Fraunhofer Institut
Toxikologie und
Experimentelle Medizin

Final Report

Range Finding Testing for a Comb ined Repeated Dose Toxicity Study with the Reproduction/ D evelopmental Toxicity Screening Test and Mammalian Ery throcyte Mi cronucleus Test via Inhalation with Roofing Asphalt Fume Condensate

Fraunhofer ITEM Study No. 02N07533

Number 1 of 2 Originals

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This final report consists of 126 pages

Contents

(Note: Figure 1 to 3 are in the text part)

Appendices

1 Statement of Study Director

Study No.: 02N07533

Test Substance: Roofing Asphalt Fume Condensate

Title: Range Finding Testing for a Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate

This nonclinical health study was not conducted in compliance with the principles of GLP but in the spirit of GLP.

The study followed the regulations of the German animal protection law (Tierschutzgesetz of May 18, 2006).

I accept the responsibility for the validity of the study.

Date: 23. 9. 2008

[redacted]

[redacted]

2 Introduction

2.1 Objectives of the Study

The objective of this dose range finding study was to evaluate the possible toxicity of Roofing Asphalt Fume Condensate after inhalation in rats and to determine the dose levels for the following "Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate".

2.2 Guidelines for Conduct of the Study

This was a non GLP study. However, the principles of Good Laboratory Practice were taken into consideration as far as possible (German Chemicals Law, Appendix 1, June 28, 2002) and the study was conducted in the spirit of Good Laboratory Practice. The study followed the regulations of the German animal protection law (Tierschutzgesetz of May 18, 2006).

2.3 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. Rats of the same strain were often used for this type of study in the laboratories of Fraunhofer ITEM.

2.4 Dates

Study initiation date:	February 6, 2008
Experimental start date: (start of inhalation)	15.02.2008
Experimental completion date:	April 9, 2008
Study completion date	September 23, 2008

2.5 Study Staff

Study Director:	[redacted]
Deputy Study Director:	[redacted]
Laboratory Animal Veterinarian:	[redacted]
Aerosol Physicist:	[redacted]
Chemist:	[redacted]
Scientist responsible for Micronucleus Pretest:	[redacted]
Statistician:	[redacted]

2.6 Dose Level Selection

The use of three doses was appropriate since no information on the effects of the test item on the investigated endpoints is available. 1000 mg/m³ THC can be used as a limit test dose (see also OPPTS 870.3465). The dose levels wee based on the assumption that the limit dose is expected to cause some mild parental toxicity. Therefore a higher dose does not seemed to be necessary. The other dosages were selected applying a stagger of about 3. Selected dose levels were: 0, 100, 300, or 1000 mg/m³.

2.7 Duration of Study

The animals were exposed to the test item or clean air by nose-only inhalation daily, 6 hours per day, 7 days per week:
Males were exposed for 14 days.
Pregnant females: were exposed from day 6 until and including day 20 of gestation.

2.8 Test Item

Roofing asphalt fume condensate.

Test item source and preparation:
Details on the roofing asphalt fume condensate used for the chamber trials are reported in 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
CASRN:	64742-93-4
Density:	0.8745 mg/l
Kinematic Viscosity:	8.3616 centi stokes at 100°F
Refractive Index:	1.4831 at 25°C
Expiry Date:	August 2020

Density, fluorescence, and refractive index of the test item were provided by the sponsor for each separate bottle filled with roofing asphalt fume condensate.

Sample identity was confirmed by determination of density and refractive index of the test item (see study 02N07532).

2.8.1 Safety Protection, Storage, Handling and Disposal

Safety precaution, storage and handling of the test substance will be done according to the TRGS 901 (Technische Regeln für Gefahrstoffe).

3 Test System

3.1 Animal Model

Wistar rats (Crl:WU), purchased from Charles River Deutschland, Sulzfeld, Germany, were used in this study. *20* males and 30 virgin females (approx. 7 weeks at delivery) were acclimatized for approx. 3 weeks prior to study start in the animal room.
The study commenced with 20 male and 22 sperm positive female rats which were randomly assigned to one of the clean air control (5) or test item exposed groups (5 to the low dose and 6 each to the mid and high dose).

3.2 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 last week of acclimation, study males and females were mated overnight and the day of finding vaginal plugs and/or sperm in vaginal smears was considered day 0 post conceptionem (p.c.). During the whole acclimation period, clinical observations were made once a day. Animals were accepted for the study only if they were in a good health condition.

3.3 Animal Identification

A unique individual identification number was assigned to each animal in the study, the cages will be labeled with this number and the animals will be identified by ear tattooing. All data collected from an animal were filed under that number.

3.4 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 (ssniff R/M-H) 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 30 - 70%. The animal room lighting was a 12-hour light/dark cycle controlled by an automatic timing device.

4 Procedures

4.1 Experimental Design and Randomization

Animals were randomized to groups as mentioned below based on body weight before study start using a computer program (PROVANTIS), excluding any statistically significant differences in body weight between the groups (males) or after successful mating based on a randomization list (females).

Animals were exposed according to the following scheme:

Group	**No. of Animals**		**Target concentration mg/m³ THC***	**Animal Numbers**	
	Males	**sperm positive females**		**Males**	**females**
1 Clean Air Control	5	5	-	1101-1105	1201-1205
2 Low Dose	5	5	100	2101-2105	2201-2205
3 Medium Dose	5	6	300	3101-3105	3201-3206
4 High Dose	5	6	1000	4101-4105	4201-4206

* Total hydrocarbons

4.2 Inhalation Exposure

Technical setup was completed 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 study report.
Exposures were 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 whole exposure unit was placed under a laboratory hood.

4.3 Aerosol Generation

The method developed by Koch (1993) and described in more detail by Pohlmann et al. (2006) 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.

The asphalt fume test atmosphere was generated using the free jet principle by means of a laboratory setup developed at the Fraunhofer ITEM. In this apparatus (Figure), liquid asphalt fume condensate was evaporated and recondenses on a large number of condensation nuclei also generated from the condensate by the apparatus. This led to a highly dispersed aerosol phase in equilibrium with the corresponding vapor phase.

In the free jet evaporation-condensation generator, a well-defined mass flux of vaporized material was issued together with a carrier (nitrogen) at high velocity through a nozzle into a stream of slowly flowing cool air. An expanding turbulent jet was formed, as a result of the surrounding air mixing with the vapor stream. The asphalt vapor was cooled and diluted downstream of the nozzle, as the jet developed. The initial vapor phase contained very fine seed particles, originating from the vapor generation process. The vapor was generated by first nebulizing the condensate, using a pneumatic nebulization nozzle, and subsequently evaporating the droplets in a heated evaporation tube. The seed particles resulted 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, x, 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 was eventually achieved, and led to formation and growth of liquid aerosol droplets by condensation of the vapor phase on the seed particles.

The setup of the fume generator is shown in Figure 1. A peristaltic pump, driven by a stepping motor, maintained the pump feed rate of the asphalt fume condensate. For the nose-only system used in the inhalation studies and the concentrations envisaged, the feed rate had to be of the order of 4.5 ml/h. 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 generates 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.

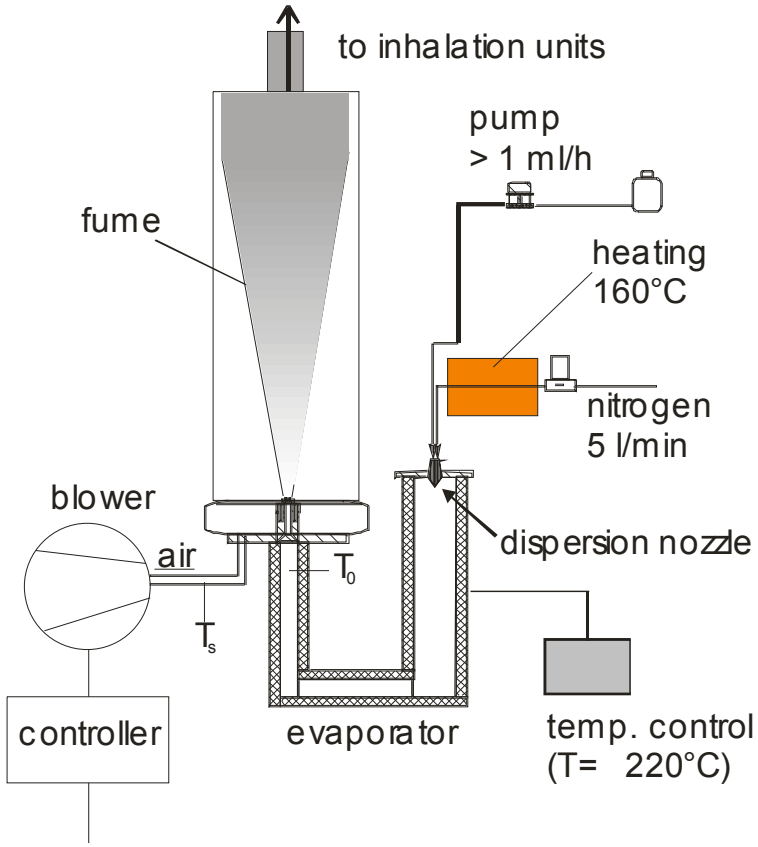

Figure 1: Aerosol generator. The red nitrogen heater has been added compared to the original setup described in Pohlmann et al., 2006.

4.4 Inhalation Units and Dilution

From the generator, the fume was directed through stainless steel tubes to the different inhalation units (Figure 2). 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 by 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 central computer.

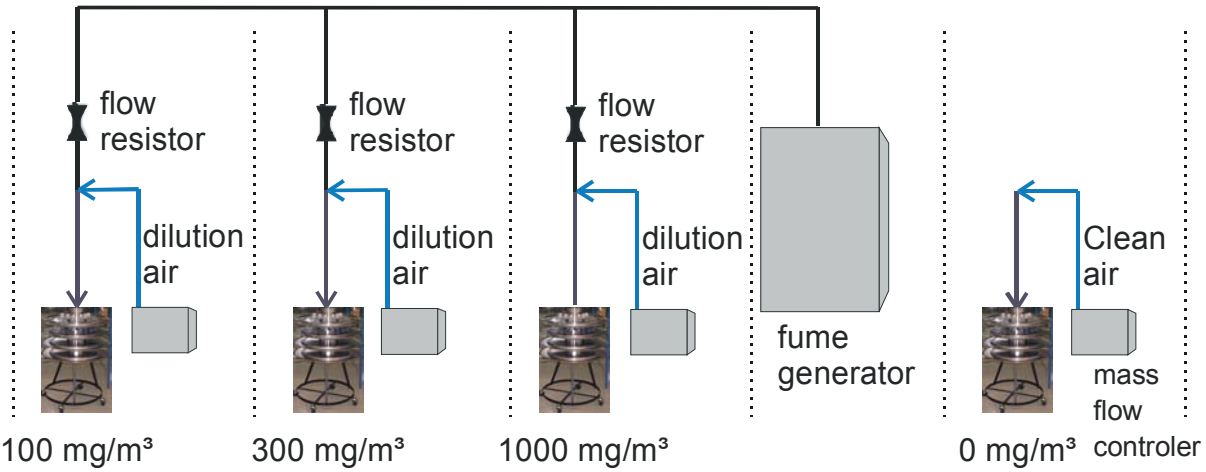

Figure 2: Scheme of the inhalation setup. Flow resistors control the flow rate of asphalt fume from the generator into the inhalation units.

The exposure to asphalt fume took place in a direct-flow nose-only inhalation exposure systems as shown in Figure 3. These inhalation exposure units were placed in closed laboratory hoods that are maintained at a constant pressure. Within each unit, fumes were supplied to each animal individually, and the exhaled air was exhausted immediately. Animals were placed around the exposure cylinder in tapered acrylic glass tubes with adjustable backstops. Target concentrations at the different inhalation units were 0, 100, 300 and 1000 mg/m³.

Figure 3: Partial view of the direct-flow nose-only inhalation exposure system (inhalation unit). The picture on the left shows the upper part of the unit with the fume inlet installed, the inhalation ports and, as an example, one acrylic glass tube installed. The picture on the right shows a top view of the inhalation unit with the fume inlet removed, providing a view of the inner inlet cylinder with the stainless steel tubes directed to the inhalation ports as well as the outer cylinder that serves as exhaust drain.

4.5 Measurement of the Exposure Atmosphere

The temperature and the relative humidity in the fume supply to the inhalation units were measured. Data on temperature and relative humidity 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. An average of two samples 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 were given in mg Total Hydrocarbon (THC)/m³ aerosol and vapor phase.
For the comparison of the asphalt fume concentration determined according to BIA method to the absolute asphalt fume concentration, samples of defined concentrations of asphalt condensate were analyzed using the BIA method. In the report both figures for the THC concentrations are presented. Samples were taken from each exposure unit. Parallel to the determination of THC the UV fluorescence in mg/kg as diphenyl anthracene (DPA) was measured in the high dose group. 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. Periodical check and optionally recalculation of the photometer sensitivity during the inhalation study using the results of chemical analyses (TCH/m³) were carried out. Particle size distributions were determined once for each concentration using a scanning mobility particle sizer (SMPS, TSI - Inc.) which will give number size distribution in a size range of about 7 - 300 nm.

4.6 Additional Chamber Measurements

Light and noise levels in the exposure room were measured pretest, at the beginning, in the middle, and at the end of the exposure period. The inhalation atmosphere was a composition of clean air from the animal house air conditioning system with less than 1% (v/v) asphalt fume added. Since the flow in the inhalation units was well controlled oxygen level was guaranteed not to be below 19% (v/v). Therefore oxygen measurements were considered not to be necessary.

