.43	144.2	3.73	2.62	2.11	101
	2111	65.7	6.92	141.7	3.74	2.71	1.98	99
	2112	63.5	6.62	141.0	4.03	2.70	2.22	100
	Mean	58.13	5.952	141.68	3.990	2.681	2.159	99.7
	S.D.	3.86	0.831	2.03	0.229	0.054	0.116	0.9
	N	12	12	12	12	12	12	12
3m	3101	51.0	6.58	140.5	4.20	2.71	2.27	101
	3102	52.6	6.55	141.9	3.81	2.56	2.17	102
	3103	50.5	4.86	144.6	4.06	2.71	2.18	100
	3104	60.4	5.83	140.3	3.74	2.67	1.90	101
	3105	55.9	5.99	141.4	4.46	2.67	2.20	101
	3106	55.2	6.84	141.8	4.20	2.64	2.07	100
	3107	55.7	5.59	143.8	4.11	2.67	2.18	100
	3108	65.1	7.79	143.7	3.77	2.72	2.16	99
	3109	52.5	5.39	144.0	4.09	2.79	2.10	99
	3110	55.1	4.84	140.4	3.70	2.67	1.92	97
	3111	56.8	5.87	139.6	4.32	2.70	2.17	98
	3112	59.4	6.63	139.7	4.03	2.67	2.05	100
	Mean	55.85	6.063	141.81	4.041	2.682	2.114	99.8
	S.D.	4.21	0.860	1.80	0.242	0.054	0.112	1.4
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 3

Males		CREA	UREA	Na	K	Ca	P04	Cl
		umol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L	mmol/L
4m	4101	52.7	5.72	144.8	3.92	2.69	2.33	100
	4102	54.8	5.36	143.3	3.88	2.64	2.03	101
	4103	56.7	5.44	140.7	4.15	2.62	2.28	100
	4104	58.6	5.25	139.4	4.12	2.65	2.31	101
	4105	58.5	5.57	142.3	4.10	2.71	2.18	100
	4106	60.4	5.61	142.1	3.88	2.68	2.15	99
	4107	67.0	7.05	143.9	4.55	2.62	2.12	100
	4108	59.8	6.50	141.7	4.43	2.66	2.06	99
	4109	59.9	6.39	141.5	4.05	2.63	2.03	100
	4110	62.9	6.64	139.0	4.39	2.57	2.06	98
	4111	59.8	7.82	142.1	4.69	2.54	1.90	99
	4112	60.5	7.89	142.5	4.27	2.70	2.20	100
Mean		59.30	6.270	141.94	4.203	2.643	2.138	99.8
S.D.		3.66	0.935	1.69	0.266	0.051	0.130	0.9
N		12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 3

Females		CREA umol/L	UREA mmol/L	Na mmol/L	K mmol/L	Ca mmol/L	P04 mmol/L	Cl mmol/L
1f	1213	52.1	6.86	142.3	4.13	2.68	1.98	100
	1214	53.6	6.84	142.3	4.16	2.71	1.55	101
	1215	52.2	7.13	140.6	4.35	2.59	1.74	100
	1216	60.3	6.05	139.7	3.84	2.56	1.50	101
	1217	62.7	7.82	138.3	4.00	2.67	1.71	102
	1218	59.4	5.63	139.9	3.67	2.71	1.50	102
	1219	69.1	6.84	139.2	3.76	2.65	1.71	102
	1220	53.6	5.28	144.0	4.04	2.65	1.44	102
	1221	63.4	6.47	139.9	4.44	2.70	1.60	100
	1222	59.0	4.44	137.5	4.79	2.56	1.71	100
	1223	65.1	6.31	139.8	3.73	2.66	1.74	100
	1224	59.8	6.02	139.8	3.92	2.62	1.61	100
	Mean	59.19	6.308	140.28	4.069	2.647	1.649	100.8
	S.D.	5.45	0.905	1.81	0.330	0.054	0.147	0.9
	N	12	12	12	12	12	12	12
2f	2213	44.4	5.61	140.8	4.14	2.66	1.69	102
	2214	48.7	6.74	141.2	4.10	2.61	1.75	101
	2215	56.1	7.90	141.5	3.61	2.63	1.77	101
	2216	60.9	7.99	138.0	4.26	2.63	1.86	102
	2217	60.2	5.86	139.7	3.75	2.66	1.81	101
	2218	53.6	5.34	141.5	3.93	2.76	1.69	101
	2219	69.7	5.58	140.0	4.15	2.68	1.56	100
	2220	63.1	5.66	141.3	3.78	2.64	1.54	102
	2221	57.0	5.50	141.6	4.31	2.68	1.69	102
	2222	66.2	9.16	139.3	4.35	2.67	1.74	100
	2223	59.9	5.78	140.6	3.90	2.66	1.62	101
	2224	63.0	6.47	140.1	4.16	2.64	1.39	100
	Mean	58.57	6.466	140.47	4.037	2.660	1.676	101.1
	S.D.	7.16	1.240	1.09	0.238	0.038	0.131	0.8
	N	12	12	12	12	12	12	12
3f	3213	52.6	6.24	143.3	4.02	2.66	1.70	101
	3214	55.7	5.57	139.3	3.96	2.64	1.87	102
	3215	51.3	6.37	141.8	3.76	2.59	1.94	101
	3216	56.8	6.75	140.9	3.96	2.69	1.82	101
	3217	67.0	7.17	137.4	4.28	2.73	1.80	98
	3218	61.1	7.26	139.4	4.36	2.65	1.73	102
	3219	57.9	6.82	142.6	4.44	2.63	1.92	101
	3220	56.7	7.50	141.9	4.02	2.67	1.61	100
	3221	56.2	6.41	142.4	4.41	2.63	1.93	100
	3222	57.1	6.57	140.1	3.93	2.71	1.61	99
	3223	58.9	5.36	141.2	3.90	2.62	1.59	101
	3224	56.7	5.41	142.4	3.61	2.65	1.40	102
	Mean	57.33	6.453	141.06	4.054	2.656	1.743	100.7
	S.D.	3.98	0.714	1.72	0.263	0.039	0.168	1.2
	N	12	12	12	12	12	12	12

Generalised Results - Animals by Parameter - Fixed Time

Study: 08016 - Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test

Day: 28 relative to Start Date

Clinical Chemistry 3

Females		CREA umol/L	UREA mmol/L	Na mmol/L	K mmol/L	Ca mmol/L	P04 mmol/L	Cl mmol/L
4f	4213	58.0	5.42	140.9	3.96	2.60	1.90	102
	4214	56.8	7.25	140.5	4.31	2.64	1.84	101
	4215	59.8	6.83	142.2	4.09	2.64	1.72	102
	4216	56.6	4.23	139.1	4.30	2.65	1.65	100
	4217	65.4	8.97	139.7	4.35	2.67	1.83	102
	4218	64.8	6.62	139.9	4.11	2.65	2.17	102
	4219	60.0	8.10	141.2	4.24	2.61	1.75	101
	4220	61.9	5.90	144.2	4.15	2.65	1.84	102
	4221	62.5	5.56	139.4	4.26	2.62	1.82	101
	4222	59.0	5.64	140.6	4.27	2.63	1.68	99
	4223	65.6	5.56	142.6	4.07	2.66	1.64	101
	4224	64.9	6.41	141.0	3.89	2.73	1.86	101
	Mean	61.28	6.374	140.94	4.167	2.646	1.808	101.2
	S.D.	3.37	1.292	1.47	0.146	0.033	0.143	0.9
	N	12	12	12	12	12	12	12

Appendix L

Histopathology Individual Data

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Date: 21-JAN-2009 Time: 13:44

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001101	Killed Necropsied on Day: 28

HARDERIAN GLANDS :

Slight uni-lateral multifocal hemorrhage

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell

infiltration : level I

Slight focal epithelial erosion(s) : level I

LUNGS :

Very slight focal foreign-body granuloma

THYROID :

Very slight uni-lateral focal mononuclear cell
infiltration

LIVER :

Slight multifocal microgranuloma(s)

TESTES :

Slight bi-lateral multifocal degeneration of
spermatocytes
Slight bi-lateral multifocal disorganization of the
germinal epithelium : stage VIII
Slight bi-lateral multifocal sertoli-cell vacuolation
Slight uni-lateral multifocal segmental depletion of
pachytene spermatocytes : early stages
Slight uni-lateral multifocal spermatid retention :
late stages

EPIDIDYMIDES :

Very slight uni-lateral multifocal exfoliation of
germ cells in the lumen

PROSTATE :

Moderate multifocal non-suppurative inflammation

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, LACRIMAL GLANDS,
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROIDS, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, LIVER, PANCREAS,
MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM,
ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL
MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL,
THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW
(FEMUR), BONE MARROW (STERNUM)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001102	Killed Necropsied on Day: 28

EYES : Slight uni-lateral focal retrobulbar haemorrhage

LACRIMAL GLANDS : Very slight uni-lateral multifocal Harderian gland change(s)

NASAL and PARANASAL CAVITIES : Very slight multifocal mucosal inflammatory cell infiltration : level I
Very slight focal mucosal psammoma bodies : level I

LUNGS : Very slight focal alveolar haemorrhage
Slight focal alveolar histiocytosis

HEART : Very slight multifocal myocardial mononuclear cell infiltration

LIVER : Very slight multifocal microgranuloma(s)

EPIDIDYIMIDES : Very slight uni-lateral focal interstitial mononuclear cell infiltration

PROSTATE : Slight multifocal intra-acinar inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH
NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, TESTES, SEMINAL VESICLES, COAGULATING GLANDS,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001103	Killed	Necropsied on Day: 28
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EYES : Slight uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES : Slight multifocal mucosal inflammatory cell infiltration : level I and II

001103 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001103	Continued from previous page

NASAL and PARANASAL CAVITIES :

Slight focal mucous (goblet) cell hyperplasia : level I

LARYNX :

Slight focal submucosal foreign-body granuloma

LUNGS :

Very slight focal alveolar haemorrhage
Very slight focal interstitial mononuclear cell infiltration

HEART :

Very slight focal myocardial mononuclear cell infiltration

MANDIBULAR LYMPH NODES :

Slight lymphoid hyperplasia

LIVER :

Slight focal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, TRACHEA, LUNG ASSOCIATED LYMPH NODES,
THYROID, PARATHYROIDS, AORTA, SALIVARY GLANDS, TONGUE,
PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR
STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES,
DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS,
URINARY BLADDER, ADRENALS, TESTES, EPIDIDYMITES,
PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL
MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL,
THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW
(FEMUR), BONE MARROW (STERNUM)

001104 Killed Necropsied on Day: 28

PITUITARY :

Moderate focal craniopharyngeal structures : within
pars nervosa

HARDERIAN GLANDS :

Slight uni-lateral focal hemorrhage

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II

LUNGS :

Very slight focal alveolar histiocytosis

HEART :

Very slight multifocal myocardial mononuclear cell
infiltration

001104 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001104	Continued from previous page

MANDIBULAR LYMPH NODES :

Unilateral section

LIVER :

Very slight focal perivascular mononuclear cell
infiltration

KIDNEYS :

Very slight uni-lateral focal interstitial
mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, EYES, LACRIMAL GLANDS, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH
NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, TESTES,
EPIDIDYMITIS, PROSTATE, SEMINAL VESICLES, COAGULATING
GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT
(KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOPOIETIC TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001105 Killed Necropsied on Day: 28