4.7 Daily and Weekly Observations

Animals were inspected at least once daily. 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.
Males: once weekly
Sperm positive females: on day 0, 4, 6, 7, 10, 14, 17 and 21 p.c.

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

Males: once weekly
Sperm positive females: on day 0, 4, 6, 7, 10, 14, 17 and 21 p.c.

4.8 Post Mortem Observations

The animals were sacrificed by $C0_2$ overdose and subsequent exsanguination. Necropsy was performed under the supervision of a veterinarian or pathologist.
Males: after 14 day of exposure
Pregnant females: day 21 of gestation

4.8.1 Gross Pathology and Histopathology

Necropsy was performed in all animals as scheduled above. The following organs and tissues were collected from each rat and fixed in 10% neutral buffered formalin: nasal and paranasal cavities, larynx, pharynx, trachea, and lungs.

In addition to the terminal body weight, selected organs listed below were weighed (paired organs separately). All animals were included in organ weight determination except non-pregnant females.

Liver
Kidneys
Thymus
Testes or Ovaries

Females: The number of implantation sites per dam was determined, using ammonium sulphide staining where no implantations were macroscopically visible. The number of corpora lutea, live/dead fetuses and resorptions as well as uterine weight were determined. Fetuses were weighed individually, sexed and examined for external abnormalities.

Histopathological examination of the respiratory tract was conducted in all 40 rats. Trimming was done according to Ruehl-Fehlert et al. 2003, Kittel et al. 2004, Morawietz et al. 2004. Bones were decalcified prior to embedding.

Tissues for microscopic examination were fixed for at least one week in 10% neutral buffered formalin, embedded in paraffin, sectioned at 3 - 4 µm, mounted on slides and stained with hematoxylin and eosin.

The slides were examined by light microscopy and the observations were recorded with an on-line computer program (PLACES 2000.1).

4.8.2 Blood Formation

A pre-requisite for a valid mammalian erythrocyte micronucleus test is an appropriate high dose, near MTD (Maximum Tolerated Dose, a dose causing marked toxicity but no mortality), and the likelihood that the test substance or its metabolites reach the target tissue. As MTD level exposure would be incompatible with a reproduction/developmental toxicity test, the highest dose used has to be defined as a dose that produces some indication of toxicity in the bone marrow. For that reason, bone marrow smears of the clean air control animals and only the high dose animals were prepared and the ratio of immature erythrocytes among total erythrocytes was determined.
At the time of necropsy one femur of each rat was collected and cleaned of the surrounding muscle tissue. Ends of the femur were cut off. The bone marrow of each animal was washed out with foetal calf serum and transferred into a clean tube. The bone marrow in the tube was pulled gently up and down until a fine cell suspension was observed in the foetal calf serum. Cellulose columns (according to Sun et al., 1999) were used to remove nucleated cells and thus to avoid artifacts, arising from granules of damaged granulocytes, which stain similar to micronuclei. Cellulose columns were prepared from equal amounts of □-cellulose and cellulose type 50350, suspended in Hank´s Balanced Salt Solution and filled into Poly-Prep Columns (BIO-RAD, München, Germany). The suspended bone marrow was carefully loaded onto the cellulose columns and allowed to drain into 15 ml centrifuge tubes. The bone marrow was then centrifuged and most of the supernatant was discarded. The remaining 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 (one for evaluation and one spare) were prepared on defatted slides. The smears were airdried for 24 h and stained according to Pappenheim with May-Grünwald- and Giemsa-solution. The slides were coded prior to microscopic analysis and examined by light microscopy under 630-1000 x magnification. The ratio of polychromatic to normochromatic erythrocytes was calculated by counting the number of polychromatic erythrocytes per at least 200 red blood cells.

5 Data Collection

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

6 Statistical Evaluation

Statistical comparison of groups was performed at the level of $\alpha=0.05$. Body weights, food consumption, and organ weight data were analyzed using analysis of variance. If the group means differ significantly according to this method, the means of the treatment groups was compared with the mean of the control group 1 using Dunnett's modification of the t-test. Kruskall-Wallis ANOVA and Mann-Whitney U-test were applied in the case of non-homogenous data.
Qualitative data were analyzed using the two-tailed FISHER test with Bonferroni correction

or Chi-square test.
Data from non-pregnant females were excluded from the statistical analysis.

7 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 will be stored at least for the period of time required by the GLP principles as laid down in the German regulations (15 years for data). The sponsor has to inform Fraunhofer ITEM if further archiving is required.

8 Results

8.1 Stability of the Test Item

The stability of the test item was measured at three time points. No degradation could be observed.

Date	Refractive index $n_D(25)$	Fluorescense as DPA equivalent (mg/kg)
18.02.2008	1.483	323
25.02.2008	1.483	321
28.02.2008	1.483	323

8.2 Exposure Atmosphere

The exposure conditions are shown in **Tables 1 –3**. Graphs of the particle size distribution are shown in **Appendix A.**

The actual concentrations of the bitumen fume measured in the exposure atmosphere were 103.5 mg/m³, 299.6 mg/³ and 1116 mg/m³ THC for the low, mid and high dose group. The number modal diameters of the particles measured with the SMPS where 230,2, 199.4, and 190.0 nm for the low, mid and high dose group. Here modal diameter instead of the median diameter is reported since the measurement range of the instrument used does not cover the whole size distribution and in this case the modal diameter best reflects the average particle size of the complete distribution.

8.3 In-Life Observations

8.3.1 Clinical Observations

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

No adverse compound-related clinical signs were observed in rats during the course of the study.

8.3.2 Mortality

No mortality occurred during the course of the study.

8.3.3 Body Weight

The data for body weight and body weight gain in rats are summarized in **Tables 4, 5 and 11.** Individual data are given in **Appendix C.**

In males, the body weight gain was significantly reduced in the 300 mg/m³ and 1000 mg/m³ THC groups, and in females in the 1000 m/m³ THC group. However, net body weight gain change was dose dependently decreased in all exposed groups, and this was determined to be statistically significant in the 300 mg/m³ and 1000 mg/mg³ THC groups.

8.3.4 Food Consumption

The data for food consumption are presented in **Table 6** . Individual data are given in **Appendix D.**

Food consumption was dose dependently decreased in all exposed groups, and this was determined to be statistically significant in the 300 mg/m³ and 1000 mg/mg³ THC groups in females, and in the 1000 mg/mg³ THC group in males.

8.4 Post Mortem Observations

8.4.1 Gross Pathology

Macroscopic findings are summarized in **Table 7**.

No compound-related effects were observed during necropsy.

8.4.2 Organ Weights

Organ weight data are given in **Tables 8 - 9** with individual data presented in **Appendices E, F.**

The only test item induced effect was a significant decrease in absolute and relative thymus weight in males and females of the 1000 mg/m³ THC groups.

Other sporadically observed differences in absolute organ weights are considered a secondary consequence of the decreased body weights.

8.4.3 Caesarean Section

Data of the caesarean section are given in **Tables 10 and 11**, individual data are presented in **Appendices G and H.**

The only test item induced effect was a dramatic decrease in fetal body weight in the 1000 mg/m³ THC group.
None of the other investigated endpoints was affected by the test item exposure.

8.4.4 Histopathological Examination

Histopathological findings are summarized in **Tables 12 and 13** with individual data presented in **Appendix I.**

Test-substance related findings

Nasal and Paranasal Cavities
Several significant changes were observed in the nasal and paranasal cavities from rats of the THC exposure groups.
(Multi)focal mucous (goblet) cell hyperplasia was diagnosed dose-dependently in the THC exposure groups only. In males, the incidences were 3/5 (very slight), 5/5 (2/5 very slight, 3/5 slight) and 5/5 (3/5 slight, 2/5 moderate) in the 100, 300 and 1000 mg/m^3 THC groups, respectively, whereas 2/5 (very slight), 6/6 (1/6 very slight, 5/6 slight) and 6/6 (3/6 slight, 3/6 moderate) females of the respective groups showed this change. In the clean air control group, no occurrence of this finding was observed. Adaptive mucous (goblet) cell hyperplasia affected the respiratory epithelial lining of the nasal airways as well as the submucosal nasal glands.

Other exposure-related findings (no occurrence in the control group) included basal-cell hyperplasia of the respiratory or olfactory epithelium and atrophy of the olfactory epithelium. Three of 5 males of the 100 mg/m^3 THC group and one male and one female of the 300 and one male of the 1000 mg/m^3 THC groups, respectively, showed mainly very slight (minimal) basal-cell hyperplasia of the respiratory epithelium. In addition, a single female of the 1000 mg/m^3 THC group revealed multifocal very slight basal-cell hyperplasia of the olfactory epithelium.
Multifocal very slight atrophy of the olfactory epithelium was observed in 2/5 and 3/6 males and females, respectively, of the 1000 mg/m^3 THC group.

(Multi)focal very slight to moderate mucosal inflammatory cell infiltration, mainly of the respiratory epithelium in levels 1 and 2 of the 4 nasal cavity sections was observed in 0/5 to 4/5 males and females per group, including the control group. Although no statistically

significant differences between the control and exposure groups were observed, this change is considered to be at least partly related to the THC exposure, since the highest incidences or severity grades were observed in the 300 and 1000 mg/m^3 THC groups.

Larynx
The only finding which could be related to THC exposure was focal very slight mucous (goblet) cell hyperplasia of the respiratory epithelial lining in a single male of the 1000 mg/m^3 THC group.

Trachea
Exposure-related (multi)focal very slight mucous (goblet) cell hyperplasia of the respiratory epithelium was seen in a single male of the 300 mg/m^3 THC group as well as in 3/5 and 2/6 males and females, respectively, of the 1000 mg/m^3 THC exposure group.

Lungs
(Multi)focal very slight to slight alveolar histiocytosis (alveolar accumulation of macrophages) was observed dose-dependently in 3/5 (very slight) males of the 300 mg/m^3 THC group and in 5/5 (2/5 very slight, 3/5 slight) males of the 1000 mg/m^3 THC group, whereas 2/5 (very slight), 5/6 (very slight) and 6/6 (1/6 very slight, 5/6 slight) females of the 100, 300 and 1000 mg/m^3 THC groups, respectively, showed this change. In the clean air control group, alveolar histiocytosis was not observed.
(Multi)focal interstitial mononuclear or (mixed) inflammatory cell infiltration occurred in a single male control animal (very slight), in 2/5 (very slight) and 4/5 (2/5 very slight, 2/5 slight) males as well as in 2/6 (very slight) and 6/6 (4/6 very slight, 2/6 slight) female rats of the 300 and 1000 mg/m^3 THC exposure groups, respectively. In addition, 1/5 and 5/5 males of the 300 and 1000 mg/m^3 THC groups, respectively, and 6/6 females of the high-dose THC group showed test-substance related (multi)focal very slight to slight alveolar inflammatory cell infiltration. This finding was also observed in a single male control animal and related to spontaneous focal alveolar haemorrhage.
As a further test substance-related finding, 2/5 males and 4/6 females of the 1000 mg/m^3 THC group developed (multi)focal very slight 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.

Other findings (not test substance-related)

A variety of sporadic findings were observed in single animals of different groups. These findings were considered to be unrelated to test-substance exposure and included focal mucosal mineralization and submucosal cyst formation in the nasal cavity, focal submucosal foreign-body granuloma and focal epithelial alteration due to aspiration or inspissation of plant fibres in the larynx, focal neuroendocrine cell hyperplasia, focal interstitial fibrosis and congestion in the lungs and lymphoid hyperplasia in the lung-associated lymph nodes (LALN). No pathological changes at all were observed in the (laryngo-)pharynx.

8.4.5 Blood Formation

Results are summarized in **Table 14** with individual data shon in **Appendix K**.

For determination of bone marrow toxicity of inhaled roofing asphalt fume condensate (RAFC), the proportion of PCE (immature) among 400 RBC (PCE and NCE) was determined and the ratio of PCE to NCE was calculated. Bone marrow toxicity was analyzed in 5 males and 5 females (negative control and 1000 mg/m^3) or in 4 females only (300 mg/m^3). An additional female of the 1000 mg/m^3 group (Animal 4206) was excluded from statistical analysis due to an abnormally high number of PCE exceeding the values of the negative control by a factor of about 4.

In male animals there was clear tendency towards impairment of blood formation by repeated exposure to 1000 mg/m^3 RAFC. The mean number of PCE/400 RBC was reduced from 133 ± 11.4 to 120 ± 13.2 and the mean ratio of PCE/NCE from 0.50 ± 0.063 to 0.43 ±0.069, but reduction did not reach statistical significance. In female animals there was statistically significant reduction in the mean number of PCE/400 RBC from 142 ± 12.1 to 110 ± 17.6 and of the PCE/NCE ratio from 0.55 ± 0.077 to 0.38 ± 0.085 by exposure to 1000 mg/m^3 RAFC. Exposure to 300 mg/m^3 RAFC only slightly diminished the number of PCE, pointing to a concentration-dependent effect.

9 Summary and Conclusions

The objective of this dose range finding study was to evaluate the possible toxicity of Roofing Asphalt Fume Condensate after inhalation in rats and to determine the dose levels for the following "Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening Test and Mammalian Erythrocyte Micronucleus Test via Inhalation with Roofing Asphalt Fume Condensate".

Five male and 5 - 6 sperm positive female Wistar (WU) rats were exposed for 6 hrs/day, 7 days/week over a period of 14 days for males and from day 6 to 20 of pregnant females to clean air, or 103.5 mg/m³, 299.6 mg/³ and 1116 mg/m³ THC for the low, mid and high dose group. The number modal diameter of the particles measured with the SMPS where 230,2, 199.4, and 190.0 nm for the low, mid and high dose group.

In males, the body weight gain was significantly reduced in the 300 mg/m³ and 1000 mg/m³ THC groups, and in females in the 1000 m/m³ THC group. However, net body weight gain change was dose dependently decreased in all exposed groups, being statistically significant in the 300 mg/m³ and 1000 mg/mg³ THC groups.

Food consumption was dose dependently decreased in all exposed groups, being statistically significant in the 300 mg/m³ and 1000 mg/mg³ THC groups in females, and in the 1000 mg/mg³ THC group in males.

The only test item induced difference on organ weights from the control was a significant decrease in absolute and relative thymus weight in males and females of the 1000 mg/m³

THC groups.

Test-substance related histopathological findings consisted of minimal to moderate mucous (goblet) cell hyperplasia in the nasal cavity (dose dependent), the larynx and trachea. Minimal basal cell hyperplasia, mainly of the respiratory epithelium, minimal atrophy of the olfactory epithelium and minimal to moderate mucosal inflammatory cell infiltration were additional test-substance related findings in the nasal cavity. In the lungs, minimal to mild alveolar accumulation of macrophages and interstitial or alveolar inflammatory cell infiltration as well as minimal bronchiolo-alveolar hyperplasia were dose-dependent changes which could be related to the test substance.

The only test item induced effect on caesarean section data was a dramatic decrease in fetal body weight in the 1000 mg/m³ THC group.

The present data on blood formation indicate that the test substance RAFC or its metabolites reached the bone marrow compartment of rats after repeated inhalative exposure and that induction of micronuclei in bone marrow erythrocytes is thus an appropriate *in vivo* endpoint for determination of the genotoxic potential of RAFC.

Based on the above described results and according to the guideline OECD 422 ("23. The highest dose level should be chosen with the aim of inducing toxic effects but not death nor obvious suffering.") exposure concentrations of **30, 100, and 300 mg/m³ THC** are recommended for the main study.

10 References

Koch, W.; Windt, H.; Carrothers, T. Generation of submicron aerosols in a free turbulent jet, in Synthesis and measurement of ultrafine particles: Proceedings of the International Workshop on the Synthesis and Measurement of Ultrafine Particles, Delft: Delftse Universitaire Pers, 1993 S.51-59

Ruehl-Fehlert C., Kittel B., Morawietz G., Deslex P., Keenan C., Mahrt C.R., Nolte T., Robinson M., Stuart B.P., Deschl U. Revised guides for organ sampling and trimming in rats and mice--Part 1. A joint publication of the RITA and NACAD groups.
Exp Toxicol Pathol. 2003; 55:91-106.

Kittel B., Ruehl-Fehlert C., Morawietz G., Klapwijk J., Elwell M.R., Lenz B., O'Sullivan M.G., Roth D.R., Wadsworth P.F. Revised guides for organ sampling and trimming in rats and mice--Part 2. A joint publication of the RITA and NACAD groups.
Exp Toxicol Pathol. 2004;55:413-31.

Morawietz G., Ruehl-Fehlert C., Kittel B., Bube A., Keane K., Halm S., Heuser A., Hellmann J. Revised guides for organ sampling and trimming in rats and mice--Part 3. A joint publication of the RITA and NACAD groups.
Exp Toxicol Pathol. 2004;55:433-49.

Pohlmann, G. , A. Preiss, W. Koch, H. Kock, M. Elend, M. Raabe (2006), “Collection,

Validation and Generation of Asphalt Fumes for Inhalation Studies in Rats. Part 3: Regeneration of Asphalt Fumes, Inhalation Setup and Validation", Ann Occup Hyg., 50 (2006), Nr.8, S.813-819

11 Tables and Figures

Table 1 : Exposure Conditions with Mean and Standard Deviation

	Control	100 mg/m³ THC	300 mg/m³ THC	1000 mg/m³ THC
Daily Exposure time (hrs)	6	6	6	6
Temperature (°C)	21.6 ± 0.3	21.9 ± 0.4	21.8 ± 0.3	22.1 ± 0.3
Humidity (% r. h.)	60.5 ± 1.9	53.8 ± 1.6	51.6 ± 2.1	45.8 ± 1.5
Air inflow (l/min)	35.0	34.1	40.8	37.7
Air outflow (l/min) [1]	30.9	29.9	34.7	33.7
THC (mg/m³)[2]	0.09 ± 0.13	103.5 ± 4.1	299.6 ± 13.1	1116 ± 14.3
n=	4	4	4	4
THC (mg/m³)[3]	-	95.5 ± 8.2	279.9 ± 24.5	1052 ± 85.5
n=	-	21	21	21
Fluorescense (mg/kg)[4]	-	-	-	276 ± 11
n=	-	-	-	4

1 generating a slight overpressure in the inhalation system
2 from chemical analysis
3 from photometric measurements
4 Fluorescence as DPA equivalent

Table 2 : Number Size Distribution

	Number concentration (1/cm³)	Modal Diameter* (nm)
100 mg/m³	7.35E+05 ± 2.55E+04	230.2 ± 4.8
300 mg/m³	5.77E+06 ± 1.15E+05	199.4 ± 8.4
1000 mg/m³	2.86E+07 ± 3.07E+06	190.0 ± 4.0

* Since the measurement range of the instrument used does not cover the whole size distribution the Modal Diameter, that is the diameter where the size distribution reaches it's maximum, was chosen to be reported instead of the Median Diameter

Table 3: Light and Noise Levels

	Control				100 mg/m³				300 mg/m³				1000 mg/m³			
	pre	start	mid	end	pre	start	mid	end	pre	start	mid	end	pre	start	mid	end
LIght lux	33.1	49.7	39.5	39.2	34.8	34.7	33.7	34.7	31.3	39.6	33.6	38.9	38.5	37.6	35.1	36.8
Noise dB	32.3	57.7	57.0	57.3	57.2	69.7	68.9	65.2	58.8	70.0	67.6	65.3	56.3	62.2	56.3	58.9

Table 4: Body Weight

RTA054-05/01 Provantis7 - Production Date: 06/03/08 12:57 Page: 1

Bodyweights - Intergroup Comparison of Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g) - Identity (No Transformation)

Group	Sex		Day numbers relative to Start Date 0	7	11	14
1	m	Mean	271.24	285.12	296.68	304.48
		S.D.	17.52	19.29	22.08	24.28
		N	5	5	5	5
2	m	Mean	275.62	285.86	294.42	301.02
		S.D.	13.80	15.85	18.27	16.44
		N	5	5	5	5
3	m	Mean	281.50	279.68	285.48	291.86
		S.D.	28.92	33.40	36.13	37.53
		N	5	5	5	5
4	m	Mean	276.94	261.02	262.40	264.34
		S.D.	23.08	27.28	27.67	27.33
		N	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 4: Body Weight (cont'd)

RTA054-05/01 Provantis7 - Production Date: 08/04/08 11:17 Page: 1

Bodyweights - Intergroup Comparison of Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g) - Identity (No Transformation)

Group	Sex		Day numbers relative to Start Date 0	4	6	7	10	14	17	21
1	f	Mean	181.22	194.78	202.78	206.06	215.06	227.86	249.30	284.28
		S.D.	4.78	5.47	7.58	7.63	8.81	10.32	14.34	26.78
		N	5	5	5	5	5	5	5	5
2	f	Mean	179.13	189.18	200.75	199.45	207.50	222.53	242.85	274.48
		S.D.	5.98	12.43	9.74	8.84	7.95	7.27	5.32	6.69
		N	4	4	4	4	4	4	4	4
3	f	Mean	182.37	195.57	202.83	202.85	208.85	218.47	237.88	270.20
		S.D.	5.93	9.96	9.78	9.18	7.50	8.20	6.01	10.44
		N	6	6	6	6	6	6	6	6
4	f	Mean	188.16	204.68	212.26	208.98	208.48	210.20*	222.80**	246.10**
		S.D.	6.78	9.70	9.75	10.63	8.27	8.68	8.12	10.28
		N	5	5	5	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 5: Body Weight Gain

RTA023-04/01 Provantis7 - Production Date: 06/03/08 12:57 Page: 1

Bodyweights - Intergroup Comparison of Bodyweight Gains

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Body Weight Gain (g) - Transformation: Identity (No Transformation)

				Day numbers relative to Start Date				
		Base Weight Day	From:	0	7	11	Abs Gain 0	% Gain 0
Group	Sex	0	To:	7	11	14	14	14
1	m	271.24	Mean	13.88	11.56	7.80	33.24	12.18
		17.52	S.D.	5.31	4.64	2.49	9.32	3.14
		5	N	5	5	5	5	5
2	m	275.62	Mean	10.24	8.56	6.60	25.40	9.22
		13.80	S.D.	6.06	2.79	2.86	7.94	2.85
		5	N	5	5	5	5	5
3	m	281.50	Mean	-1.82**	5.80	6.38	10.36**	3.50**
		28.92	S.D.	6.12	4.14	2.24	11.15	3.60
		5	N	5	5	5	5	5
4	m	276.94	Mean	-15.92**	1.38**	1.94**	-12.60**	-4.64**
		23.08	S.D.	6.26	4.59	1.50	9.55	3.45
		5	N	5	5	5	5	5

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

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 5: Body Weight Gain (cont'd)

RTA023-04/01 Provantis7 - Production Date: 08/04/08 11:18 Page: 1

Bodyweights - Intergroup Comparison of Bodyweight Gains

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Body Weight Gain (g) - Transformation: Identity (No Transformation)

Group	Sex	Base Weight Day 0		Day numbers relative to Start Date							Abs Gain 0	% Gain 0
			From:	0	4	6	7	10	14	17	21	21
			To:	4	6	7	10	14	17	21		
1	f	181.22	Mean	13.56	8.00	3.28	9.00	12.80	21.44	34.98	103.06	56.83
		4.78	S.D.	2.49	3.77	0.81	1.49	2.92	6.25	14.15	25.14	13.51
		5	N	5	5	5	5	5	5	5	5	5
2	f	179.13	Mean	10.05	11.58	-1.30*	8.05	15.03	20.33	31.63	95.35	53.32
		5.98	S.D.	6.80	2.92	1.47	2.13	2.48	3.79	2.78	6.61	4.81
		4	N	4	4	4	4	4	4	4	4	4
3	f	182.37	Mean	13.20	7.27	0.02	6.00	9.62	19.42	32.32	87.83	48.26
		5.93	S.D.	4.68	2.08	2.07	3.29	3.22	3.87	8.35	10.66	6.43
		6	N	6	6	6	6	6	6	6	6	6
4	f	188.16	Mean	16.52	7.58	-3.28**	-0.50**	1.72**	12.60*	23.30	57.94**	30.80**
		6.78	S.D.	5.13	2.68	3.20	5.71	2.93	2.90	3.39	6.43	3.31
		5	N	5	5	5	5	5	5	5	5	5

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

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 6: Food Consumption

RTA074-05/01 Provantis7 - Production Date: 06/03/08 12:59 Page: 1

Food Consumption - Intergroup Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex		From: 0 / To: 7	7 / 11	11 / 14	Mean 0 / 14	Total 0 / 14
1	m	Mean	19.75429	19.93500	20.85333	20.18087	280.58000
		S.D.	1.32570	1.63980	1.59871	1.43620	19.38342
		N	5	5	5	5	5
2	m	Mean	18.99429	19.33000	19.96667	19.43032	270.18000
		S.D.	1.83702	2.07217	1.82346	1.90538	26.53652
		N	5	5	5	5	5
3	m	Mean	17.04286	17.31500	18.24000	17.53262	243.28000
		S.D.	2.30157	2.47264	2.16646	2.26836	31.89353
		N	5	5	5	5	5
4	m	Mean	13.15429**	14.74000**	15.18667**	14.36032**	196.60000
		S.D.	1.70819	2.04959	1.22760	1.63418	23.45602
		N	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 6: Food Consumption (cont'd)

RTA074-05/01 Provantis7 - Production Date: 08/04/08 11:19 Page: 1

Food Consumption - Intergroup Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	From: / To:	0 / 4	4 / 6	6 / 7	7 / 10	10 / 14	14 / 17	17 / 21	Mean 0 / 21	Total 0 / 21
1	f	Mean	17.78500	15.73000	14.58000	17.63333	18.65500	20.67333	21.34500	18.05738	392.1000
		S.D.	0.49705	1.39041	3.49671	0.53333	0.59802	1.22778	0.84620	0.73205	8.77012
		N	5	5	5	5	5	5	5	5	5
2	f	Mean	15.37500	17.13750	13.90000	16.04167	18.11875	20.31667	18.85625**	17.10655	366.6500
		S.D.	3.06886	1.39903	1.71075	0.74951	0.29887	0.26874	1.11512	0.27941	9.28386
		N	4	4	4	4	4	4	4	4	4
3	f	Mean	16.73333	16.39167	14.10000	14.77778**	16.81667*	18.76667	18.42083**	16.57242*	355.4000
		S.D.	1.60870	2.28154	1.14193	0.83843	1.47722	0.84984	0.78953	0.83919	18.32321
		N	6	6	6	6	6	6	6	6	6
4	f	Mean	17.67500	18.03000	12.56000	11.64667**	11.08000**	14.44667**	14.01000**	14.20690**	297.9600
		S.D.	1.01842	1.36867	1.72424	1.73183	0.41848	4.59393	1.49704	0.92648	21.29291
		N	5	5	5	5	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 7: Macroscopic Findings

Group/ Observation	**Control**		**100 mg/m³**		**300 mg/m³**		**1000 mg/m³**	
Sex	m	f	m	f	m	f	m	f
n*	5	5	5	5	5	6	5	6
Lung								
red/glassy areas					1		1	
LALN								
enlarged							2	
Thymus								
red areas	2							
reduced in size						4	4	4
Kidney(s)								
dilated	1			1	1			1
cyst(s)			1					
Testes								
reduced in size							1	