EYES :

Slight bi-lateral multifocal retrobulbar haemorrhage

HARDERIAN GLANDS :

Slight uni-lateral focal hemorrhage

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level II

LARYNX :

Very slight focal submucosal inflammatory cell
infiltration

LUNGS :

Very slight focal osseous metaplasia

LIVER :

Very slight multifocal microgranuloma(s)

EPIDIDYMITIS :

Very slight uni-lateral multifocal interstitial
mononuclear cell infiltration

001105 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001105	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDES, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, TESTES, PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

001106 Killed Necropsied on Day: 28

EYES :
LACRIMAL GLANDS : Slight uni-lateral focal retrobulbar haemorrhage
Very slight uni-lateral multifocal mononuclear cell infiltration
HEART : Very slight multifocal myocardial mononuclear cell infiltration
LIVER : Slight multifocal microgranuloma(s)
Very slight multifocal perivascular mononuclear cell infiltration
PROSTATE : Very slight focal interstitial mononuclear cell infiltration
Very slight focal intra-acinar inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDES, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, TESTES, EPIDIDYMITES, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE,

001106 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001106	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

001107 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight focal mucosal inflammatory cell infiltration :
level II

HEART :

Slight focal myocardial mononuclear cell infiltration

GLANDULAR STOMACH :

Very slight focal submucosal inflammatory cell
infiltration

LIVER :

Very slight multifocal microgranuloma(s)

KIDNEYS :

Very slight uni-lateral focal basophilic tubule(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROIDS, AORTA, SALIVARY
GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX
(LARYNGO-), OESOPHAGUS, FORESTOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, TESTES,
EPIDIDYIMIDES, PROSTATE, SEMINAL VESICLES, COAGULATING
GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT
(KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001108 Killed Necropsied on Day: 28

EYES :

Slight uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II

HEART :

Very slight focal myocardial mononuclear cell
infiltration

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001108	Continued from previous page

MANDIBULAR LYMPH NODES :

Moderate lymphoid hyperplasia

LIVER :

Very slight multifocal microgranuloma(s)

KIDNEYS :

Very slight uni-lateral focal basophilic tubule(s)
Very slight uni-lateral focal interstitial
mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROID, AORTA, SALIVARY
GLANDS, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, TESTES,
EPIDIDYMIDES, PROSTATE, SEMINAL VESICLES, COAGULATING
GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT
(KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001109 Killed Necropsied on Day: 28

EYES :

Slight uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level II

MANDIBULAR LYMPH NODES :

Unilateral section

LIVER :

Very slight multifocal microgranuloma(s)

KIDNEYS :

Very slight uni-lateral focal basophilic tubule(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROID, HEART, AORTA,
SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX
(LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH,

001109 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001109	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM,
JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER,
ADRENALS, TESTES, EPIDIDYIMIDES, PROSTATE, SEMINAL
VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN,
STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL
CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001110 Killed Necropsied on Day: 28

EYES : Severe uni-lateral multifocal retrobulbar haemorrhage

HARDERIAN GLANDS : Slight uni-lateral multifocal hemorrhage

HEART : Very slight focal myocardial mononuclear cell
infiltration

MANDIBULAR LYMPH NODES : Unilateral section

LIVER : Slight focal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, NASAL
and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG
ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDS, AORTA,
SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX
(LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH,
PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM,
JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY
BLADDER, ADRENALS, TESTES, EPIDIDYIMIDES, PROSTATE,
SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS,
SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE,
SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001111	Killed Necropsied on Day: 28

EYES :
Moderate uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II

GLANDULAR STOMACH :
Very slight focal submucosal inflammatory cell
infiltration

LIVER :
Slight multifocal microgranuloma(s)

KIDNEYS :
Very slight uni-lateral focal basophilic tubule(s)

TESTES :
Very slight uni-lateral multifocal degeneration of
pachytene spermatocytes
Slight uni-lateral multifocal depletion of pachytene
spermatocytes : all stages
Slight uni-lateral multifocal degeneration of round
spermatids
Slight uni-lateral focal tubular atrophy

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROIDS, HEART, AORTA,
SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX
(LARYNGO-), OESOPHAGUS, FORESTOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS,
EPIDIDYMIDES, PROSTATE, SEMINAL VESICLES, COAGULATING
GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT
(KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001112	Killed	Necropsied on Day: 28
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PITUITARY :
Pars nervosa not sectioned

EYES :
Moderate uni-lateral focal retrobulbar haemorrhage

THYROID :
Uni-lateral focal ectopic thymic tissue

PARATHYROIDS :
Unilateral section

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Males

Animal Ref	Findings
001112	Continued from previous page

HEART :
Very slight focal myocardial mononuclear cell infiltration

LIVER :
Very slight multifocal microgranuloma(s)

KIDNEYS :
Very slight uni-lateral focal basophilic tubule(s)

EPIDIDYMIDES :
Very slight uni-lateral multifocal exfoliation of germ cells in the lumen

THYMUS :
Very slight multifocal congestion

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PARATHYROIDS, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH
NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, TESTES,
PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL
MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

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TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001201	Killed Necropsied on Day: 41

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001202 Killed Necropsied on Day: 45

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001203 Killed Necropsied on Day: 43

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001204 Killed Necropsied on Day: 43

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001205 Killed Necropsied on Day: 42

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001206 Killed Necropsied on Day: 41

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001207 Killed Necropsied on Day: 41

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001208	Killed Necropsied on Day: 44

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001209 Killed Necropsied on Day: 46

NASAL and PARANASAL CAVITIES :
Very slight focal mucosal mononuclear cell
infiltration : level I

001210 Killed Necropsied on Day: 44

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001211 Killed Necropsied on Day: 43

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001212 Killed Necropsied on Day: 42

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

001213 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level I and IIPARATHYROIDES :
Unilateral sectionHEART :
Very slight multifocal myocardial mononuclear cell
infiltrationKIDNEYS :
Very slight bi-lateral multifocal tubular
mineralisation
Very slight uni-lateral focal tubular dilatation with
luminal hyaline substances

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001213	Continued from previous page

KIDNEYS : Slight uni-lateral diffuse renal pelvic dilatation

THYMUS : Slight diffuse congestion

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS, LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDS, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, LIVER, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

001214 Killed Necropsied on Day: 28

PARATHYROIDS : Unilateral section

LIVER : Very slight multifocal microgranuloma(s)

UTERUS : Moderate diffuse dilatation of the uterine horn(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDS, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001215	Killed Necropsied on Day: 28

EYES :
LARYNX :
SALIVARY GLANDS :
TONGUE :
THYMUS :

Slight uni-lateral multifocal retrobulbar haemorrhage
Slight focal submucosal inflammatory cell infiltration
Very slight focal mononuclear cell infiltration :
mandibular gland
Slight focal intramuscular foreign-body granuloma :
due to inspissation of plant fibre
Slight multifocal haemorrhage

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, TRACHEA,
LUNGS, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, HEART, AORTA, MANDIBULAR LYMPH NODES,
PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH,
GLANDULAR STOMACH, LIVER, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, SPLEEN, HAEMATOP./LYMPHORET.TISSUE,
BONE MARROW (FEMUR), BONE MARROW (STERNUM)

001216	Killed	Necropsied on Day: 28
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NASAL and PARANASAL CAVITIES :
LARYNX :
MANDIBULAR LYMPH NODES :
LIVER :
UTERUS :
THYMUS :

Very slight multifocal mucosal inflammatory cell
infiltration : level I
Very slight focal mucosal psammoma bodies : level III
Slight focal submucosal foreign-body granuloma
Slight lymphoid hyperplasia
Very slight focal perivascular mononuclear cell
infiltration
Slight diffuse dilatation of the uterine horn(s)
Slight multifocal congestion

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001216	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH
NODES, THYROID, PARATHYROIDES, HEART, AORTA, SALIVARY
GLANDS, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, VAGINA, FALLOPIAN TUBES, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL
MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

001217 Killed Necropsied on Day: 28

EYES :
TRACHEA :
THYROID :
HEART :
LIVER :
KIDNEYS :

Slight uni-lateral focal retrobulbar haemorrhage
See block 38
Uni-lateral focal ectopic thymic tissue
Very slight multifocal myocardial mononuclear cell
infiltration
Slight focal microgranuloma(s)
Very slight uni-lateral focal basophilic tubule(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PARATHYROIDES, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH
NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS,
OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS,
SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE,
SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001218	Killed Necropsied on Day: 28

EYES :
Moderate uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell infiltration : level I
Very slight multifocal mucous (goblet) cell hyperplasia : level I

LIVER :
Very slight multifocal microgranuloma(s)

KIDNEYS :
Very slight bi-lateral multifocal tubular mineralisation

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROIDS, HEART, AORTA,
SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX
(LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH,
PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM,
JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001219	Killed	Necropsied on Day: 28
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EYES :
Slight uni-lateral focal retrobulbar haemorrhage

HARDERIAN GLANDS :
Slight uni-lateral focal necrosis

NASAL and PARANASAL CAVITIES :
Slight focal mucous (goblet) cell hyperplasia : level I
Slight focal mucosal psammoma bodies : level I

THYROID :
Uni-lateral focal ectopic thymic tissue

LIVER :
Very slight multifocal microgranuloma(s)

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STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001219	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PARATHYROIDES, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

001220 Killed Necropsied on Day: 28

EYES : Severe uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell infiltration : level I
Very slight multifocal mucous (goblet) cell hyperplasia : level I

LARYNX : Slight focal submucosal foreign-body granuloma

PARATHYROIDES : Unilateral section

LIVER : Very slight multifocal microgranuloma(s)

UTERUS : Slight diffuse dilatation of the uterine horn(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS, LACRIMAL GLANDS, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDES, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001221	Killed Necropsied on Day: 28

EYES : Slight uni-lateral multifocal retrobulbar haemorrhage

LACRIMAL GLANDS : Very slight uni-lateral focal Harderian gland change(s)

NASAL and PARANASAL CAVITIES : Very slight multifocal mucosal inflammatory cell infiltration : level I and II

LIVER : Very slight multifocal microgranuloma(s)
Slight focal hepatocellular necrosis

KIDNEYS : Slight uni-lateral diffuse renal pelvic dilatation

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
THYROID, PARATHYROIDS, HEART, AORTA, SALIVARY GLANDS,
MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-),
OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS,
MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM,
ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS,
OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS,
SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE,
SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

001222	Killed	Necropsied on Day: 28
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EYES : Slight uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES : Very slight focal mucosal inflammatory cell infiltration : level I

MANDIBULAR LYMPH NODES : Slight lymphoid hyperplasia

LIVER : Slight multifocal microgranuloma(s)
Slight multifocal hepatocellular necrosis

UTERUS : No microscopic evidence of macroscopic finding

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Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001222	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROIDS, HEART, AORTA,
SALIVARY GLANDS, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

001223 Killed Necropsied on Day: 28

PITUITARY :

Pars nervosa not sectioned

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II

LARYNX :

Very slight focal submucosal foreign-body granuloma

LUNGS :

Very slight focal alveolar histiocytosis

HEART :

Very slight focal myocardial mononuclear cell
infiltration

LIVER :

Very slight multifocal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, TRACHEA, LUNG ASSOCIATED LYMPH NODES,
THYROID, PARATHYROIDS, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Clean Air Control Treatment: CleanAir Sex: Females

Animal Ref	Findings
001224	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

PARATHYROIDES :