*including non-pregnant females

Table 8: Organ Weights

RTA055-05/01 Provantis7 - Production Date: 04/03/08 13:54 Page: 1

Generalised Results - Group Summary by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex		Liver Weight g	Kidney Wt left g	Kidney Wt right g	Thymus Weight g	Testis Wt left g	Testis Wt right g
			Identity	Identity	Identity	Identity	Identity	Identity
1	m	Mean	12.740	1.206	1.202	0.432	1.658	1.654
		S.D.	1.031	0.108	0.115	0.092	0.076	0.093
		N	5	5	5	5	5	5
2	m	Mean	13.310	1.212	1.232	0.478	1.634	1.596
		S.D.	0.780	0.082	0.102	0.131	0.082	0.083
		N	5	5	5	5	5	5
3	m	Mean	12.828	1.136	1.180	0.374	1.572	1.562
		S.D.	2.288	0.136	0.160	0.096	0.101	0.090
		N	5	5	5	5	5	5
4	m	Mean	10.950	1.090	1.118	0.244*	1.556	1.540
		S.D.	1.266	0.160	0.171	0.057	0.169	0.187
		N	5	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 8: Organ Weights (cont'd)

RTA055-05/01 Provantis7 - Production Date: 08/04/08 11:21 Page: 1

Generalised Results - Group Summary by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex		Liver Weight g	Kidney Wt left g	Kidney Wt right g	Thymus Weight g	Ovary Wt left g	Ovary Wt right g
			Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	11.034	0.792	0.814	0.232	0.0664	0.0824
		S.D.	0.780	0.068	0.093	0.041	0.0105	0.0097
		N	5	5	5	5	5	5
2	f	Mean	9.810*	0.740	0.765	0.243	0.0673	0.0700
		S.D.	0.953	0.056	0.066	0.022	0.0136	0.0157
		N	4	4	4	4	4	4
3	f	Mean	10.222	0.782	0.850	0.177*	0.0708	0.0640*
		S.D.	0.412	0.064	0.113	0.027	0.0099	0.0111
		N	6	6	6	6	6	6
4	f	Mean	9.598**	0.742	0.756	0.112**	0.0674	0.0634*
		S.D.	0.514	0.031	0.050	0.036	0.0104	0.0065
		N	5	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 9: Organ Weight/Body Weight Ratios

RTA055-05/01 Provantis7 - Production Date: 04/03/08 13:51 Page: 1

Generalised Results - Group Summary by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex		Terminal Bweight g	Liver /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Thym. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	m	Mean	299.52	42.57144	4.02878	4.01036	1.43920	5.57812	5.56568
		S.D.	23.38	1.98608	0.21973	0.14948	0.26683	0.69885	0.72755
		N	5	5	5	5	5	5	5
2	m	Mean	298.50	44.60990	4.06008	4.12884	1.60420	5.48748	5.36744
		S.D.	15.72	1.95577	0.15665	0.28466	0.45339	0.41113	0.52400
		N	5	5	5	5	5	5	5
3	m	Mean	289.54	44.10354	3.93138	4.07606	1.28106	5.48696	5.44582
		S.D.	37.12	3.11409	0.22142	0.18232	0.23451	0.67391	0.57902
		N	5	5	5	5	5	5	5
4	m	Mean	260.06	42.06816	4.18136	4.28438	0.93552*	6.01878	5.95626
		S.D.	27.14	0.94345	0.24604	0.25432	0.20114	0.74686	0.80642
		N	5	5	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 9: Organ Weight/Body Weight Ratios (cont'd)

RTA055-05/01 Provantis7 - Production Date: 08/04/08 11:23 Page: 1

Generalised Results - Group Summary by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex		Terminal Bweight g	Liver /Bodywt g/kg	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg
			Identity	Identity	Identity	Identity	Identity	Identity	Identity
1	f	Mean	280.16	39.66032	2.85966	2.94364	0.84526	0.239166	0.294564
		S.D.	26.64	4.48490	0.48040	0.57674	0.23478	0.046799	0.027464
		N	5	5	5	5	5	5	5
2	f	Mean	270.98	36.22000	2.73203	2.82460	0.89650	0.247518	0.259108
		S.D.	6.87	3.60495	0.21420	0.25298	0.10095	0.045603	0.063358
		N	4	4	4	4	4	4	4
3	f	Mean	267.60	38.19965	2.92465	3.18462	0.66293	0.265287	0.238267
		S.D.	10.92	0.34008	0.27118	0.49395	0.11782	0.039751	0.033129
		N	6	6	6	6	6	6	6
4	f	Mean	244.40**	39.30278	3.03996	3.09770	0.45568**	0.275988	0.259756
		S.D.	9.28	2.28646	0.17957	0.24659	0.13189	0.042522	0.028776
		N	5	5	5	5	5	5	5

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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Table 10: Summary of Cesarean Section Data

SUMMARY OF CESAREAN SECTION DATA

		Control Clean Air		Low Dose 100 mg/m3	Mid Dose 300 mg/m3	High Dose 1000 mg/m3
Pregnant	N	5		4	6	5
Dams with no Viable Fetuses	N	0		0	0	0
Dams with Viable Fetuses	N	5		4	6	5
Corpora Lutea	TOTAL	64		45	74	64
No. per animal	MEAN	12.8	d	11.3	12.3	12.8
	S.D.	4.32		3.30	0.82	1.10
	p-value	0.813				
Implantation Sites	TOTAL	47		40	60	60
No. per animal	MEAN	9.4	d	10.0	10.0	12.0
	S.D.	5.18		2.45	2.61	1.41
	p-value	0.614				
Preimplantation Loss	TOTAL	17		5	14	4
Dams with loss	N	4	f	3	5	2
	p-value			1.000	1.000	1.000
Dams with loss > 2	N	4	f	0	2	1
	p-value			0.143	0.727	0.619
No. per animal	MEAN	3.4	d	1.3	2.3	0.8
	S.D.	2.07		0.96	2.07	1.30
	p-value	0.127				
% per animal	MEAN%	31.6	d	9.8	19.6	6.0
	S.D.	27.52		7.22	18.90	10.01
	p-value	0.171				
Live Fetuses	TOTAL	46		39	59	59
No. per animal	MEAN	9.2	d	9.8	9.8	11.8
	S.D.	4.97		2.50	2.64	1.30
	p-value	0.595				
Males	TOTAL	24		23	29	40
	MEAN%	51.5	d	57.7	49.2	66.9
	S.D.	5.83		10.24	11.26	13.11
	p-value	0.065				
Females	TOTAL	22		16	30	19
	MEAN%	48.5	d	42.3	50.8	33.1
	S.D.	5.83		10.24	11.26	13.11
	p-value	0.065				

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

Table 10: Summary of Cesarean Section Data (cont'd)

SUMMARY OF CESAREAN SECTION DATA

		Control Clean Air		Low Dose 100 mg/m3	Mid Dose 300 mg/m3	High Dose 1000 mg/m3
Postimplantation Loss	TOTAL	1		1	1	1
Dams with loss	N	1	f	1	1	1
	p-value			1.000	1.000	1.000
Dams with loss > 2	N	0	f	0	0	0
	p-value					
No. per animal	MEAN	0.2	d	0.3	0.2	0.2
	S.D.	0.45		0.50	0.41	0.45
	p-value	0.993				
% implants per animal	MEAN%	1.4	d	2.5	1.7	1.5
	S.D.	3.19		5.00	4.08	3.44
	p-value	0.977				
Dead Fetuses	TOTAL	0		0	0	0
No. per animal	MEAN	0.0		0.0	0.0	0.0
	S.D.	0.00		0.00	0.00	0.00
	p-value					
% of implants per animal	MEAN%	0.0		0.0	0.0	0.0
	S.D.	0.00		0.00	0.00	0.00
	p-value					
Resorptions: Early	TOTAL	0		1	1	0
No. per animal	MEAN	0.0	d	0.3	0.2	0.0
	S.D.	0.00		0.50	0.41	0.00
	p-value	0.549				
% of implants per animal	MEAN%	0.0	d	2.5	1.7	0.0
	S.D.	0.00		5.00	4.08	0.00
	p-value	0.549				
Resorptions: Late	TOTAL	1		0	0	1
No. per animal	MEAN	0.2	d	0.0	0.0	0.2
	S.D.	0.45		0.00	0.00	0.45
	p-value	0.585				
% of implants per animal	MEAN%	1.4	d	0.0	0.0	1.5
	S.D.	3.19		0.00	0.00	3.44
	p-value	0.584				

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

Table 10: Summary of Cesarean Section Data (cont'd)

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

SUMMARY OF CESAREAN SECTION DATA

		Control Clean Air	Low Dose 100 mg/m3	Mid Dose 300 mg/m3	High Dose 1000 mg/m3
Fetal Body Weight (g)	MEAN	4.8 d	4.7	4.5	2.9**
	S.D.	0.21	0.27	0.24	0.51
	N	5	4	6	5
	p-value	0.000	0.908	0.367	0.000
Male Fetuses	MEAN	4.9 d	4.8	4.6	3.0**
	S.D.	0.30	0.33	0.32	0.52
	p-value	0.000	0.930	0.481	0.000
Female Fetuses	MEAN	4.7 d	4.5	4.4	2.8**
	S.D.	0.13	0.24	0.21	0.54
	p-value	0.000	0.777	0.400	0.000

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

Table 11: Summary of Gravid Uterine Weight and Net Body Weight Change

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

SUMMARY OF GRAVID UTERINE WEIGHT AND NET BODY WEIGHT CHANGE (GRAMS)

		Control Clean Air	Low Dose 100 mg/m3	Mid Dose 300 mg/m3	High Dose 1000 mg/m3
NET BODY WT. CHANGE	MEAN	81 d	74	67	34**
	S.D.	23.7	7.3	12.8	3.5
	N	5	4	6	5
	p-value	0.000	0.769	0.269	0.000
GRAVID UTERINE WT.	MEAN	57 d	59	58	48
	S.D.	28.0	11.6	13.9	3.3
	N	5	4	6	5
	p-value	0.701			
NET WEIGHT CHANGE MINUS UTERINE WT.	MEAN	25 d	15	9**	-14**
	S.D.	4.8	9.7	3.8	4.6
	N	5	4	6	5
	p-value	0.000	0.055	0.001	0.000

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

NET BODY WT. CHANGE = TERMINAL BODY WT. MINUS DAY 6 BODY WEIGHT
NET WEIGHT CHANGE = NET BODY WT. CHANGE MINUS UTERINE WEIGHT

Table 12: Histopathological Findings

Page: 1
Date:14-APR-2008 Time:13:23

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
	ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
NASAL and PARANASAL CAVITIES		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		3 (60%)	0 (0%)	0 (0%)	0 (0%)	3 (60%)	1 (20%)	0 (0%)	0 (0%)
Mucous (goblet) cell hyperplasia		0 (0%)	3 (60%)	5** (100%)	5** (100%)	0 (0%)	2 (40%)	6** (100%)	6** (100%)
Basal-cell hyperplasia, respiratory epithelium		0 (0%)	3 (60%)	1 (20%)	1 (20%)	0 (0%)	1 (20%)	1 (17%)	0 (0%)
Basal-cell hyperplasia, olfactory epithelium		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Atrophy, olfactory epithelium		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)
Mucosal inflammatory cell infiltration		2 (40%)	2 (40%)	4 (80%)	3 (60%)	2 (40%)	0 (0%)	3 (50%)	2 (33%)
Mucosal mineralisation		1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (17%)
Submucosal cyst		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PHARYNX (LARYNGO-)		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	6 (100%)	6 (100%)
LARYNX		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		2 (40%)	4 (80%)	3 (60%)	3 (60%)	4 (80%)	3 (60%)	4 (67%)	4 (67%)
Mucous (goblet) cell hyperplasia		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epithelial alteration		1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mucosal mononuclear/inflammatory cell infiltration		3 (60%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)	2 (40%)	2 (33%)	2 (33%)

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 12: **Histopathological Findings**

Page: 2
Date:14-APR-2008 Time:13:23

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings

	INCIDENCE OF LESIONS (PERCENT)							
	Males				Females			
LESIONS / TREATMENT	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
LARYNX	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
Submucosal foreign-body granuloma	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TRACHEA	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected	5 (100%)	5 (100%)	4 (80%)	2 (40%)	5 (100%)	5 (100%)	6 (100%)	4 (67%)
Mucous (goblet) cell hyperplasia	0 (0%)	0 (0%)	1 (20%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)
LUNGS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected	3 (60%)	5 (100%)	1 (20%)	0 (0%)	5 (100%)	3 (60%)	0** (0%)	0** (0%)
Alveolar histiocytosis	0 (0%)	0 (0%)	3 (60%)	5** (100%)	0 (0%)	2 (40%)	5* (83%)	6** (100%)
Interstitial mononuclear/inflammatory cell infiltration	1 (20%)	0 (0%)	2 (40%)	4 (80%)	0 (0%)	0 (0%)	2 (33%)	6** (100%)
Alveolar inflammatory cell infiltration	1 (20%)	0 (0%)	1 (20%)	5* (100%)	0 (0%)	0 (0%)	0 (0%)	6** (100%)
Bronchiolo-alveolar hyperplasia	0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	4 (67%)
Neuroendocrine cell hyperplasia	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alveolar haemorrhage	1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Interstitial fibrosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Congestion	0 (0%)	0 (0%)	0 (0%)	1 (20%)	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

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Table 12: Histopathological Findings

Page: 3
Date:14-APR-2008 Time:13:23

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings

		INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
LESIONS	TREATMENT	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
ANIMAL TOTALS		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
LUNG ASSOCIATED LYMPH NODES		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		5 (100%)	5 (100%)	5 (100%)	3 (60%)	5 (100%)	5 (100%)	6 (100%)	6 (100%)
Lymphoid hyperplasia		0 (0%)	0 (0%)	0 (0%)	2 (40%)	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

*** Listing Complete ***

Table 13: Histopathological Findings (with score expansion)

Page: 1
Date: 8-APR-2008 Time:10:38

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
	ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
NASAL and PARANASAL CAVITIES		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		3 (60%)	0 (0%)	0 (0%)	0 (0%)	3 (60%)	1 (20%)	0 (0%)	0 (0%)
Mucous (goblet) cell hyperplasia									
very slight		0 (0%)	3 (60%)	2 (40%)	0 (0%)	0 (0%)	2 (40%)	1 (17%)	0 (0%)
slight		0 (0%)	0 (0%)	3 (60%)	3 (60%)	0 (0%)	0 (0%)	5* (83%)	3 (50%)
moderate		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)
Score Expanded Totals		0 (0%)	3 (60%)	5** (100%)	5** (100%)	0 (0%)	2 (40%)	6** (100%)	6** (100%)
Basal-cell hyperplasia, respiratory epithelium									
very slight		0 (0%)	2 (40%)	1 (20%)	0 (0%)	0 (0%)	1 (20%)	1 (17%)	0 (0%)
slight		0 (0%)	1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		0 (0%)	3 (60%)	1 (20%)	1 (20%)	0 (0%)	1 (20%)	1 (17%)	0 (0%)
Basal-cell hyperplasia, olfactory epithelium									
very slight		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Atrophy, olfactory epithelium									
very slight		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)
Mucosal inflammatory cell infiltration									
very slight		1 (20%)	1 (20%)	1 (20%)	1 (20%)	1 (20%)	0 (0%)	3 (50%)	2 (33%)
slight		1 (20%)	1 (20%)	3 (60%)	1 (20%)	1 (20%)	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

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Table 13: Histopathological Findings (with score expansion)

Page: 2
Date: 8-APR-2008 Time:10:38

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings (with score expansion)

		INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
LESIONS	TREATMENT	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
	ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
NASAL and PARANASAL CAVITIES		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
Mucosal inflammatory cell infiltration									
moderate		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		2 (40%)	2 (40%)	4 (80%)	3 (60%)	2 (40%)	0 (0%)	3 (50%)	2 (33%)
Mucosal mineralisation									
very slight		1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (17%)
Score Expanded Totals		1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	1 (17%)
Submucosal cyst		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PHARYNX (LARYNGO-)		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	5 (100%)	6 (100%)	6 (100%)
LARYNX		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		2 (40%)	4 (80%)	3 (60%)	3 (60%)	4 (80%)	3 (60%)	4 (67%)	4 (67%)
Mucous (goblet) cell hyperplasia									
very slight		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Epithelial alteration									
very slight		1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (20%)	0 (0%)	1 (20%)	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

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Table 13: **Histopathological Findings (with score expansion)**

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings (with score expansion)

		INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
LESIONS	TREATMENT	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
	ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
LARYNX		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
Mucosal mononuclear/inflammatory cell infiltration									
very slight		2 (40%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)	2 (40%)	2 (33%)	1 (17%)
slight		1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Score Expanded Totals		3 (60%)	1 (20%)	1 (20%)	2 (40%)	1 (20%)	2 (40%)	2 (33%)	2 (33%)
Submucosal foreign-body granuloma									
slight		1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
TRACHEA		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		5 (100%)	5 (100%)	4 (80%)	2 (40%)	5 (100%)	5 (100%)	6 (100%)	4 (67%)
Mucous (goblet) cell hyperplasia									
very slight		0 (0%)	0 (0%)	1 (20%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)
Score Expanded Totals		0 (0%)	0 (0%)	1 (20%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)
LUNGS		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected		3 (60%)	5 (100%)	1 (20%)	0 (0%)	5 (100%)	3 (60%)	0** (0%)	0** (0%)
Alveolar histiocytosis									
very slight		0 (0%)	0 (0%)	3 (60%)	2 (40%)	0 (0%)	2 (40%)	5* (83%)	1 (17%)
slight		0 (0%)	0 (0%)	0 (0%)	3 (60%)	0 (0%)	0 (0%)	0 (0%)	5* (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 13: Histopathological Findings (with score expansion)

Page: 4
Date: 8-APR-2008 Time:10:38

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings (with score expansion)

LESIONS	TREATMENT	INCIDENCE OF LESIONS (PERCENT)							
		Males				Females			
		Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
	ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
LUNGS		(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
Alveolar histiocytosis									
Score Expanded Totals		0 (0%)	0 (0%)	3 (60%)	5** (100%)	0 (0%)	2 (40%)	5* (83%)	6** (100%)
Interstitial mononuclear/inflammatory cell infiltration									
very slight		1 (20%)	0 (0%)	2 (40%)	2 (40%)	0 (0%)	0 (0%)	2 (33%)	3 (50%)
slight		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	3 (50%)
Score Expanded Totals		1 (20%)	0 (0%)	2 (40%)	4 (80%)	0 (0%)	0 (0%)	2 (33%)	6** (100%)
Alveolar inflammatory cell infiltration									
very slight		1 (20%)	0 (0%)	1 (20%)	4 (80%)	0 (0%)	0 (0%)	0 (0%)	4 (67%)
slight		0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	2 (33%)
Score Expanded Totals		1 (20%)	0 (0%)	1 (20%)	5* (100%)	0 (0%)	0 (0%)	0 (0%)	6** (100%)
Bronchiolo-alveolar hyperplasia									
very slight		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	4 (67%)
Score Expanded Totals		0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	4 (67%)
Neuroendocrine cell hyperplasia									
slight		0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Alveolar haemorrhage									
very slight		1 (20%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals		1 (20%)	0 (0%)	1 (20%)	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 13: Histopathological Findings (with score expansion)

Page: 5
Date: 8-APR-2008 Time:10:38

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE

STUDY : 02N07533

Summary of Histopathological Findings (with score expansion)

	INCIDENCE OF LESIONS (PERCENT)							
	Males				Females			
LESIONS / TREATMENT	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC	Clean Air	100 mg/m3 THC	300 mg/m3 THC	1000 mg/m3 THC
ANIMAL TOTALS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
LUNGS	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
Interstitial fibrosis								
very slight	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Score Expanded Totals	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)
Congestion								
severe	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals	0 (0%)	0 (0%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
LUNG ASSOCIATED LYMPH NODES	(5)	(5)	(5)	(5)	(5)	(5)	(6)	(6)
No abnormality detected	5 (100%)	5 (100%)	5 (100%)	3 (60%)	5 (100%)	5 (100%)	6 (100%)	6 (100%)
Lymphoid hyperplasia								
slight	0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Score Expanded Totals	0 (0%)	0 (0%)	0 (0%)	2 (40%)	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

*** Listing Complete ***

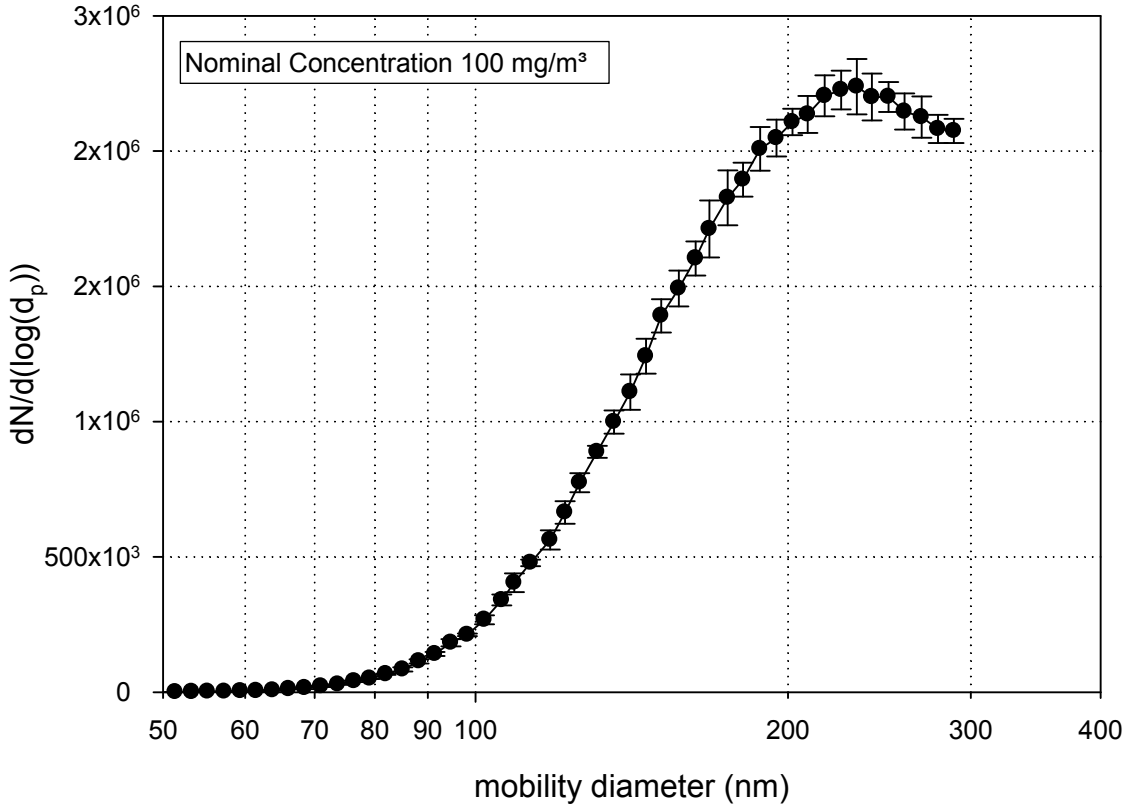
Table 14: **Blood Formation**

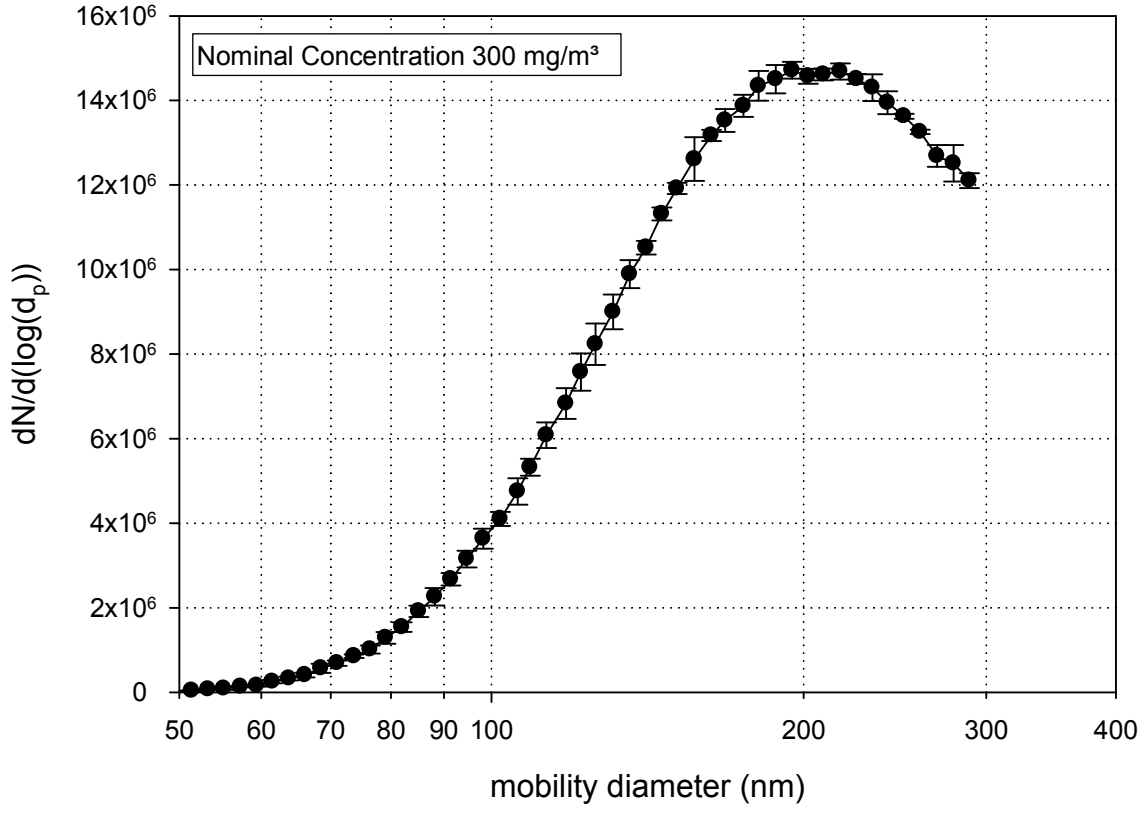
Study No.: 02N07533		**Males**		**Females**	
RAFC [mg/m^3]	**Animals**	**PCE/400 RBC**	**PCE/NCE**	**PCE/400 RBC**	**PCE/NCE**
0	5	133 ± 11.4	0.50 ± 0.063	142 ± 12.1	0.55 ± 0.077
300	4	n.d.	n.d.	135 ± 22.4	0.52 ± 0.128
1000	5	120 ± 13.2	0.43 ± 0.069	110 ± 17.6**	0.38 ± 0.085**