Unilateral section

GLANDULAR STOMACH :

Very slight multifocal mucosal inflammatory cell
infiltration

LIVER :

Very slight focal microgranuloma(s)

PANCREAS :

Very slight focal mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED
LYMPH NODES, THYROID, PARATHYROIDES, HEART, AORTA,
SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX
(LARYNGO-), OESOPHAGUS, FORESTOMACH, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Males

Animal Ref	Findings
002101	Killed Necropsied on Day: 28

LUNGS :
Slight multifocal interstitial mononuclear cell
infiltrationNO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002102 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002103 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and IILUNGS :
Very slight focal alveolar haemorrhage
Very slight multifocal alveolar histiocytosisNO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

002104 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Males

Animal Ref	Findings
002105	Killed Necropsied on Day: 28

LUNGS :

Slight multifocal interstitial mononuclear cell
infiltration
Slight focal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002106 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

LARYNX :

Very slight focal submucosal inflammatory cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

002107 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight focal mucosal psammoma bodies : level III

LARYNX :

Very slight multifocal submucosal mononuclear cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Males

Animal Ref	Findings
002108	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level I
Very slight focal mucosal psammoma bodies : level III

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

002109 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level II

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

002110 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002111 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Slight multifocal mucous (goblet) cell hyperplasia :
level I

LUNGS :

Very slight focal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

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STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Males

Animal Ref	Findings
002112	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I, II and III

LUNGS :

Very slight focal alveolar haemorrhage
Very slight focal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

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STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Females

Animal Ref	Findings
002213	Killed Necropsied on Day: 28

LARYNX :

Very slight focal submucosal foreign-body granuloma

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, TRACHEA, LUNGS, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002214 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002215 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002216 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002217 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II

LUNG ASSOCIATED LYMPH NODES :

Slight lymphoid hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, PHARYNX (LARYNGO-)

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STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Females

Animal Ref	Findings
002218	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

LARYNX :

Very slight multifocal submucosal inflammatory cell
infiltration

LUNGS :

Very slight multifocal interstitial mononuclear cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002219	Killed	Necropsied on Day: 28
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LARYNX :

Slight focal submucosal foreign-body granuloma

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, TRACHEA, LUNGS, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002220	Killed	Necropsied on Day: 28
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LUNG ASSOCIATED LYMPH NODES :

Slight lymphoid hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
PHARYNX (LARYNGO-)

002221	Killed	Necropsied on Day: 28
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NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

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STUDY : 02G08016

Dose Group : Low Dose Treatment: 30mg/m3THC Sex: Females

Animal Ref	Findings
002222	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

LARYNX :

Very slight multifocal submucosal mononuclear cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

002223 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

LUNGS :

Very slight focal interstitial mononuclear cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

002224 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Males

Animal Ref	Findings
003101	Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003102 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level I and II

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

003103 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

TRACHEA :
Very slight focal submucosal inflammatory cell
infiltration

LUNG ASSOCIATED LYMPH NODES :
Slight lymphoid hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, LUNGS, PHARYNX (LARYNGO-)

003104 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

LUNGS :
Very slight focal alveolar histiocytosis
Very slight focal osseous metaplasia

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Individual Animal Listing

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Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Males

Animal Ref	Findings
003104	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

003105 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

003106 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level I, II and III

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

003107 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Very slight focal mucosal psammoma bodies : level I

LUNGS :
Very slight focal interstitial inflammatory cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

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STUDY : 02G08016

Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Males

Animal Ref	Findings
003108	Killed Necropsied on Day: 28

LUNGS :

Very slight focal osseous metaplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003109	Killed	Necropsied on Day: 28
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NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

003110	Killed	Necropsied on Day: 28
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LARYNX :

Very slight focal submucosal mononuclear cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, TRACHEA, LUNGS, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003111	Killed	Necropsied on Day: 28
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LARYNX :

Very slight multifocal submucosal mononuclear cell
infiltration

LUNGS :

Very slight multifocal alveolar haemorrhage
Slight focal alveolar histiocytosis
Very slight focal interstitial inflammatory cell
infiltration
Very slight focal alveolar inflammatory cell
infiltration

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Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Males

Animal Ref	Findings
003111	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, TRACHEA, LUNG ASSOCIATED
LYMPH NODES, PHARYNX (LARYNGO-)

003112 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

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STUDY : 02G08016

Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Females

Animal Ref	Findings
003213	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Very slight focal mucosal psammoma bodies : level ILARYNX :
Slight focal dilatation of the submucosal glandsNO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX
(LARYNGO-)

003214 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003215 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level I and IINO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

003216 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003217 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

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STUDY : 02G08016

Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Females

Animal Ref	Findings
003218	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II

LARYNX :

Very slight multifocal submucosal mononuclear cell
infiltration

LUNGS :

Slight diffuse chronic passive congestion
Very slight multifocal alveolar haemorrhage
Very slight multifocal alveolar histiocytosis
Moderate diffuse alveolar dilatation

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003219	Killed	Necropsied on Day: 28
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NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003220	Killed	Necropsied on Day: 28
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LUNGS :

Slight focal interstitial mononuclear cell
infiltration
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG
ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003221	Killed	Necropsied on Day: 28
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NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

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STUDY : 02G08016

Dose Group : Medium Dose Treatment: 100mg/m3THC Sex: Females

Animal Ref	Findings
003222	Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

003223 Killed Necropsied on Day: 28

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS,
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003224 Killed Necropsied on Day: 28

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucosal inflammatory cell
infiltration : level I and II

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES,
PHARYNX (LARYNGO-)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m³THC Sex: Males

Animal Ref	Findings
004101	Killed Necropsied on Day: 28

EYES :
LUNGS :
LIVER :
TESTES :
EPIDIDYMIDES :

Slight uni-lateral focal retrobulbar haemorrhage
Very slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal microgranuloma(s)
Severe uni-lateral diffuse degeneration of spermatocytes
Severe uni-lateral diffuse degeneration of round spermatids : with formation of multinucleated giant cells
Severe uni-lateral diffuse disorganization of the germinal epithelium
Moderate uni-lateral multifocal sertoli-cell vacuolation
Uni-lateral aspermia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004102	Killed	Necropsied on Day: 28
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NASAL and PARANASAL CAVITIES :
LUNGS :

Slight focal mucous (goblet) cell hyperplasia : level I
Very slight focal mucosal inflammatory cell infiltration : level III
Slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia

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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m³THC Sex: Males

Animal Ref	Findings
004102	Continued from previous page

LUNGS :
Very slight focal interstitial mononuclear cell infiltration

LIVER :
Slight multifocal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS, LACRIMAL GLANDS, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, TESTES, EPIDIDYIMIDES, PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004103 Killed Necropsied on Day: 28

EYES :
Slight uni-lateral focal retrobulbar haemorrhage
Slight uni-lateral focal intraocular haemorrhage

HARDERIAN GLANDS :
Slight uni-lateral multifocal haemorrhage

LUNGS :
Very slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Slight multifocal congestion

THYROID :
Very slight uni-lateral focal mononuclear cell infiltration

HEART :
Very slight multifocal myocardial mononuclear cell infiltration

MANDIBULAR LYMPH NODES :
Slight congestion

LIVER :
Very slight multifocal microgranuloma(s)

KIDNEYS :
Very slight uni-lateral focal basophilic tubule(s)

TESTES :
Slight uni-lateral multifocal tubular dilatation

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TOXICOLOGY AND EXPERIMENTAL MEDICINE
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STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings
004103	Continued from previous page

TESTES :

Slight uni-lateral multifocal depletion of round spermatids
Very slight uni-lateral multifocal spermatid retention : late stages

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PARATHYROIDES, AORTA, SALIVARY GLANDS, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, EPIDIDYMITES, PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004104 Killed Necropsied on Day: 28

EYES :

Slight uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :

Very slight focal mucous (goblet) cell hyperplasia : level I

LUNGS :

Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal interstitial mononuclear cell infiltration

HEART :

Very slight multifocal myocardial mononuclear cell infiltration

KIDNEYS :

Very slight uni-lateral focal basophilic tubule(s)
No microscopic evidence of macroscopic finding

TESTES :

Very slight uni-lateral multifocal sloughing of germ cells in the lumen

EPIDIDYMITES :

Very slight uni-lateral multifocal interstitial mononuclear cell infiltration

SPINAL CORD :

Thoracic and lumbar segments not submitted

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TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m³THC Sex: Males

Animal Ref	Findings
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NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH
NODES, THYROID, PARATHYROIDES, AORTA, SALIVARY GLANDS,
MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-),
OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, LIVER,
PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM,
JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER,
ADRENALS, PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004105 Killed Necropsied on Day: 28

LUNGS :
Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal interstitial mononuclear cell
infiltration

PARATHYROIDES :
Unilateral section

HEART :
Very slight multifocal myocardial mononuclear cell
infiltration

LIVER :
Slight multifocal microgranuloma(s)

KIDNEYS :
Very slight uni-lateral focal basophilic tubule(s)
Slight uni-lateral diffuse renal pelvic dilatation

EPIDIDYMIDES :
Very slight uni-lateral multifocal interstitial
mononuclear cell infiltration

PROSTATE :
Moderate multifocal non-suppurative inflammation

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m³THC Sex: Males

Animal Ref	Findings
004105	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, TESTES, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004106 Killed Necropsied on Day: 28

LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal interstitial mononuclear cell infiltration

HEART :
Very slight multifocal myocardial mononuclear cell infiltration

LIVER :
Very slight multifocal microgranuloma(s)

THYMUS :
Very slight focal haemorrhage

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, TESTES, EPIDIDYIMIDES, PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings
004107	Killed Necropsied on Day: 28

EYES :
Slight bi-lateral multifocal retrobulbar haemorrhage
Slight uni-lateral focal retrobulbar mononuclear cell infiltration

HARDERIAN GLANDS :
Slight uni-lateral focal yellow-brown pigment deposit(s)

NASAL and PARANASAL CAVITIES :
Very slight focal mucosal inflammatory cell infiltration

LUNGS :
Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal interstitial mononuclear cell infiltration
Very slight focal bronchial mucous (goblet) cell hyperplasia

HEART :
Very slight multifocal myocardial mononuclear cell infiltration

GLANDULAR STOMACH :
Very slight multifocal mucosal inflammatory cell infiltration

LIVER :
Slight multifocal microgranuloma(s)
Very slight multifocal perivascular mononuclear cell infiltration
Slight multifocal hepatocellular necrosis

KIDNEYS :
No microscopic evidence of macroscopic finding

EPIDIDYMIDES :
Very slight uni-lateral focal interstitial mononuclear cell infiltration

PROSTATE :
Slight multifocal interstitial mononuclear cell infiltration
Very slight multifocal intra-acinar inflammatory cell infiltration

THYMUS :
Very slight focal haemorrhage

BONE MARROW (FEMUR) :
Slight focal fibrosis

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STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings
004107	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH
NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, TESTES, SEMINAL VESICLES, COAGULATING GLANDS,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, SPLEEN, HAEMATOP./LYMPHORET.TISSUE,
BONE MARROW (STERNUM)

004108 Killed Necropsied on Day: 28

EYES :

Slight uni-lateral focal retrobulbar haemorrhage

HARDERIAN GLANDS :

Slight uni-lateral focal yellow-brown pigment
deposit(s)
Slight uni-lateral focal atrophy

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I

LUNGS :

Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia

PARATHYROIDES :

Unilateral section

MANDIBULAR LYMPH NODES :

Slight lymphoid hyperplasia

PANCREAS :

Slight focal mononuclear cell infiltration

EPIDIDYMIDES :

Very slight uni-lateral focal interstitial
mononuclear cell infiltration

PROSTATE :

Slight multifocal interstitial mononuclear cell
infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, HEART, AORTA, SALIVARY GLANDS, TONGUE,
PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR
STOMACH, LIVER, MESENTERY, MESENTERIAL LYMPH NODES,

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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings
004108	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS,
URINARY BLADDER, ADRENALS, TESTES, SEMINAL VESICLES,
COAGULATING GLANDS, MAMMARY GLANDS, SKIN, STERNUM, FEMUR,
JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS
OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004109 Killed Necropsied on Day: 28

EYES :
LUNGS : Severe uni-lateral focal retrobulbar haemorrhage
Slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia
MANDIBULAR LYMPH NODES :
Unilateral section
LIVER :
Very slight multifocal microgranuloma(s)
PANCREAS :
Slight focal islet-cell hyperplasia
KIDNEYS :
Slight uni-lateral hydronephrosis
Very slight uni-lateral focal basophilic tubule(s)
PROSTATE :
Very slight focal intra-acinar inflammatory cell
infiltration
Very slight focal interstitial inflammatory cell
infiltration
THYMUS :
No microscopic evidence of macroscopic finding

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROIDS, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, MESENTERY, MESENTERIAL
LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON,
RECTUM, URINARY BLADDER, ADRENALS, TESTES, EPIDIDYIMIDES,
SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY GLANDS,
SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE,
SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m³THC Sex: Males

Animal Ref	Findings
004110	Killed Necropsied on Day: 28

EYES :
Severe bi-lateral multifocal retrobulbar haemorrhage

LARYNX :
Very slight focal submucosal inflammatory cell infiltration

LUNGS :
Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia

PANCREAS :
Slight focal acinar-cell atrophy

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, TRACHEA,
LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDES,
HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES,
TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH,
GLANDULAR STOMACH, LIVER, MESENTERY, MESENTERIAL LYMPH
NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM,
KIDNEYS, URINARY BLADDER, ADRENALS, TESTES, EPIDIDYMITES,
PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004111	Killed	Necropsied on Day: 28
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NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Slight multifocal mucous (goblet) cell hyperplasia :
level I

LUNGS :
Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia

PARATHYROIDES :
Unilateral section

HEART :
Very slight focal myocardial mononuclear cell
infiltration

LIVER :
Slight focal microgranuloma(s)

PANCREAS :
Very slight focal mononuclear cell infiltration

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Dose Group : High Dose Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings
004111	Continued from previous page

KIDNEYS :

Very slight uni-lateral focal basophilic tubule(s)
Very slight uni-lateral focal tubular dilatation with
luminal hyaline substances

EPIDIDYMIDES :

Very slight uni-lateral focal interstitial
mononuclear cell infiltration

MAMMARY GLANDS :

See block 10

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH
NODES, THYROID, PARATHYROID, AORTA, SALIVARY GLANDS,
MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-),
OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, TESTES,
PROSTATE, SEMINAL VESICLES, COAGULATING GLANDS, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL
MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL,
THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW
(FEMUR), BONE MARROW (STERNUM)

004112 Killed Necropsied on Day: 28

EYES :

Slight uni-lateral focal retrobulbar haemorrhage

NASAL and PARANASAL CAVITIES :

Slight multifocal mucosal inflammatory cell
infiltration : level I and II
Slight multifocal mucous (goblet) cell hyperplasia :
level I

LUNGS :

Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia

THYROID :

Uni-lateral focal ectopic thymic tissue

HEART :

Very slight multifocal myocardial mononuclear cell
infiltration
Very slight focal myocardial degeneration

LIVER :

Very slight multifocal microgranuloma(s)

NERVUS OPTICUS :

Unilateral section

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TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings
004112	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH
NODES, PARATHYROIDES, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, TESTES, EPIDIDYIMIDES, PROSTATE, SEMINAL
VESICLES, COAGULATING GLANDS, MAMMARY GLANDS, SKIN,
STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL
CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

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FRAUNHOFER INSTITUTE OF
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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004201	Killed Necropsied on Day: 44

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

004202 Killed Necropsied on Day: 44

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

004203 Killed Necropsied on Day: 46

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I and II

004204 Killed Necropsied on Day: 46

NASAL and PARANASAL CAVITIES :
Slight multifocal mucosal inflammatory cell
infiltration : level I

004205 Killed Necropsied on Day: 41

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level I
Very slight multifocal mucous (goblet) cell
hyperplasia : level I

004206 Killed Necropsied on Day: 44

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

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Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004207	Killed Necropsied on Day: 42

NASAL and PARANASAL CAVITIES :
Slight focal dilatation of the submucosal glands :
level I
Very slight focal mucosal psammoma bodies : level IV

004208 Killed Necropsied on Day: 45

NASAL and PARANASAL CAVITIES :
Very slight focal mucosal inflammatory cell
infiltration : level III

004209 Killed Necropsied on Day: 43

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level I

004210 Killed Necropsied on Day: 42

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES

004211 Killed Necropsied on Day: 43

NASAL and PARANASAL CAVITIES :
Very slight focal mucosal inflammatory cell
infiltration : level I

004212 Killed Necropsied on Day: 45

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucosal inflammatory cell
infiltration : level II

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004213	Killed Necropsied on Day: 28

LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia

THYROID :
Uni-lateral focal ectopic thymic tissue

HEART :
Very slight multifocal myocardial mononuclear cell infiltration

LIVER :
Very slight multifocal microgranuloma(s)

THYMUS :
No microscopic evidence of macroscopic finding

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PARATHYROIDS,
AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE,
PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH,
GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH
NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM,
KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, UTERUS,
VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM,
FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD,
NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004214	Killed	Necropsied on Day: 28
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EYES :
Slight uni-lateral focal retrobulbar haemorrhage

LARYNX :
Very slight focal submucosal inflammatory cell infiltration

LUNGS :
Very slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal interstitial mononuclear cell infiltration

HEART :
Very slight multifocal myocardial mononuclear cell infiltration

LIVER :
Very slight focal microgranuloma(s)

PANCREAS :
Very slight focal mononuclear cell infiltration

004214 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004214	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, TRACHEA,
LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDES,
AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE,
PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH,
GLANDULAR STOMACH, MESENTERY, MESENTERIAL LYMPH NODES,
DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS,
URINARY BLADDER, ADRENALS, OVARIES, UTERUS, VAGINA,
FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR,
JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS
OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004215 Killed Necropsied on Day: 28

EYES : Slight uni-lateral multifocal retrobulbar haemorrhage

LUNGS : Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal interstitial inflammatory cell
infiltrationLIVER : Very slight multifocal microgranuloma(s)
Very slight focal perivascular mononuclear cell
infiltration

UTERUS : Moderate diffuse dilatation of the uterine horn(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROIDES, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, VAGINA, FALLOPIAN TUBES, MAMMARY
GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004216	Killed Necropsied on Day: 28

EYES :
Slight uni-lateral focal retrobulbar haemorrhage

HARDERIAN GLANDS :
Slight uni-lateral focal necrosis

LACRIMAL GLANDS :
Slight uni-lateral focal mononuclear cell infiltration

LUNGS :
Very slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal bronchial mucous (goblet) cell hyperplasia
Very slight focal interstitial mononuclear cell infiltration

MANDIBULAR LYMPH NODES :
Unilateral section

LIVER :
Very slight multifocal microgranuloma(s)

PANCREAS :
Slight focal mononuclear cell infiltration

UTERUS :
Moderate diffuse dilatation of the uterine horn(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDS, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004217	Killed	Necropsied on Day: 28
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EYES :
Slight uni-lateral focal retrobulbar haemorrhage

LUNGS :
Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Slight multifocal interstitial inflammatory cell infiltration

004217 Continued on the next page

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004217	Continued from previous page

HEART :
Very slight multifocal myocardial mononuclear cell infiltrationMANDIBULAR LYMPH NODES :
Unilateral sectionLIVER :
Very slight multifocal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH
NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004218 Killed Necropsied on Day: 28

EYES :
Slight uni-lateral focal retrobulbar haemorrhage
LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal interstitial inflammatory cell infiltration
THYROID :
Uni-lateral focal ectopic thymic tissue
PARATHYROID :
Unilateral section
GLANDULAR STOMACH :
Very slight multifocal submucosal inflammatory cell infiltration
LIVER :
Slight focal microgranuloma(s)
Slight multifocal hepatocellular necrosis

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004218	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PARATHYROID, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004219 Killed Necropsied on Day: 28

EYES :

Moderate uni-lateral focal retrobulbar haemorrhage

HARDERIAN GLANDS :

Slight uni-lateral focal hemorrhage

NASAL and PARANASAL CAVITIES :

Very slight multifocal mucous (goblet) cell hyperplasia : level I

LUNGS :

Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal interstitial mononuclear cell infiltration

LIVER :

Slight multifocal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004220	Killed Necropsied on Day: 28

EYES : Slight uni-lateral focal retrobulbar haemorrhage

LUNGS : Slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia

LIVER : Very slight multifocal microgranuloma(s)

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROID, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,
FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004221	Killed	Necropsied on Day: 28
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EYES : Slight uni-lateral focal retrobulbar haemorrhage

TRACHEA : Bifurcation not on section

LUNGS : Slight multifocal alveolar histiocytosis
Slight multifocal bronchiolo-alveolar hyperplasia
Very slight multifocal bronchial mucous (goblet) cell
hyperplasia

PARATHYROID : Unilateral section

LIVER : Slight focal microgranuloma(s)
Slight focal hepatocellular necrosis

UTERUS : Slight diffuse dilatation of the uterine horn(s)

VAGINA : Focal squamous cyst(s)

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Date: 21-JAN-2009 Time: 13:44

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004221	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER, ADRENALS, OVARIES, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

004222 Killed Necropsied on Day: 28

EYES : Slight uni-lateral multifocal retrobulbar haemorrhage

HARDERIAN GLANDS : Slight uni-lateral focal necrosis

LUNGS : Very slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia

HEART : Slight focal myocardial mononuclear cell infiltration

LIVER : Very slight multifocal microgranuloma(s)

KIDNEYS : No microscopic evidence of macroscopic finding
Very slight uni-lateral focal interstitial mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROID, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY, MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM, CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS, SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE MARROW (STERNUM)

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m³THC Sex: Females

Animal Ref	Findings
004223	Killed Necropsied on Day: 28

EYES :
LARYNX :
LUNGS :
MANDIBULAR LYMPH NODES :

Slight uni-lateral focal retrobulbar haemorrhage
Very slight focal submucosal foreign-body granuloma
Very slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal bronchial mucous (goblet) cell hyperplasia
Unilateral section

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, TRACHEA,
LUNG ASSOCIATED LYMPH NODES, THYROID, PARATHYROIDS,
HEART, AORTA, SALIVARY GLANDS, MANDIBULAR LYMPH NODES,
TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS, FORESTOMACH,
GLANDULAR STOMACH, LIVER, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, KIDNEYS, URINARY BLADDER,
ADRENALS, OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES,
MAMMARY GLANDS, SKIN, STERNUM, FEMUR, JOINT (KNEE),
SKELETAL MUSCLE, SPINAL CORD, NERVUS OPTICUS,
NERVE-PERIPHERAL, THYMUS, SPLEEN,
HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR), BONE
MARROW (STERNUM)