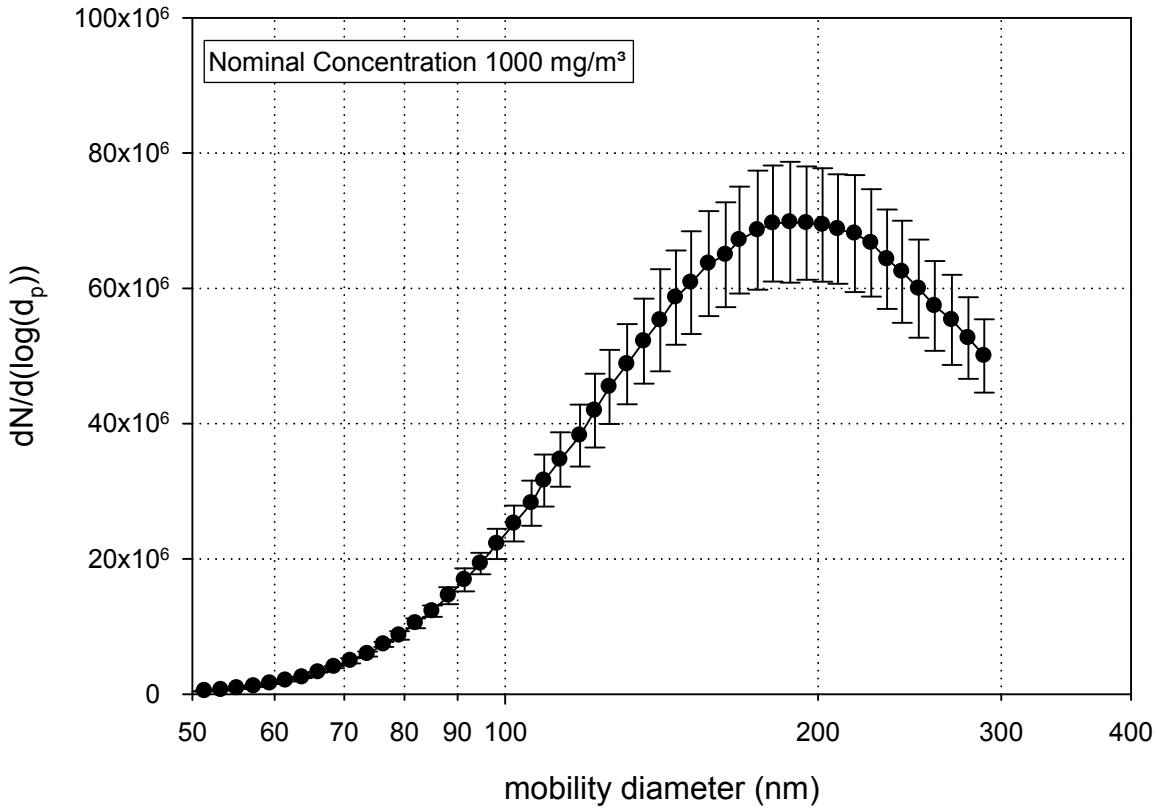
RAFC = Roofing asphalt fume condensate
PCE = Polychromatic erythrocytes
RBC = Red blood cells
NCE = Normochromatic erythrocytes
n.d. = Not determined
Data represent means ± standard deviations
** = Significantly different from control animals: $p \leq 0.01$, Student's *t*-test for unpaired values.

Appendix A

Particle Size Distributions measured


Nominal Concentration 100 mg/m³
3x10⁶
2x10⁶
2x10⁶
1x10⁶
500x10³
0
dN/d(log(dp))
50
60
70
80
90
100
200
300
400
mobility diameter (nm)


Nominal Concentration 300 mg/m³
16x10⁶
14x10⁶
12x10⁶
10x10⁶
8x10⁶
6x10⁶
4x10⁶
2x10⁶
0
dN/d(log(dp))
50
60
70
80
90
100
200
300
400
mobility diameter (nm)


Nominal Concentration 1000 mg/m³
100x10⁶
80x10⁶
60x10⁶
40x10⁶
20x10⁶
0
dN/d(log(dp))
50
60
70
80
90
100
200
300
400
mobility diameter (nm)

Appendix B

Clinical Observations
Individual Data

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 1

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date											
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
1	m	1101	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		1102	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		1103	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		1104	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		1105	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 2

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date											
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
2	m	2101	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		2102	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		2103	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		2104	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		2105	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 3

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date										
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
3	m	3101	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		3102	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		3103	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		3104	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		3105	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 4

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date											
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
4	m	4101	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		4102	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		4103	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		4104	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.
		4105	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	.	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	X	.	.	.	.	.

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 5

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date												
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
1	f	1201	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		1202	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		1203	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	.	X	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		1204	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	.	X	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		1205	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 6

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date												
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
2	f	2201	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		2202	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		2203	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	.	X	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		2204	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		2205	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 7

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date													
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
3	f	3201	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		3202	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		3203	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	.	X	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		3204	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		3205	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		3206	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA001-01/00 Provantis7 - Production Date: 27/03/08 8:22 Page: 8

Clinical Observations - Clinical Signs by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

				Day numbers relative to Start Date													
Group	Sex	Animal	Clinical Sign	3	4	5	6	10	11	12	13	14	17	18	19	20	21
4	f	4201	No Abnormalities Detected	.	.	.	X	.	.	.	X	.	.	.	.	X	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4202	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	.	X	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4203	No Abnormalities Detected	.	.	X	.	.	.	X	.	.	.	.	X	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4204	No Abnormalities Detected	.	X	.	.	.	X	.	.	.	.	X	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4205	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X
		4206	No Abnormalities Detected	X	.	.	.	X	.	.	.	.	X	.	.	.	.
			Killed - terminal kill	.	.	.	.	.	.	.	.	.	.	.	.	.	X

Severity Codes: X = Present

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Appendix C

Body Weight
Individual Data

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 1

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	7	11	14
1	m	1101	241.7	250.7	257.9	261.5
		1102	281.2	295.0	302.3	312.2
		1103	285.2	294.5	308.5	316.4
		1104	269.3	291.3	302.5	311.9
		1105	278.8	294.1	312.2	320.4
		Mean	271.24	285.12	296.68	304.48
		S.D.	17.52	19.29	22.08	24.28
		N	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 2

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	7	11	14
2	m	2101	286.7	290.3	297.0	301.7
		2102	261.7	274.7	282.0	292.1
		2103	285.0	303.7	315.3	318.1
		2104	259.4	264.8	270.5	278.3
		2105	285.3	295.8	307.3	314.9
		Mean	275.62	285.86	294.42	301.02
		S.D.	13.80	15.85	18.27	16.44
		N	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 3

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	7	11	14
3	m	3101	269.9	265.3	266.6	272.5
		3102	266.7	268.9	279.1	285.0
		3103	252.9	245.7	247.4	253.9
		3104	327.2	334.1	343.3	353.2
		3105	290.8	284.4	291.0	294.7
		Mean	281.50	279.68	285.48	291.86
		S.D.	28.92	33.40	36.13	37.53
		N	5	5	5	5

* = Result to left has an associated comment or marker

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 4

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	7	11	14
4	m	4101	280.6	267.5	274.5	276.7
		4102	271.3	252.3	252.1	251.7
		4103	293.0	272.4	267.0	270.0
		4104	299.3	293.1	296.4	297.9
		4105	240.5	219.8	222.0	225.4
		Mean	276.94	261.02	262.40	264.34
		S.D.	23.08	27.28	27.67	27.33
		N	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:46 Page: 1

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	4	6	7	10	14	17	21
1	f	1201	186.3	202.1	212.6	216.0	227.3	240.4	267.4	313.8
		1202	181.7	196.2	198.7	201.1	208.5	217.2	229.6	246.2
		1203	175.3	187.0	192.6	196.2	204.8	217.9	244.8	290.9
		1204	185.3	195.5	206.3	208.9	218.4	235.3	258.2	301.1
		1205	177.5	193.1	203.7	208.1	216.3	228.5	246.5	269.4
		Mean	181.22	194.78	202.78	206.06	215.06	227.86	249.30	284.28
		S.D.	4.78	5.47	7.58	7.63	8.81	10.32	14.34	26.78
		N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	4	6	7	10	14	17	21
2	f	2201	181.2	191.8	201.3	201.6	211.7	223.1	239.8	267.4
		2202	176.1	189.6	204.6	197.3	205.2	199.2	200.2	207.6
		2203	170.4	170.9	186.8	186.4	195.7	212.1	237.4	270.3
		2204	180.9	197.3	207.7	205.2	212.7	228.2	249.3	281.4
		2205	184.0	196.7	207.2	204.6	209.9	226.7	244.9	278.8
		Mean	178.52	189.26	201.52	199.02	207.04	217.86	234.32	261.10
		S.D.	5.35	10.77	8.61	7.72	6.96	12.18	19.62	30.46
		N	5	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:46 Page: 3

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	4	6	7	10	14	17	21
3	f	3201	181.2	191.2	200.1	198.3	206.8	215.8	237.5	272.7
		3202	186.6	198.5	207.9	205.5	207.6	217.9	238.8	275.4
		3203	175.7	188.2	197.3	199.0	204.7	208.7	228.5	261.4
		3204	175.1	182.5	187.5	189.1	199.1	212.0	235.7	271.5
		3205	188.1	208.0	214.0	212.7	220.2	229.2	247.0	284.8
		3206	187.5	205.0	210.2	212.5	214.7	227.2	239.8	255.4
		Mean	182.37	195.57	202.83	202.85	208.85	218.47	237.88	270.20
		S.D.	5.93	9.96	9.78	9.18	7.50	8.20	6.01	10.44
		N	6	6	6	6	6	6	6	6

* = Result to left has an associated comment or marker

RTA051-02/00 Provantis7 - Production Date: 12/03/08 7:46 Page: 4

Bodyweights - Individual Bodyweights

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Bodyweight (g)

Group	Sex	Animal	Day numbers relative to Start Date 0	4	6	7	10	14	17	21
4	f	4201	190.1	204.9	211.3	212.0	211.7	212.9	223.2	247.7
		4202	190.7	204.7	216.8	214.8	210.9	217.5	226.6	249.5
		4203	176.4	189.1	195.8	190.1	195.4	197.2	211.9	229.7
		4204	193.9	209.5	217.1	215.0	206.8	205.9	218.8	245.7
		4205	178.1	188.6	197.7	187.6	182.1	178.3	179.4	188.0
		4206	189.7	215.2	220.3	213.0	217.6	217.5	233.5	257.9
		Mean	186.48	202.00	209.83	205.42	204.08	204.88	215.57	236.42
		S.D.	7.32	10.88	10.56	12.91	13.06	15.16	19.15	25.44
		N	6	6	6	6	6	6	6	6

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Appendix D

Food Consumption
Individual Data

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 1

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	11	Total 0
			To:	7	11	14	14
1	m	1101		17.8000	17.4750	18.2333	249.2000
		1102		19.7857	19.2250	20.5000	276.9000
		1103		20.4571	20.2500	22.2667	291.0000
		1104		21.3571	21.2500	21.7333	299.7000
		1105		19.3714	21.4750	21.5333	286.1000
			----	--------	--------	--------	---------
			Mean	19.75429	19.93500	20.85333	280.58000
			S.D.	1.32570	1.63980	1.59871	19.38342
			N	5	5	5	5

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 2

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	11	Total 0
			To:	7	11	14	14
2	m	2101		17.7000	18.1500	18.8000	252.9000
		2102		18.9571	18.9250	19.5000	266.9000
		2103		21.5429	22.0750	22.3667	306.2000
		2104		16.8714	16.8250	17.9000	239.1000
		2105		19.9000	20.6750	21.2667	285.8000
			----	--------	--------	--------	---------
			Mean	18.99429	19.33000	19.96667	270.18000
			S.D.	1.83702	2.07217	1.82346	26.53652
			N	5	5	5	5

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 3

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	11	Total 0
			To:	7	11	14	14
3	m	3101		17.0571	16.3250	17.4333	237.0000
		3102		16.0143	17.2750	17.5667	233.9000
		3103		14.8429	14.2500	16.5333	210.5000
		3104		20.9000	21.0500	22.0333	296.6000
		3105		16.4000	17.6750	17.6333	238.4000
			Mean	17.04286	17.31500	18.24000	243.28000
			S.D.	2.30157	2.47264	2.16646	31.89353
			N	5	5	5	5

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 4

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From:	0	7	11	Total 0
			To:	7	11	14	14
4	m	4101		13.8286	15.6750	15.2667	205.3000
		4102		13.1857	15.6500	15.5000	201.4000
		4103		12.7000	13.2250	14.4000	185.0000
		4104		15.3714	17.1000	17.0000	227.0000
		4105		10.6857	12.0500	13.7667	164.3000
			----	--------	--------	--------	---------
			Mean	13.15429	14.74000	15.18667	196.60000
			S.D.	1.70819	2.04959	1.22760	23.45602
			N	5	5	5	5

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 1

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From: / To:	0 / 4	4 / 6	6 / 7	7 / 10	10 / 14	14 / 17	17 / 21	Total 0 / 21
1	f	1201		17.9250	17.8500	16.8000	18.2000	19.3750	21.2667	21.6000	406.500
		1202		18.6000	14.8000	15.1000	17.7333	18.0500	18.9000	21.1750	385.900
		1203		17.4750	14.6500	10.8000	17.1667	18.2000	20.2333	22.3750	384.500
		1204		17.4750	14.9000	11.3000	18.0667	19.2000	20.7667	21.5250	390.400
		1205		17.4500	16.4500	18.9000	17.0000	18.4500	22.2000	20.0500	393.200
			Mean	17.78500	15.73000	14.58000	17.63333	18.65500	20.67333	21.34500	392.1000
			S.D.	0.49705	1.39041	3.49671	0.53333	0.59802	1.22778	0.84620	8.77012
			N	5	5	5	5	5	5	5	5