004224	Killed	Necropsied on Day: 28
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LUNGS :
LIVER :
KIDNEYS :

Slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal microgranuloma(s)
Very slight uni-lateral focal interstitial mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

CEREBRUM, CEREBELLUM, PITUITARY, EYES, HARDERIAN GLANDS,
LACRIMAL GLANDS, NASAL and PARANASAL CAVITIES, LARYNX,
TRACHEA, LUNG ASSOCIATED LYMPH NODES, THYROID,
PARATHYROIDS, HEART, AORTA, SALIVARY GLANDS, MANDIBULAR
LYMPH NODES, TONGUE, PHARYNX (LARYNGO-), OESOPHAGUS,

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FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02G08016

Dose Group : High Dose Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings
004224	Continued from previous page

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-

FORESTOMACH, GLANDULAR STOMACH, PANCREAS, MESENTERY,
MESENTERIAL LYMPH NODES, DUODENUM, JEJUNUM, ILEUM,
CAECUM, COLON, RECTUM, URINARY BLADDER, ADRENALS,
OVARIES, UTERUS, VAGINA, FALLOPIAN TUBES, MAMMARY GLANDS,
SKIN, STERNUM, FEMUR, JOINT (KNEE), SKELETAL MUSCLE,
SPINAL CORD, NERVUS OPTICUS, NERVE-PERIPHERAL, THYMUS,
SPLEEN, HAEMATOP./LYMPHORET.TISSUE, BONE MARROW (FEMUR),
BONE MARROW (STERNUM)

*** Listing Complete ***

Appendix M

Spermatology Individual Data

20-NOV-2008 13:07

Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

CAUDA EPIDIDYMAL SPERM COUNT

ANIMAL NUMBER	SPERM COUNT millions
1101	13.500
1102	38.500
1103	10.000
1104	28.500
1105	38.500
1106	45.000
1107	60.000
1108	23.000
1109	40.000
1110	40.500
1111	20.000
1112	100.000
MEAN	38.125
S.D.	24.142
N	12
2101	12.000
2102	19.000
2103	25.000
2104	51.000
2105	38.500
2106	18.000
2107	23.000
2108	70.000
2109	60.000
2110	20.000
2111	20.000
2112	30.500
MEAN	32.250
S.D.	18.625
N	12
3101	27.000
3102	31.500
3103	26.500
3104	15.500
3105	21.000
3106	50.000
3107	20.500
3108	12.500
3109	26.000
3110	30.000
3111	35.000
3112	30.000
MEAN	27.125
S.D.	9.784
N	12
4101	18.500
4102	8.000
4103	15.000
4104	38.000
4105	35.000
4106	38.000
4107	36.000
4108	20.000
4109	18.000
4110	22.000
4111	30.000
4112	16.000
MEAN	24.542
S.D.	10.343
N	12

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SPERM MORPHOLOGY

ANIMAL NUMBER	PERCENT ABNORMAL SPERM
1101	7.0
1102	1.0
1103	5.5
1104	4.0
1105	3.0
1106	5.5
1107	2.0
1108	4.0
1109	2.0
1110	4.5
1111	6.0
1112	3.0
MEAN	4.0
S.D.	1.8
N	12
2101	3.0
2102	3.0
2103	2.5
2104	2.5
2105	1.5
2106	2.5
2107	3.0
2108	3.5
2109	1.5
2110	4.0
2111	2.5
2112	4.0
MEAN	2.8
S.D.	0.8
N	12
3101	1.5
3102	3.5
3103	8.0
3104	1.5
3105	2.0
3106	3.0
3107	6.0
3108	4.0
3109	2.0
3110	2.0
3111	7.5
3112	1.5
MEAN	3.5
S.D.	2.4
N	12
4101	2.5
4102	3.0
4103	3.0
4104	2.5
4105	2.0
4106	3.0
4107	4.0
4108	1.0
4109	3.0
4110	3.0
4111	2.5
4112	4.0
MEAN	2.8
S.D.	0.8
N	12

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

SPERM MOTILITY

ANIMAL NUMBER	PERCENT MOTILITY
1101	50
1102	55
1103	60
1104	70
1105	75
1106	40
1107	65
1108	55
1109	55
1110	20
1111	10
1112	35
MEAN	49
S.D.	20
N	12
2101	55
2102	45
2103	50
2104	80
2105	50
2106	60
2107	60
2108	85
2109	25
2110	45
2111	20
2112	60
MEAN	53
S.D.	19
N	12
3101	50
3102	55
3103	85
3104	40
3105	40
3106	40
3107	80
3108	65
3109	60
3110	20
3111	80
3112	85
MEAN	58
S.D.	21
N	12
4101	55
4102	40
4103	50
4104	75
4105	70
4106	60
4107	60
4108	60
4109	55
4110	50
4111	40
4112	0
MEAN	51
S.D.	19
N	12

Appendix N

Mating and Pregnancy and F1 Generation Individual Data

20-NOV-2008 13:09

Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL COHABITATION DATA

Clean Air Control

PRENATAL PART				
MALE#	DATE OF COHAB.	FEMALE#	MATING DATE	MATING DAYS
1101	29-JUL-08	1201	30-JUL-08	1
1102	29-JUL-08	1202	2-AUG-08	4
1103	29-JUL-08	1203	#	
1104	30-JUL-08	1204	4-AUG-08	5
1105	30-JUL-08	1205	#	
1106	30-JUL-08	1206	31-JUL-08	1
1107	31-JUL-08	1207	1-AUG-08	1
1108	31-JUL-08	1208	4-AUG-08	4
1109	31-JUL-08	1209	5-AUG-08	5
1110	1-AUG-08	1210	4-AUG-08	3
1111	1-AUG-08	1211	4-AUG-08	3
1112	1-AUG-08	1212	2-AUG-08	1

animal was pregnant although no sperm was detected

Low Dose (30 mg/m3)

PRENATAL PART				
MALE#	DATE OF COHAB.	FEMALE#	MATING DATE	MATING DAYS
2101	29-JUL-08	2201	#	
2102	29-JUL-08	2202	31-JUL-08	2
2103	29-JUL-08	2203	1-AUG-08	3
2104	30-JUL-08	2204	*	
2105	30-JUL-08	2205	31-JUL-08	1
2106	30-JUL-08	2206	1-AUG-08	2
2107	31-JUL-08	2207	7-AUG-08	7
2108	31-JUL-08	2208	3-AUG-08	3
2109	31-JUL-08	2209	1-AUG-08	1
2110	1-AUG-08	2210	5-AUG-08	4
2111	1-AUG-08	2211	2-AUG-08	1
2112	1-AUG-08	2212	2-AUG-08	1

animal was pregnant although no sperm was detected

* animal was not pregnant and no sperm was detected

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL COHABITATION DATA

Medium Dose (100 mg/m3)

PRENATAL PART				
MALE#	DATE OF COHAB.	FEMALE#	MATING DATE	MATING DAYS
3101	29-JUL-08	3201	31-JUL-08	2
3102	29-JUL-08	3202	2-AUG-08	4
3103	29-JUL-08	3203	31-JUL-08	2
3104	30-JUL-08	3204	31-JUL-08	1
3105	30-JUL-08	3205	4-AUG-08	5
3106	30-JUL-08	3206	#	
3107	31-JUL-08	3207	4-AUG-08	4
3108	31-JUL-08	3208	1-AUG-08	1
3109	31-JUL-08	3209	3-AUG-08	3
3110	1-AUG-08	3210	3-AUG-08	2
3111	1-AUG-08	3211	3-AUG-08	2
3112	1-AUG-08	3212	3-AUG-08	2

animal was pregnant although no sperm was detected

High Dose (300 mg/m3)

PRENATAL PART				
MALE#	DATE OF COHAB.	FEMALE#	MATING DATE	MATING DAYS
4101	29-JUL-08	4201	2-AUG-08	4
4102	29-JUL-08	4202	2-AUG-08	4
4103	29-JUL-08	4203	3-AUG-08	5
4104	30-JUL-08	4204	4-AUG-08	5
4105	30-JUL-08	4205	31-JUL-08	1
4106	30-JUL-08	4206	2-AUG-08	3
4107	31-JUL-08	4207	#	
4108	31-JUL-08	4208	4-AUG-08	4
4109	31-JUL-08	4209	4-AUG-08	4
4110	1-AUG-08	4210	2-AUG-08	1
4111	1-AUG-08	4211	#	
4112	1-AUG-08	4212	6-AUG-08	5

animal was pregnant although no sperm was detected

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL GESTATION BODY WEIGHTS (GRAMS)

Clean Air Control

ANIMAL#		DAY OF GESTATION			
		0	7	14	21
1201x	NP	191	201	210	214
1202		177	198	217	268
1204		176	199	224	266
1206		188	207	229	281
1207		189	208	226	286
1208		190	213	241	298
1209		186	214	236	291
1210		188	198	222	278
1211		189	207	229	295
1212		202	225	251	317
MEAN		187	208	230	287
S.D.		7.6	8.7	10.5	15.8
N		9	9	9	9
NP=NOT PREGNANT		x=EXCLUDED FROM MEAN			

Low Dose (30 mg/m3)

ANIMAL#		DAY OF GESTATION			
		0	7	14	21
2202		186	202	219	271
2203		194	215	245	317
2205		191	213	231	291
2206x	NP	193	196	209	211
2207		200	212	232	297
2208		189	203	220	285
2209x	NP	187	194	202	203
2210		200	224	244	291
2211		198	220	245	306
2212		194	205	229	273
MEAN		194	212	233	291
S.D.		5.3	8.1	10.6	15.5
N		8	8	8	8
NP=NOT PREGNANT		x=EXCLUDED FROM MEAN			

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL GESTATION BODY WEIGHTS (GRAMS)

Medium Dose (100 mg/m3)

ANIMAL#	DAY OF GESTATION			
	0	7	14	21
3201	192	207	226	288
3202	191	211	236	293
3203	205	224	248	299
3204	199	211	240	297
3205	198	214	234	297
3207	214	240	258	319
3208	187	211	232	290
3209x NP	204	226	224	221
3210	196	213	233	294
3211	202	217	231	286
3212	196	216	233	281
MEAN	198	216	237	294
S.D.	7.6	9.3	9.4	10.3
N	10	10	10	10

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

High Dose (300 mg/m3)

ANIMAL#	DAY OF GESTATION			
	0	7	14	21
4201	194	206	231	291
4202	200	219	237	297
4203	196	213	235	293
4204	201	217	231	280
4205x NP	197	217	225	231
4206	197	211	228	268
4208	193	209	226	248
4209	197	207	229	§
4210	194	213	234	288
4212	204	225	240	305
MEAN	197	213	232	284
S.D.	3.6	6.3	4.6	18.3
N	9	9	9	8

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

§ animal gave birth on day 21 pc

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL GESTATION BODY WEIGHT GAIN (GRAMS)

Clean Air Control

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
1201x NP	10	9	4
1202	21	19	51
1204	23	25	42
1206	20	22	52
1207	20	17	60
1208	23	29	57
1209	28	21	55
1210	10	24	56
1211	18	22	65
1212	22	26	66
MEAN	21	23	56
S.D.	5.0	3.5	7.4
N	9	9	9