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 2

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From: / To:	0 / 4	4 / 6	6 / 7	7 / 10	10 / 14	14 / 17	17 / 21	Total 0 / 21
2	f	2201		16.1250	15.7500	15.4000	16.9333	17.7250	20.3333	20.3500	375.500
		2202		15.0750	16.8000	12.4000	16.0667	12.0750	13.2333	13.6500	297.100
		2203		10.8500	19.0500	15.1000	16.1000	18.0750	20.4667	18.7500	353.600
		2204		17.4750	16.6000	13.4000	16.0333	18.2500	19.9333	17.6500	368.000
		2205		17.0500	17.1500	11.7000	15.1000	18.4250	20.5333	18.6750	369.500
			Mean	15.31500	17.07000	13.60000	16.04667	16.91000	18.90000	17.81500	352.7400
			S.D.	2.66110	1.22096	1.62635	0.64919	2.71521	3.17630	2.52064	32.12605
			N	5	5	5	5	5	5	5	5

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 3

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From: / To:	0 / 4	4 / 6	6 / 7	7 / 10	10 / 14	14 / 17	17 / 21	Total 0 / 21
3	f	3201		16.9750	17.0000	14.2000	15.4667	17.2250	19.5000	18.3750	363.400
		3202		17.1250	18.7000	14.6000	14.0000	16.7250	19.7667	18.8500	364.100
		3203		15.6500	17.9000	12.7000	14.0000	14.3250	17.3667	17.9750	334.400
		3204		15.5500	12.1500	12.8000	14.7667	17.0500	18.8000	17.1500	336.800
		3205		19.6500	16.1500	14.7000	16.0667	18.9250	18.4333	19.4250	382.500
		3206		15.4500	16.4500	15.6000	14.3667	16.6500	18.7333	18.7500	351.200
			Mean	16.73333	16.39167	14.10000	14.77778	16.81667	18.76667	18.42083	355.4000
			S.D.	1.60870	2.28154	1.14193	0.83843	1.47722	0.84984	0.78953	18.32321
			N	6	6	6	6	6	6	6	6

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA071-01/00 Provantis7 - Production Date: 12/03/08 7:38 Page: 4

Food Consumption - Individual Food Consumption by Animal

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day numbers relative to Start Date

Group	Sex	Animal	From: / To:	0 / 4	4 / 6	6 / 7	7 / 10	10 / 14	14 / 17	17 / 21	Total 0 / 21
4	f	4201		18.5000	17.4500	14.0000	12.5667	10.8250	12.5000	13.5750	295.700
		4202		18.4250	19.8500	13.0000	10.9000	11.0750	11.0667	12.5250	286.700
		4203		16.6250	17.0000	10.6000	12.5333	10.7750	13.0667	13.1250	283.500
		4204		18.3250	16.7500	14.3000	8.9667	10.9250	13.0667	14.4500	288.700
		4205		13.8500	16.3500	5.8000	6.3333	8.3750	11.2000	11.6750	226.700
		4206		16.5000	19.1000	10.9000	13.2667	11.8000	22.5333	16.3750	335.200
			Mean	17.03750	17.75000	11.43333	10.76111	10.62917	13.90556	13.62083	286.0833
			S.D.	1.80781	1.40321	3.16143	2.66545	1.16602	4.31743	1.64366	34.77128
			N	6	6	6	6	6	6	6	6

* = 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 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Appendix E

Organ Weights
Individual Data

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:31 Page: 1

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Testis Wt left g	Testis Wt right g
1	m	1101	1.07	1.02	11.35	0.33	1.74	1.74
		1102	1.17	1.20	12.30	0.47	1.65	1.67
		1103	1.34	1.33	12.92	0.39	1.60	1.65
		1104	1.16	1.20	12.96	0.57	1.73	1.71
		1105	1.29	1.26	14.17	0.40	1.57	1.50
		Mean	1.206	1.202	12.740	0.432	1.658	1.654
		S.D.	0.108	0.115	1.031	0.092	0.076	0.093
		N	5	5	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:31 Page: 2

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Testis Wt left g	Testis Wt right g
2	m	2101	1.18	1.10	12.96	0.34	1.62	1.59
		2102	1.17	1.23	13.91	0.34	1.64	1.62
		2103	1.35	1.28	13.96	0.60	1.52	1.46
		2104	1.14	1.18	12.11	0.60	1.64	1.68
		2105	1.22	1.37	13.61	0.51	1.75	1.63
		Mean	1.212	1.232	13.310	0.478	1.634	1.596
		S.D.	0.082	0.102	0.780	0.131	0.082	0.083
		N	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:31 Page: 3

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Testis Wt left g	Testis Wt right g
3	m	3101	1.02	1.09	11.40	0.36	1.65	1.65
		3102	1.05	1.07	12.98	0.32	1.52	1.50
		3103	1.07	1.07	10.00	0.25	1.58	1.51
		3104	1.35	1.44	15.99	0.47	1.68	1.67
		3105	1.19	1.23	13.77	0.47	1.43	1.48
		Mean	1.136	1.180	12.828	0.374	1.572	1.562
		S.D.	0.136	0.160	2.288	0.096	0.101	0.090
		N	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:31 Page: 4

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Testis Wt left g	Testis Wt right g
4	m	4101	1.06	1.14	11.22	0.27	1.36	1.33
		4102	1.00	0.98	10.69	0.30	1.73	1.76
		4103	1.13	1.18	11.26	0.26	1.66	1.61
		4104	1.34	1.36	12.54	0.24	1.64	1.64
		4105	0.92	0.93	9.04	0.15	1.39	1.36
		Mean	1.090	1.118	10.950	0.244	1.556	1.540
		S.D.	0.160	0.171	1.266	0.057	0.169	0.187
		N	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:32 Page: 1

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Ovary Wt left g	Ovary Wt right g
1	f	1201	0.81	0.82	11.79	0.21	0.075	0.079
		1202	0.86	0.92	10.70	0.29	0.067	0.068
		1203	0.69	0.67	11.31	0.20	0.051	0.093
		1204	0.76	0.80	9.84	0.20	0.062	0.089
		1205	0.84	0.86	11.53	0.26	0.077	0.083
		Mean	0.792	0.814	11.034	0.232	0.0664	0.0824
		S.D.	0.068	0.093	0.780	0.041	0.0105	0.0097
		N	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:32 Page: 2

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Ovary Wt left g	Ovary Wt right g
2	f	2201	0.70	0.73	9.26	0.27	0.052	0.091
		2202	0.79	0.80	8.27	0.28	0.068	0.061
		2203	0.81	0.83	10.80	0.23	0.064	0.053
		2204	0.69	0.69	8.77	0.22	0.068	0.068
		2205	0.76	0.81	10.41	0.25	0.085	0.068
		Mean	0.750	0.772	9.502	0.250	0.0674	0.0682
		S.D.	0.053	0.059	1.075	0.025	0.0118	0.0142
		N	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:32 Page: 3

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Ovary Wt left g	Ovary Wt right g
3	f	3201	0.74	0.83	10.31	0.13	0.079	0.073
		3202	0.79	0.86	10.24	0.17	0.084	0.059
		3203	0.69	0.71	9.76	0.19	0.063	0.059
		3204	0.77	0.79	10.38	0.18	0.065	0.062
		3205	0.83	0.86	10.86	0.18	0.059	0.081
		3206	0.87	1.05	9.78	0.21	0.075	0.050
		Mean	0.782	0.850	10.222	0.177	0.0708	0.0640
		S.D.	0.064	0.113	0.412	0.027	0.0099	0.0111
		N	6	6	6	6	6	6

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:32 Page: 4

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Kidney Wt left g	Kidney Wt right g	Liver Weight g	Thymus Weight g	Ovary Wt left g	Ovary Wt right g
4	f	4201	0.75	0.78	8.82	0.09	0.070	0.063
		4202	0.69	0.67	10.04	0.14	0.065	0.060
		4203	0.74	0.76	9.54	0.09	0.060	0.067
		4204	0.77	0.77	10.09	0.08	0.084	0.055
		4205	0.80	0.83	8.07	0.29	0.043	0.045
		4206	0.76	0.80	9.50	0.16	0.058	0.072
		Mean	0.752	0.768	9.343	0.142	0.0633	0.0603
		S.D.	0.037	0.054	0.775	0.079	0.0136	0.0095
		N	6	6	6	6	6	6

* = Result to left has an associated comment or marker

Appendix F

Organ Weight Ratios / Body Weight
Individual Data

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:33 Page: 1

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
1	m	1101	258.3	4.1425	3.9489	43.9412	1.2776	6.7364	6.7364
		1102	308.1	3.7975	3.8948	39.9221	1.5255	5.3554	5.4203
		1103	311.5	4.3018	4.2697	41.4767	1.2520	5.1364	5.2970
		1104	304.5	3.8095	3.9409	42.5616	1.8719	5.6814	5.6158
		1105	315.2	4.0926	3.9975	44.9556	1.2690	4.9810	4.7589
		Mean	299.52	4.02878	4.01036	42.57144	1.43920	5.57812	5.56568
		S.D.	23.38	0.21973	0.14948	1.98608	0.26683	0.69885	0.72755
		N	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:33 Page: 2

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
2	m	2101	300.3	3.9294	3.6630	43.1568	1.1322	5.3946	5.2947
		2102	289.7	4.0387	4.2458	48.0152	1.1736	5.6610	5.5920
		2103	314.3	4.2953	4.0725	44.4162	1.9090	4.8361	4.6452
		2104	276.5	4.1230	4.2676	43.7975	2.1700	5.9313	6.0759
		2105	311.7	3.9140	4.3953	43.6638	1.6362	5.6144	5.2294
		Mean	298.50	4.06008	4.12884	44.60990	1.60420	5.48748	5.36744
		S.D.	15.72	0.15665	0.28466	1.95577	0.45339	0.41113	0.52400
		N	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:33 Page: 3

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
3	m	3101	270.6	3.7694	4.0281	42.1286	1.3304	6.0976	6.0976
		3102	282.5	3.7168	3.7876	45.9469	1.1327	5.3805	5.3097
		3103	252.2	4.2427	4.2427	39.6511	0.9913	6.2649	5.9873
		3104	350.4	3.8527	4.1096	45.6336	1.3413	4.7945	4.7660
		3105	292.0	4.0753	4.2123	47.1575	1.6096	4.8973	5.0685
		Mean	289.54	3.93138	4.07606	44.10354	1.28106	5.48696	5.44582
		S.D.	37.12	0.22142	0.18232	3.11409	0.23451	0.67391	0.57902
		N	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:33 Page: 4

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 14 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Testis /Bodywt g/kg	R.Testis /Bodywt g/kg
4	m	4101	270.9	3.9129	4.2082	41.4175	0.9967	5.0203	4.9096
		4102	247.6	4.0388	3.9580	43.1745	1.2116	6.9871	7.1082
		4103	266.9	4.2338	4.4211	42.1881	0.9741	6.2196	6.0322
		4104	293.6	4.5640	4.6322	42.7112	0.8174	5.5858	5.5858
		4105	221.3	4.1573	4.2024	40.8495	0.6778	6.2811	6.1455
		Mean	260.06	4.18136	4.28438	42.06816	0.93552	6.01878	5.95626
		S.D.	27.14	0.24604	0.25432	0.94345	0.20114	0.74686	0.80642
		N	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:34 Page: 1

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg
1	f	1201	309.4	2.6180	2.6503	38.1060	0.6787	0.24240	0.25533
		1202	242.7	3.5435	3.7907	44.0874	1.1949	0.27606	0.28018
		1203	286.8	2.4059	2.3361	39.4351	0.6974	0.17782	0.32427
		1204	297.3	2.5563	2.6909	33.0979	0.6727	0.20854	0.29936
		1205	264.6	3.1746	3.2502	43.5752	0.9826	0.29101	0.31368
		Mean	280.16	2.85966	2.94364	39.66032	0.84526	0.239166	0.294564
		S.D.	26.64	0.48040	0.57674	4.48490	0.23478	0.046799	0.027464
		N	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:34 Page: 2

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg
2	f	2201	261.9	2.6728	2.7873	35.3570	1.0309	0.19855	0.34746
		2202	204.3	3.8669	3.9158	40.4797	1.3705	0.33284	0.29858
		2203	269.5	3.0056	3.0798	40.0742	0.8534	0.23748	0.19666
		2204	277.1	2.4901	2.4901	31.6492	0.7939	0.24540	0.24540
		2205	275.4	2.7596	2.9412	37.7996	0.9078	0.30864	0.24691
		Mean	257.64	2.95900	3.04284	37.07194	0.99130	0.264582	0.267002
		S.D.	30.41	0.54037	0.53492	3.65729	0.22930	0.054916	0.057639
		N	5	5	5	5	5	5	5

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:34 Page: 3

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg
3	f	3201	271.0	2.7306	3.0627	38.0443	0.4797	0.29151	0.26937
		3202	271.2	2.9130	3.1711	37.7581	0.6268	0.30973	0.21755
		3203	257.2	2.6827	2.7605	37.9471	0.7387	0.24495	0.22939
		3204	270.2	2.8497	2.9238	38.4160	0.6662	0.24056	0.22946
		3205	283.1	2.9318	3.0378	38.3610	0.6358	0.20841	0.28612
		3206	252.9	3.4401	4.1518	38.6714	0.8304	0.29656	0.19771
		Mean	267.60	2.92465	3.18462	38.19965	0.66293	0.265287	0.238267
		S.D.	10.92	0.27118	0.49395	0.34008	0.11782	0.039751	0.033129
		N	6	6	6	6	6	6	6

* = Result to left has an associated comment or marker

RTA052-02/00 Provantis7 - Production Date: 27/03/08 8:34 Page: 4

Generalised Results - Animals by Parameter - Fixed Time

07533 - Range Finding Testingfor a Combined Repeated Dose Toxicity Study with th
e Reproduction/Developmental Toxicity Screening Test and Mammalian E

Day: 21 relative to Start Date

Group	Sex	Animal	Terminal Bweight g	L.Kidney /Bodywt g/kg	R.Kidney /Bodywt g/kg	Liver /Bodywt g/kg	Thym. /Bodywt g/kg	L.Ovary /Bodywt g/kg	R.Ovary /Bodywt g/kg
4	f	4201	242.7	3.0902	3.2138	36.3412	0.3708	0.28842	0.25958
		4202	250.6	2.7534	2.6736	40.0638	0.5587	0.25938	0.23943
		4203	229.6	3.2230	3.3101	41.5505	0.3920	0.26132	0.29181
		4204	245.6	3.1352	3.1352	41.0831	0.3257	0.34202	0.22394
		4205	186.5	4.2895	4.4504	43.2708	1.5550	0.23056	0.24129
		4206	253.5	2.9980	3.1558	37.4753	0.6312	0.22880	0.28402
		Mean	234.75	3.24822	3.32315	39.96412	0.63890	0.268417	0.256678
		S.D.	25.05	0.53481	0.59465	2.60893	0.46404	0.042314	0.026819
		N	6	6	6	6	6	6	6

* = Result to left has an associated comment or marker

Group 1 - Control Clean air Group 2 - 100 mg/m3 Group 3 - 300 mg/m3 Group 4 - 1000 mg/m3

Appendix G

Cesarean Section
Individual Data

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL FEMALE REPRODUCTION DATA AND MEAN FETAL WEIGHT DATA

Clean Air

ANIMAL#	CORPORA LUTEA	%PREIMPL. LOSS	IMPLANT SITES	FETUSES LIVE	FETUSES DEAD (n)	FETUSES DEAD %	RESORPTIONS EARLY	RESORPTIONS LATE	RESORPTIONS TOTAL (n)	RESORPTIONS TOTAL %	SEX MALE	SEX FEMALE	AVERAGE FETAL BODY WEIGHT MALES	AVERAGE FETAL BODY WEIGHT FEMALES	AVERAGE FETAL BODY WEIGHT LITTER
1201	16	18.8	13	13	0	0.0	0	0	0	0.0	6	7	4.7	4.6	4.7
1202	7	71.4	2	2	0	0.0	0	0	0	0.0	1	1	5.4	4.9	5.2
1203	12	0.0	12	12	0	0.0	0	0	0	0.0	6	6	5.0	4.7	4.9
1204	18	22.2	14	13	0	0.0	0	1	1	7.1	8	5	4.6	4.6	4.6
1205	11	45.5	6	6	0	0.0	0	0	0	0.0	3	3	4.9	4.6	4.8
MEAN	12.8	31.6	9.4	9.2	0.0	0.0	0.0	0.2	0.2	1.4	4.8	4.4	4.9	4.7	4.8
S.D.	4.32	27.52	5.18	4.97	0.00	0.00	0.00	0.45	0.45	3.19	2.77	2.41	0.30	0.13	0.21
N	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL FEMALE REPRODUCTION DATA AND MEAN FETAL WEIGHT DATA

Low Dose

ANIMAL#	CORPORA LUTEA	%PREIMPL. LOSS	IMPLANT SITES	FETUSES LIVE	FETUSES DEAD (n)	FETUSES DEAD %	RESORPTIONS EARLY	RESORPTIONS LATE	RESORPTIONS TOTAL (n)	RESORPTIONS TOTAL %	SEX MALE	SEX FEMALE	AVERAGE FETAL BODY WEIGHT MALES	AVERAGE FETAL BODY WEIGHT FEMALES	AVERAGE FETAL BODY WEIGHT LITTER
2201	7	0.0	7	7	0	0.0	0	0	0	0.0	4	3	5.2	4.8	5.1
2202	NP														
2203	12	16.7	10	10	0	0.0	0	0	0	0.0	6	4	4.9	4.4	4.7
2204	15	13.3	13	13	0	0.0	0	0	0	0.0	9	4	4.5	4.3	4.4
2205	11	9.1	10	9	0	0.0	1	0	1	10.0	4	5	4.7	4.6	4.6
MEAN	11.3	9.8	10.0	9.8	0.0	0.0	0.3	0.0	0.3	2.5	5.8	4.0	4.8	4.5	4.7
S.D.	3.30	7.22	2.45	2.50	0.00	0.00	0.50	0.00	0.50	5.00	2.36	0.82	0.33	0.24	0.27
N	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

NP=NOT PREGNANT

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL FEMALE REPRODUCTION DATA AND MEAN FETAL WEIGHT DATA

Mid Dose

ANIMAL#	CORPORA LUTEA	%PREIMPL. LOSS	IMPLANT SITES	FETUSES LIVE	FETUSES DEAD (n)	FETUSES DEAD %	RESORPTIONS EARLY	RESORPTIONS LATE	RESORPTIONS TOTAL (n)	RESORPTIONS TOTAL %	SEX MALE	SEX FEMALE	AVERAGE FETAL BODY WEIGHT MALES	AVERAGE FETAL BODY WEIGHT FEMALES	AVERAGE FETAL BODY WEIGHT LITTER
3201	12	0.0	12	12	0	0.0	0	0	0	0.0	7	5	4.1	4.2	4.2
3202	13	15.4	11	11	0	0.0	0	0	0	0.0	5	6	4.6	4.3	4.5
3203	12	16.7	10	9	0	0.0	1	0	1	10.0	3	6	5.0	4.8	4.8
3204	13	7.7	12	12	0	0.0	0	0	0	0.0	7	5	4.5	4.2	4.4
3205	13	23.1	10	10	0	0.0	0	0	0	0.0	4	6	5.0	4.5	4.7
3206	11	54.5	5	5	0	0.0	0	0	0	0.0	3	2	4.7	4.6	4.6
MEAN	12.3	19.6	10.0	9.8	0.0	0.0	0.2	0.0	0.2	1.7	4.8	5.0	4.6	4.4	4.5
S.D.	0.82	18.90	2.61	2.64	0.00	0.00	0.41	0.00	0.41	4.08	1.83	1.55	0.32	0.21	0.24
N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL FEMALE REPRODUCTION DATA AND MEAN FETAL WEIGHT DATA

High Dose

	CORPORA	%PREIMPL.	IMPLANT	FETUSES			RESORPTIONS				SEX		AVERAGE FETAL BODY WEIGHT		
ANIMAL#	LUTEA	LOSS	SITES	LIVE	DEAD (n)	DEAD %	EARLY	LATE	TOTAL (n)	TOTAL %	MALE	FEMALE	MALES	FEMALES	LITTER
4201	13	0.0	13	13	0	0.0	0	0	0	0.0	10	3	2.3	2.2	2.3
4202	11	0.0	11	11	0	0.0	0	0	0	0.0	6	5	3.3	3.0	3.1
4203	13	23.1	10	10	0	0.0	0	0	0	0.0	6	4	3.5	3.5	3.5
4204	14	7.1	13	13	0	0.0	0	0	0	0.0	11	2	2.6	2.4	2.6
4205	NP														
4206	13	0.0	13	12	0	0.0	0	1	1	7.7	7	5	3.2	3.1	3.2
MEAN	12.8	6.0	12.0	11.8	0.0	0.0	0.0	0.2	0.2	1.5	8.0	3.8	3.0	2.8	2.9
S.D.	1.10	10.01	1.41	1.30	0.00	0.00	0.00	0.45	0.45	3.44	2.35	1.30	0.52	0.54	0.51
N	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

NP=NOT PREGNANT

Appendix H

Gravid Uterine Weight and Net Body Weight Change
Individual Data

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL GRAVID UTERINE WEIGHT AND NET BODY WEIGHT CHANGE (GRAMS)

Clean Air

ANIMAL#	UTERUS WEIGHT	ADJUSTED WEIGHT	NET WEIGHT CHANGE FROM DAY 6	WEIGHT CHANGE FROM DAY 6
1201	79	235	22	101
1202	15	231	33	48
1203	74	217	25	98
1204	75	226	20	95
1205	40	229	25	66
MEAN	57.	228.	25.	82.
S.D.	28.0	6.7	4.8	23.7
N	5	5	5	5

ADJUSTED WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 6 = TERMINAL CORRECTED BODY WEIGHT MINUS DAY 6 BODY WEIGHT

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL GRAVID UTERINE WEIGHT AND NET BODY WEIGHT CHANGE (GRAMS)

Low Dose

ANIMAL#		UTERUS WEIGHT	ADJUSTED WEIGHT	NET WEIGHT CHANGE FROM DAY 6	WEIGHT CHANGE FROM DAY 6
2201		46	221	20	66
2202x	NP	0	207	3	3
2203		62	208	21	83
2204		73	208	1	74
2205		53	225	18	72
MEAN		59.	216.	15.	74.
S.D.		11.6	8.9	9.7	7.3
N		4	4	4	4

ADJUSTED WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 6 = TERMINAL CORRECTED BODY WEIGHT MINUS DAY 6 BODY WEIGHT

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL GRAVID UTERINE WEIGHT AND NET BODY WEIGHT CHANGE (GRAMS)

Mid Dose

ANIMAL#	UTERUS WEIGHT	ADJUSTED WEIGHT	NET WEIGHT CHANGE FROM DAY 6	WEIGHT CHANGE FROM DAY 6
3201	67	206	6	73
3202	64	212	4	68
3203	56	205	8	64
3204	71	200	13	84
3205	61	224	10	71
3206	32	223	13	45
MEAN	58.	212.	9.	67.
S.D.	13.9	10.0	3.8	12.8
N	6	6	6	6

ADJUSTED WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 6 = TERMINAL CORRECTED BODY WEIGHT MINUS DAY 6 BODY WEIGHT

27-MAR-2008 11:40

Study No.: 02N07533
API

Range Finding Testing for a Combined Repeated Dose Toxicity
Study with Roofing Asphalt Fume Condensate

INDIVIDUAL GRAVID UTERINE WEIGHT AND NET BODY WEIGHT CHANGE (GRAMS)

High Dose

ANIMAL#	UTERUS WEIGHT	ADJUSTED WEIGHT	NET WEIGHT CHANGE FROM DAY 6	WEIGHT CHANGE FROM DAY 6
4201	43	205	-7	36
4202	47	202	-14	33
4203	47	183	-13	34
4204	48	198	-19	29
4205x NP	0	188	-10	-10
4206	53	205	-15	38
MEAN	48.	199.	-14.	34.
S.D.	3.3	9.4	4.6	3.5
N	5	5	5	5

ADJUSTED WEIGHT = TERMINAL BODY WEIGHT MINUS GRAVID UTERINE WEIGHT
NET WEIGHT CHANGE FROM DAY 6 = TERMINAL CORRECTED BODY WEIGHT MINUS DAY 6 BODY WEIGHT

NP=NOT PREGNANT x=EXCLUDED FROM MEAN

Apppendix I

Histopathology
Individual Data

Page: 1
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

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

Animal Ref	Findings	
001101	Killed	Necropsied on Day: 14

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001102	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Very slight focal submucosal mineralisation
Very slight multifocal submucosal inflammatory cell infiltration
LARYNX :
Very slight focal submucosal mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001103	Killed	Necropsied on Day: 14

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001104	Killed	Necropsied on Day: 14

LARYNX :
Very slight focal submucosal inflammatory cell infiltration
Very slight focal epithelial alteration : due to aspiration of plant fibres
LUNGS :
Very slight focal alveolar haemorrhage
Very slight focal alveolar inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 2
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
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Individual Animal Listing

STUDY : 02N07533

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

Animal Ref	Findings
001105	Killed Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration

LARYNX :
Slight focal submucosal mononuclear cell infiltration
Slight focal submucosal foreign-body granuloma : due to inspissation of plant fibres

LUNGS :
Very slight focal interstitial mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 3
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
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Individual Animal Listing

STUDY : 02N07533

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

Animal Ref	Findings	
001201	Killed	Necropsied on Day: 21

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001202	Killed	Necropsied on Day: 21

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001203	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight focal submucosal inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001204	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

001205	Killed	Necropsied on Day: 21

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-)

Page: 4
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Low Dose THC Treatment: 100mg/m3THC Sex: Males

Animal Ref	Findings	
002101	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight focal respiratory epithelial basal-cell hyperplasia
LARYNX :
Very slight focal submucosal mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Animal Ref	Findings	
002102	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Very slight focal mucous (goblet) cell hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Animal Ref	Findings	
002103	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucous (goblet) cell hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Animal Ref	Findings	
002104	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration
Very slight focal respiratory epithelial basal-cell hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 5
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02NO7533

Dose Group : Low Dose THC Treatment: 1OOmg/m3THC Sex: Males

Animal Ref	Findings
OO2105	Killed Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Very slight multifocal respiratory epithelial basal-cell hyperplasia
Very slight multifocal mucous (goblet) cell hyperplasia
Very slight multifocal submucosal inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 6
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Low Dose THC Treatment: 100mg/m3THC Sex: Females

Animal Ref	Findings	
002201	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight focal mucous (goblet) cell hyperplasia
LARYNX :
Very slight focal submucosal mononuclear cell infiltration
LUNGS :
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002202	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucous (goblet) cell hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002203	Killed	Necropsied on Day: 21

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
NASAL and PARANASAL CAVITIES, LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

002204	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight focal olfactory epithelial mineralisation
LUNGS :
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 7
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Low Dose THC Treatment: 100mg/m3THC Sex: Females

Animal Ref	Findings
002205	Killed Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight multifocal respiratory epithelial basal-cell hyperplasia

LARYNX :
Very slight focal submucosal mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 8
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Medium Dose THC Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings	
003101	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight multifocal interstitial mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Animal Ref	Findings	
003102	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Very slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight focal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