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

Low Dose (30 mg/m3)

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
2202	16	18	52
2203	22	30	72
2204x NP			
2205	23	18	60
2206x NP	3	13	2
2207	12	20	65
2208	15	17	65
2209x NP	8	8	1
2210	24	20	47
2211	22	24	61
2212	11	24	44
MEAN	18	21	58
S.D.	5.1	4.4	9.7
N	8	8	8

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL GESTATION BODY WEIGHT GAIN (GRAMS)

Medium Dose (100 mg/m3)

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
3201	15	19	62
3202	20	25	57
3203	18	25	50
3204	12	28	57
3205	16	19	63
3207	26	18	61
3208	24	21	58
3209x NP	22	-2	-2
3210	17	20	61
3211	16	13	55
3212	19	17	49
MEAN	18	21	57
S.D.	4.1	4.3	4.9
N	10	10	10

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

High Dose (300 mg/m3)

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
4201	11	26	60
4202	19	18	61
4203	17	21	59
4204	16	14	49
4205x NP	21	8	5
4206	14	17	41
4208	15	17	22
4209	10	23	
4210	19	22	53
4212	22	15	65
MEAN	16	19	51
S.D.	3.8	3.9	14.0
N	9	9	8

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL GESTATION FOOD CONSUMPTION -- (GRAMS/ANIMAL/DAY)

Clean Air Control

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
1201x NP	14	15	14
1202	14	15	18
1204	15	17	20
1206	16	17	20
1207	16	17	19
1208	16	18	20
1209	15	18	21
1210	13	16	19
1211	16	17	21
1212	17	19	23
MEAN	15	17	20
S.D.	1.0	1.1	1.6
N	9	9	9

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

Low Dose (30 mg/m3)

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
2202	15	16	17
2203	16	18	22
2204x NP			
2205	16	16	20
2206x NP	13	14	13
2207	14	18	20
2208	15	16	19
2209x NP	15	16	15
2210	17	19	21
2211	17	18	21
2212	14	16	17
MEAN	15	17	20
S.D.	1.2	1.2	1.7
N	8	8	8

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL GESTATION FOOD CONSUMPTION -- (GRAMS/ANIMAL/DAY)

Medium Dose (100 mg/m3)

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
3201	14	17	20
3202	16	17	19
3203	16	18	21
3204	15	16	19
3205	16	17	20
3207	15	17	20
3208	16	17	19
3209x NP	16	14	14
3210	14	16	19
3211	15	17	19
3212	16	17	19
MEAN	15	17	20
S.D.	0.6	0.6	0.6
N	10	10	10

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

High Dose (300 mg/m3)

ANIMAL#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
4201	14	17	18
4202	14	16	20
4203	14	15	18
4204	14	15	18
4205x NP	16	17	15
4206	14	15	18
4208	14	15	17
4209	13	15	18
4210	16	18	21
4212	15	16	20
MEAN	14	16	19
S.D.	0.9	0.9	1.3
N	9	9	9

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL FLUID CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

Clean Air Control

FEMALE#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
1201x NP	27	29	25
1202	24	24	32
1204	25	28	32
1206	24	26	32
1207	22	22	29
1208	24	28	35
1209	23	28	35
1210	21	25	30
1211	24	25	33
1212	27	33	44
MEAN	24	27	34
S.D.	1.7	3.0	4.4
N	9	9	9

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

Low Dose (30 mg/m3)

FEMALE#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
2202	24	24	30
2203	26	29	35
2204x NP	27	28	34
2205	23	23	24
2206x NP	21	27	33
2207	22	24	29
2208	24	24	22
2209x NP	24	28	33
2210	29	31	38
2211	23	26	30
2212	24	27	33
MEAN	24	27	33
S.D.	2.5	2.4	3.0
N	8	8	8

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL FLUID CONSUMPTION DURING GESTATION -- GRAMS/ANIMAL/DAY

Medium Dose (100 mg/m3)

FEMALE#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
3201	22	26	33
3202	24	25	32
3203	29	31	39
3204	48	49	58
3205	28	30	39
3207	25	24	34
3208	24	27	33
3209x NP	29	24	22
3210	26	26	32
3211	30	29	37
3212	27	1	33
MEAN	28	27	37
S.D.	7.2	11.6	7.9
N	10	10	10

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

High Dose (300 mg/m3)

FEMALE#	DAY OF GESTATION		
	0 - 7	7 - 14	14 - 21
4201	23	27	34
4202	25	26	35
4203	24	26	35
4204	25	27	33
4205x NP	30	31	29
4206	22	26	31
4208	26	27	33
4209	28	32	37
4210	29	31	39
4212	36	35	38
MEAN	26	29	35
S.D.	4.2	3.3	2.7
N	9	9	9

NP=NOT PREGNANT

x=EXCLUDED FROM MEAN

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL POSTPARTUM BODY WEIGHTS (GRAMS)

Clean Air Control

Animal No.	DAY OF LACTATION	
	0	4
1202	195	215
1203	212	235
1204	207	
1205	203	219
1206	216	243
1207	219	224
1208	224	247
1209	217	233
1210	197	222
1211	224	223
1212	235	260
MEAN	214	232
S.D.	12.1	14.1
N	11	10

Low Dose (30 mg/m3)

Animal No.	DAY OF LACTATION	
	0	4
2201	203	229
2202	203	228
2203	226	251
2205	220	231
2207	223	234
2208	202	220
2210	220	241
2211	224	255
2212	199	224
MEAN	213	235
S.D.	11.3	12.0
N	9	9

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL POSTPARTUM BODY WEIGHTS (GRAMS)

Medium Dose (100 mg/m3)

Animal No.	DAY OF LACTATION	
	0	4
3201	225	225
3202	216	242
3203	237	260
3204	222	237
3205	220	227
3206	229	255
3207	254	260
3208	216	234
3210	213	226
3211	213	237
3212	212	236
MEAN	223	240
S.D.	12.7	13.0
N	11	11

High Dose (300 mg/m3)

Animal No.	DAY OF LACTATION	
	0	4
4201	212	237
4202	227	237
4203	214	235
4204	211	229
4206	216	234
4208	204	223
4209	222	230
4210	216	234
4211	210	230
4212	243	244
MEAN	217	233
S.D.	11.0	5.7
N	10	10

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL POSTPARTUM BODY WEIGHT GAIN (GRAMS)

Clean Air Control

FEMALE#	DAY OF LACTATION	
	0	4
1202	20	
1203	23	
1205	16	
1206	26	
1207	4	
1208	23	
1209	16	
1210	25	
1211	-1	
1212	25	
MEAN	18	
S.D.	9.2	
N	10	

Low Dose (30 mg/m3)

FEMALE#	DAY OF LACTATION	
	0	4
2201	26	
2202	25	
2203	25	
2205	10	
2207	10	
2208	17	
2210	22	
2211	31	
2212	25	
MEAN	21	
S.D.	7.3	
N	9	

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL POSTPARTUM BODY WEIGHT GAIN (GRAMS)

Medium Dose (100 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
3201	1
3202	26
3203	23
3204	15
3205	7
3206	26
3207	6
3208	18
3210	13
3211	24
3212	24
MEAN	17
S.D.	9.1
N	11

High Dose (300 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
4201	25
4202	11
4203	20
4204	18
4206	18
4208	19
4209	8
4210	18
4211	20
4212	1
MEAN	16
S.D.	7.2
N	10

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL POSTPARTUM FOOD CONSUMPTION -- GRAMS/ANIMAL/DAY

Clean Air Control

FEMALE#	DAY OF LACTATION	
	0	4
1202	24	
1203	24	
1205	21	
1206	26	
1207	19	
1208	28	
1209	22	
1210	28	
1211	25	
1212	32	
MEAN	25	
S.D.	3.8	
N	10	

Low Dose (30 mg/m3)

FEMALE#	DAY OF LACTATION	
	0	4
2201	26	
2202	26	
2203	27	
2205	20	
2207	24	
2208	25	
2210	27	
2211	28	
2212	21	
MEAN	25	
S.D.	2.8	
N	9	

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL POSTPARTUM FOOD CONSUMPTION -- GRAMS/ANIMAL/DAY

Medium Dose (100 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
3201	22
3202	26
3203	28
3204	23
3205	23
3206	31
3207	25
3208	27
3210	23
3211	27
3212	27
MEAN	26
S.D.	2.7
N	11

High Dose (300 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
4201	28
4202	23
4203	27
4204	24
4206	23
4208	21
4209	21
4210	25
4211	27
4212	25
MEAN	24
S.D.	2.6
N	10

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL FLUID CONSUMPTION DURING LACTATION -- GRAMS/ANIMAL/DAY

Clean Air Control

FEMALE#	DAY OF LACTATION
	0 - 4
1202	35
1203	38
1205	38
1206	37
1207	31
1208	43
1209	35
1210	43
1211	37
1212	48
MEAN	38
S.D.	5.1
N	10

Low Dose (30 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
2201	40
2202	41
2203	38
2205	34
2207	37
2208	41
2210	41
2211	43
2212	35
MEAN	39
S.D.	3.1
N	9

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL MATERNAL FLUID CONSUMPTION DURING LACTATION -- GRAMS/ANIMAL/DAY

Medium Dose (100 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
3201	31
3202	38
3203	40
3204	64
3205	37
3206	46
3207	35
3208	40
3210	38
3211	45
3212	38
MEAN	41
S.D.	8.7
N	11

High Dose (300 mg/m3)

FEMALE#	DAY OF LACTATION
	0 - 4
4201	46
4202	38
4203	44
4204	41
4206	34
4208	34
4209	35
4210	38
4211	40
4212	40
MEAN	39
S.D.	3.9
N	10

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Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL DELIVERY AND LITTER DATA

Clean Air Control

FEMALE#	LITTER DELIVERED			NUMBER OF LIVE PUPS										TOTAL IMPLAN- TATIONS N	DURATION OF GESTATION (DAYS) N
	LIVE N	DEAD N	TOTAL N	DAYS											
				0		1		2		3		4			
				M	F	M	F	M	F	M	F	M	F		
1201															
1202	10	0	10	3	7	3	7	3	7	3	7	3	7	12	23
1203	12	0	12	7	5	7	5	7	5	7	5	7	5	12	n. a.*
1204	7	1	8	4	3	0	0	0	0	0	0	0	0	11	23
1205	9	0	9	3	6	3	6	2	6	2	6	2	6	9	n. a.*
1206	8	0	8	3	5	3	5	3	5	3	5	3	5	10	22
1207	11	0	11	9	2	9	2	9	2	9	2	9	2	11	22
1208	11	0	11	6	5	6	5	6	5	6	5	6	5	11	22
1209	9	0	9	5	4	5	4	5	4	5	4	5	4	10	23
1210	10	0	10	3	7	3	7	3	7	3	7	3	7	10	23
1211	11	0	11	9	2	9	2	9	2	9	2	9	2	12	22
1212	9	0	9	7	2	7	2	7	2	7	2	7	2	10	23
MEAN	9.7	0.1	9.8	5.4	4.4	5.5	4.5	5.4	4.5	5.4	4.5	5.4	4.5	10.7	22.6
S.D.	1.5	0.3	1.3	2.4	1.9	2.5	2.0	2.6	2.0	2.6	2.0	2.6	2.0	1.0	0.5
N	11	11	11	11	11	10	10	10	10	10	10	10	10	11	9

*n. a. = not applicable since day 0 pc could not be determined

Low Dose (30 mg/m3)

FEMALE#	LITTER DELIVERED			NUMBER OF LIVE PUPS										TOTAL IMPLAN- TATIONS N	DURATION OF GESTATION (DAYS) N
	LIVE N	DEAD N	TOTAL N	DAYS											
				0		1		2		3		4			
				M	F	M	F	M	F	M	F	M	F		
2201	9	2	11	5	4	5	4	5	4	5	4	5	4	11	n. a.*
2202	10	0	10	6	4	6	4	6	4	6	4	6	4	10	
2203	12	0	12	7	5	7	5	7	5	7	5	7	5	13	
2204															
2205	10	0	10	7	3	7	3	7	3	7	3	7	3	12	22
2206															
2207	11	0	11	3	8	3	8	3	8	3	8	3	8	11	22
2208	12	0	12	8	4	8	4	8	4	8	4	8	4	13	22
2209															
2210	9	0	9	5	4	5	4	5	4	5	4	5	4	9	23
2211	11	0	11	5	6	5	6	5	6	5	6	5	6	12	22
2212	9	0	9	6	3	6	3	6	3	6	3	6	3	9	22
MEAN	10.3	0.2	10.6	5.8	4.6	5.8	4.6	5.8	4.6	5.8	4.6	5.8	4.6	11.1	22.1
S.D.	1.2	0.7	1.1	1.5	1.6	1.5	1.6	1.5	1.6	1.5	1.6	1.5	1.6	1.5	0.4
N	9	9	9	9	9	9	9	9	9	9	9	9	9	9	8

*n. a. = not applicable since day 0 pc could not be determined

20-NOV-2008 13:13

Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL DELIVERY AND LITTER DATA

Medium Dose (100 mg/m3)

FEMALE#	LITTER DELIVERED			NUMBER OF LIVE PUPS										TOTAL IMPLAN- TATIONS N	DURATION OF GESTATION (DAYS) N		
	LIVE N	DEAD N	TOTAL N	DAYS													
				0		1		2		3		4					
				M	F	M	F	M	F	M	F	M	F				
3201	9	0	9	4	5	4	5	4	5	4	5	4	5	11	22		
3202	11	0	11	5	6	5	6	4	6	4	6	4	6	11	23		
3203	8	0	8	4	4	4	4	4	4	4	4	4	4	10	22		
3204	11	0	11	6	5	5	5	5	5	5	5	5	5	12	22		
3205	12	0	12	4	8	4	8	4	8	4	8	4	8	13	22		
3206	13	0	13	4	9	4	9	4	9	4	9	4	9	13	n. a.*		
3207	9	0	9	5	4	5	4	5	4	5	4	5	4	10	22		
3208	11	0	11	3	8	3	8	3	8	3	8	3	8	11	22		
3209																	
3210	10	0	10	4	6	4	6	3	6	3	6	3	6	11	22		
3211	10	0	10	5	5	5	5	5	5	5	5	5	5	14	22		
3212	9	0	9	5	4	5	4	5	4	5	4	5	4	10	22		
MEAN	10.3	0.0	10.3	4.5	5.8	4.4	5.8	4.2	5.8	4.2	5.8	4.2	5.8	11.5	22.1		
S.D.	1.5	0.0	1.5	0.8	1.8	0.7	1.8	0.8	1.8	0.8	1.8	0.8	1.8	1.4	0.3		
N	11	11	11	11	11	11	11	11	11	11	11	11	11	11	10		

*n. a. = not applicable since day 0 pc could not be determined

High Dose (300 mg/m3)

FEMALE#	LITTER DELIVERED			NUMBER OF LIVE PUPS										TOTAL IMPLAN- TATIONS N	DURATION OF GESTATION (DAYS) N		
	LIVE N	DEAD N	TOTAL N	DAYS													
				0		1		2		3		4					
				M	F	M	F	M	F	M	F	M	F				
4201	11	0	11	6	5	6	5	6	5	6	5	6	5	11	22		
4202	11	0	11	5	6	5	6	5	6	5	6	5	6	11	22		
4203	11	0	11	6	5	6	5	6	5	6	5	6	5	11	23		
4204	10	0	10	5	5	5	5	5	5	5	5	5	5	10	23		
4205																	
4206	6	0	6	4	2	4	2	4	2	4	2	4	2	7	23		
4207														12			
4208	5	0	5	3	2	3	2	3	2	3	2	3	2	10	23		
4209	8	0	8	3	5	3	5	3	5	3	5	3	5	8	21		
4210	8	0	8	3	5	3	5	3	5	3	5	3	5	8	23		
4211	9	0	9	5	4	5	4	5	4	5	4	5	4	10	n. a.*		
4212	11	0	11	7	4	7	4	7	4	7	4	7	4	12	22		
MEAN	9.0	0.0	9.0	4.7	4.3	4.7	4.3	4.7	4.3	4.7	4.3	4.7	4.3	9.8	22.4		
S.D.	2.2	0.0	2.2	1.4	1.3	1.4	1.3	1.4	1.3	1.4	1.3	1.4	1.3	1.6	0.7		
N	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9		

*n. a. = not applicable since day 0 pc could not be determined

20-NOV-2008 13:14

Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

Clean Air Control			INDIVIDUAL PUP BODY WEIGHTS (GRAMS)														LACTATION DAY 0		
FEMALE#	MEAN		PUP#																
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1201																			
1202	6.0	5.5	5.7	6.2	5.7	6.0	5.9	6.3	6.1	6.3	6.7								
1203	5.4	5.3	5.4	5.2	4.6	5.5	5.8	5.7	5.1	5.6	5.4	6.0	5.5						
1204	4.6	4.5	4.4	4.4	4.4	5.1	5.1	4.6	S										
1205	5.7	5.9	5.8	6.2	5.3	5.9	5.8	5.9	5.8	5.0									
1206	5.5	5.5	5.7	5.3	5.8	5.3	5.4	5.8	5.4										
1207	5.3	5.6	5.7	5.1	5.6	4.9	5.3	5.2	5.4	5.6	4.4	5.4							
1208	5.6	5.0	5.2	5.4	6.0	6.0	5.4	5.6	5.9	6.1	6.0	5.2							
1209	6.5	6.0	5.8	6.7	6.4	7.1	6.4	6.6	7.1	6.5									
1210	6.7	7.0	5.8	7.1	6.4	6.6	6.6	6.4	7.3	7.0	6.3								
1211	5.6	5.8	5.5	5.8	5.5	5.3	5.6	5.8	5.5	5.1	5.6	5.8							
1212	6.9	6.9	7.3	7.1	6.0	7.1	6.8	7.4	6.8	7.0									
MEAN	5.8																		
S.D.	0.67																		
N	11																		

PUP STATUS CODES: S-STILLBORN

Low Dose (30 mg/m3)																	LACTATION DAY 0		
FEMALE#	MEAN 1	2	PUP# 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
2201	6.6	6.2	6.6	6.8	6.6	7.3	6.8	7.4	5.6	6.6	S	S							
2202	5.6	6.1	5.7	4.9	5.5	5.4	5.3	5.5	5.6	5.7	5.9								
2203	5.7	6.1	6.0	5.6	5.7	5.8	5.4	5.8	4.8	5.6	6.1	6.0	5.7						
2204																			
2205	5.7	5.7	5.7	5.2	5.7	5.6	5.5	6.2	5.9	5.8	5.6								
2206																			
2207	5.4	6.1	5.9	4.0	5.5	5.2	5.1	5.0	5.9	5.6	5.6	5.5							
2208	5.3	5.5	5.3	5.0	4.7	5.3	5.6	5.8	5.3	5.2	5.2	5.5	5.2						
2209																			
2210	6.4	6.7	6.8	6.2	6.2	6.1	6.5	6.2	6.9	6.0									
2211	5.7	5.9	5.5	6.0	5.3	6.1	6.1	5.6	5.6	5.8	5.3	5.1							
2212	5.7	5.4	5.9	6.0	6.0	5.6	5.6	5.5	5.7	5.5									
MEAN	5.8																		
S.D.	0.45																		
N	9																		

PUP STATUS CODES: S-STILLBORN

20-NOV-2008 13:14

Study No.: 02G08016
API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

[illegible][illegible]

15-MAY-2009 08:08

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

Clean Air Control		INDIVIDUAL PUP BODY WEIGHTS (GRAMS)															LACTATION DAY 4			
FEMALE#	MEAN	1	PUP# 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1201																				
1202	10.0	9.6	9.9	10.3	9.3	9.6	9.7	10.3	10.5	10.2	10.8									
1203	9.2	9.1	9.4	8.8	7.8	9.3	9.5	9.3	8.4	9.9	9.3	9.7	9.5							
1204																				
1205	9.6	9.9	9.5	10.5	8.2	8.9	10.0	10.2	9.3	M										
1206	9.7	9.3	10.6	9.6	10.0	9.4	9.5	9.9	9.4											
1207	7.7	8.2	8.5	7.6	8.2	7.0	7.7	8.0	7.6	8.1	5.8	7.9								
1208	9.6	8.6	8.8	9.6	10.9	10.5	9.5	9.6	10.0	9.2	9.6	9.0								
1209	8.6	7.1	8.6	8.5	8.8	9.3	9.1	8.7	8.9	8.7										
1210	10.8	11.6	9.8	11.5	10.3	10.0	10.5	10.8	11.4	11.3	10.7									
1211	10.2	10.7	10.2	10.5	9.3	10.1	10.0	10.5	10.2	9.5	10.1	10.7								
1212	12.2	11.4	12.4	12.4	11.1	12.1	11.9	13.1	12.4	12.9										
MEAN	9.8																			
S.D.	1.21																			
N	10																			

PUP STATUS CODES: M-MISSING

15-MAY-2009 08:08

Study No.: 02G08016

API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

Low Dose (30 mg/m3)		INDIVIDUAL PUP BODY WEIGHTS (GRAMS)														LACTATION DAY 4				
FEMALE#	MEAN	1	PUP# 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
2201	11.2	10.6	11.4	11.2	11.3	12.3	11.2	12.4	9.7	10.8	S	S								
2202	9.3	9.9	9.6	8.5	9.2	9.2	9.1	9.4	8.9	9.2	9.9									
2203	9.0	9.4	9.4	9.1	9.2	8.9	8.7	8.5	7.8	9.1	9.0	9.5	9.1							
2204																				
2205	8.8	8.9	8.8	8.4	8.8	8.8	8.5	9.5	8.8	9.4	8.5									
2206																				
2207	9.2	10.0	10.1	7.2	9.2	8.8	9.0	8.9	10.0	9.6	9.2	9.3								
2208	8.7	9.0	8.6	8.7	8.2	8.7	8.0	9.2	9.0	8.8	8.6	9.2	8.2							
2209																				
2210	10.3	10.5	10.9	10.1	9.9	10.0	11.0	9.9	11.1	9.5										
2211	9.4	9.8	9.0	9.8	9.0	9.7	10.0	9.4	9.1	9.7	9.1	9.1								
2212	9.7	9.8	9.8	9.9	10.1	9.6	9.9	9.3	9.9	9.0										
MEAN	9.5																			
S.D.	0.80																			
N	9																			

PUP STATUS CODES: S-STILLBORN

15-MAY-2009 08:08

Study No.: 02G08016
API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

[illegible]

MEAN	9.3
S.D.	0.77
N	11

PUP STATUS CODES: D-DIED M-MISSING

15-MAY-2009 08:08

Study No.: 02G08016
API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

High Dose (300 mg/m3)		INDIVIDUAL PUP BODY WEIGHTS (GRAMS)													LACTATION DAY 4					
FEMALE#	MEAN	PUP#																		
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
4201	9.4	9.9	9.3	10.1	9.9	9.1	8.9	10.3	9.6	8.8	8.9	8.9								
4202	9.1	9.7	9.4	8.9	8.9	9.7	9.1	8.6	8.6	9.0	8.4	9.5								
4203	9.5	9.7	9.9	9.6	9.7	10.2	9.4	10.1	9.2	8.3	9.3	9.3								
4204	9.4	9.2	9.7	9.0	10.2	9.7	9.4	9.1	9.1	8.4	10.1									
4205																				
4206	11.3	11.5	11.0	11.6	11.5	11.0	11.2													
4207																				
4208	9.5	9.5	9.9	9.3	10.0	8.7														
4209	9.6	8.0	8.9	10.3	9.9	9.1	9.9	10.1	10.6											
4210	11.6	12.2	11.9	12.4	10.9	10.9	10.4	11.6	12.4											
4211	10.2	10.4	9.9	9.9	11.0	9.9	9.7	10.4	10.9	9.8										
4212	9.7	10.0	9.4	10.0	9.9	9.9	8.9	9.7	9.8	9.5	9.6	9.4								

MEAN	9.9
S.D.	0.85
N	10

20-NOV-2008 13:14

Study No.: 02G08016
APICombined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL PUP SEX AND STATUS POST PARTUM

Clean Air Control

FEMALE#	PUP #																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
1202	FA	FA	FA	FA	FA	FA	MA	FA	MA	MA													
1203	FA	MA	FA	MA	FA	MA	MA	FA	MA	MA	MA	FA											
1204	FB 0	MB 0	MB 0	FB 0	MB 0	MB 0	FB 0	MS															
1205	FA	FA	MA	FA	FA	FA	FA	MA	MM 2														
1206	FA	MA	FA	MA	FA	FA	MA	FA	MA	FA													
1207	MA	MA	FA	MA	FA	MA	MA	MA	MA	MA	MA												
1208	FA	FA	FA	MA	MA	FA	MA	MA	MA	MA	MA	FA											
1209	FA	FA	MA	MA	MA	MA	FA	MA	FA	MA	FA												
1210	FA	FA	MA	FA	FA	MA	FA	MA	FA	FA													
1211	MA	MA	MA	MA	FA	MA	MA	MA	FA	MA	MA												
1212	MA	MA	MA	MA	MA	FA	MA	FA	MA	FA	MA												

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN

PUP STATUS CODES: A-ALIVE S-STILLBORN M-MISSING B-SACRIFICED MORIBUND

NUMBER CODES: DAY OF FINDING

Low Dose (30 mg/m3)

FEMALE#	PUP #																						
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
2201	MA	FA	FA	FA	MA	MA	MA	FA	MA	MS	MS												
2202	MA	MA	FA	MA	FA	FA	MA	FA	MA	MA													
2203	MA	MA	MA	MA	FA	FA	FA	MA	FA	MA	FA	MA											
2205	FA	MA	FA	MA	MA	FA	MA	MA	MA	MA													
2207	MA	MA	FA	FA	FA	FA	FA	MA	FA	FA	FA												
2208	MA	MA	FA	FA	MA	MA	MA	MA	FA	FA	MA	MA											
2210	MA	FA	MA	FA	MA	MA	FA	MA	FA	MA													
2211	MA	FA	MA	FA	MA	MA	FA	FA	MA	FA	FA												
2212	MA	MA	MA	MA	FA	MA	FA	FA	MA														

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN

PUP STATUS CODES: A-ALIVE S-STILLBORN

Study No.: 02G08016
API

Combined Repeated Dose Toxicity Study with the Reproduction/
Developmental Toxicity Screening Test and Mammalian Erythrocyte
Micronucleus Test via Inhalation with Roofing Asphalt Fume Cond.

INDIVIDUAL PUP SEX AND STATUS POST PARTUM

Medium Dose (100 mg/m3)

FEMALE#	PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
3201	FA	MA	MA	MA	MA	FA	FA	FA	FA	FA	MA	FA												
3202	MA	FA	FA	FA	FA	MA	MD 2	MA	FA	MA	FA													
3203	MA	FA	FA	MA	FA	FA	MA	MA	MA															
3204	MA	FA	MM 1	MA	MA	FA	FA	FA	MA	MA	FA	FA												
3205	FA	FA	FA	FA	MA	MA	FA	FA	MA	MA	MA	FA	FA											
3206	FA	FA	FA	FA	FA	FA	MA	FA	FA	MA	FA	FA	MA	MA										
3207	MA	FA	MA	MA	MA	FA	FA	MA	FA	FA	MA													
3208	MA	MA	MA	FA	FA	FA	FA	FA	FA	FA	FA	FA												
3210	FA	MA	FA	MA	FA	FA	MM 2	FA	FA	FA	MA	MA												
3211	MA	MA	FA	FA	FA	FA	MA	MA	FA	MA														
3212	MA	MA	FA	FA	MA	MA	FA	FA	MA															

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN
PUP STATUS CODES: A-ALIVE D-DIED M-MISSING
NUMBER CODES: DAY OF FINDING

High Dose (300 mg/m3)

FEMALE#	PUP #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
4201	MA	MA	MA	FA	FA	FA	MA	MA	MA	FA	FA	MA												
4202	MA	FA	MA	FA	FA	MA	MA	MA	FA	FA	FA	MA												
4203	FA	FA	MA	FA	MA	MA	MA	FA	FA	FA	MA	MA												
4204	FA	FA	FA	MA	MA	FA	FA	MA	MA	MA														
4206	MA	MA	MA	MA	FA	FA																		
4208	MA	FA	MA	MA	FA																			
4209	FA	MA	MA	FA	FA	MA	FA	FA																
4210	MA	MA	MA	FA	FA	FA	FA	FA																
4211	FA	FA	MA	MA	MA	FA	FA	MA	MA															
4212	MA	FA	MA	MA	MA	FA	FA	FA	MA	MA	MA													

SEX CODES: M-MALE F-FEMALE U-UNCERTAIN
PUP STATUS CODES: A-ALIVE

Appendix O

Blood Formation and Micronucleus Induction Individual Data

Mammalian Erythrocyte Micronucleus Test, Blood Formation and Micronuclei**Study No.:** 02G08016**Vehicle (Negative Control):** Clean air**Bone Marrow Preparation:** 24 hours after start of the last exposure

Sex	Animal No.	PCE per 500 RBC	NCE per 500 RBC	PCE / NCE	MN per 2000 PCE
Males	1101	250	250	1.00	0
	1102	254	246	1.03	0
	1104	252	248	1.02	1
	1105	245	255	0.96	2
	1107	250	250	1.00	2
	Mean ± SD	250 ± 3.3	250 ± 3.3	1.00 ± 0.027	1.0 ± 1.00
Females	1213	246	254	0.97	0
	1214	246	254	0.97	1
	1216	246	254	0.97	2
	1217	253	247	1.02	1
	1219	243	257	0.95	1
	Mean ± SD	247 ± 3.7	253 ± 3.7	0.98 ± 0.029	1.0 ± 0.71

PCE: Polychromatic Erythrocytes
NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation

Mammalian Erythrocyte Micronucleus Test, Blood Formation and Micronuclei**Study No:** 02G08016**Positive Control:** Cyclophosphamide monohydrate, 60 mg/kg b.w., p. o.**Bone Marrow Preparation:** 24 hours after oral application

Sex	Animal No.	PCE per 500 RBC	NCE per 500 RBC	PCE / NCE	MN per 2000 PCE
Males	5101	244	256	0.95	18
	5102	251	249	1.01	16
	5103	247	253	0.98	16
	5104	245	255	0.96	15
	5105	254	246	1.03	10
	Mean ± SD	248 ± 4.2	252 ± 4.2	0.99 ± 0.034	15.0** ± 3.00
Females	5201	256	244	1.05	13
	5202	248	252	0.98	11
	5203	252	248	1.02	14
	5204	248	252	0.98	14
	5205	252	248	1.02	12
	Mean ± SD	251 ± 3.3	249 ± 3.3	1.01* ± 0.030	12.8** ± 1.30

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* : $P < 0.05$, Mann-Whitney U-Test** : $P < 0.01$, Mann-Whitney U-Test

Mammalian Erythrocyte Micronucleus Test, Blood Formation and Micronuclei**Study No.:** 02G08016**Test Item:** Roofing asphalt fume condensate**Concentration:** 30 mg/m³**Bone Marrow Preparation:** 24 hours after start of the last exposure

Sex	Animal No.	PCE per 500 RBC	NCE per 500 RBC	PCE / NCE	MN per 2000 PCE
Males	2101	253	247	1.02	0
	2102	255	245	1.04	2
	2104	250	250	1.00	0
	2105	256	244	1.05	1
	2107	248	252	0.98	0
	Mean ± SD	252 ± 3.4	248 ± 3.4	1.02 ± 0.027	0.6 ± 0.89
Females	2213	252	248	1.02	1
	2214	241	259	0.93	1
	2216	249	252	0.99	1
	2217	249	251	0.99	4
	2219	246	254	0.97	2
	Mean ± SD	247 ± 4.2	253 ± 4.2	0.98 ± 0.032	1.8 ± 1.30

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NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation

Mammalian Erythrocyte Micronucleus Test, Blood Formation and Micronuclei**Study No.:** 02G08016**Test Item:** Roofing asphalt fume condensate**Concentration:** 100 mg/m³**Bone Marrow Preparation:** 24 hours after start of the last exposure

Sex	Animal No.	PCE per 500 RBC	NCE per 500 RBC	PCE / NCE	MN per 2000 PCE
Males	3101	251	249	1.01	1
	3102	245	255	0.96	1
	3104	252	248	1.02	1
	3107	253	247	1.02	3
	3108	248	252	0.98	1
	Mean ± SD	250 ± 3.3	250 ± 3.3	1.00 ± 0.026	1.4 ± 0.89
Females	3213	247	253	0.98	0
	3214	253	247	1.02	0
	3216	244	256	0.95	1
	3219	242	258	0.94	0
	3220	251	249	1.01	2
	Mean ± SD	247 ± 4.6	253 ± 4.6	0.98 ± 0.036	0.6 ± 0.89

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NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation

Mammalian Erythrocyte Micronucleus Test, Blood Formation and Micronuclei**Study No.:** 02G08016**Test Item:** Roofing asphalt fume condensate**Concentration:** 300 mg/m³**Bone Marrow Preparation:** 24 hours after start of the last exposure

Sex	Animal No.	PCE per 500 RBC	NCE per 500 RBC	PCE / NCE	MN per 2000 PCE
Males	4101	260	240	1.08	0
	4104	246	254	0.97	0
	4105	255	245	1.04	2
	4107	248	252	0.98	3
	4108	256	244	1.05	2
	Mean ± SD	253 ± 5.8	247 ± 5.8	1.03 ± 0.048	1.4 ± 1.34
Females	4213	252	248	1.02	2
	4216	257	243	1.06	1
	4217	252	248	1.02	1
	4219	246	254	0.97	3
	4220	251	249	1.01	0
	Mean ± SD	252 ± 3.9	248 ± 3.9	1.01 ± 0.032	1.4 ± 1.14

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NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation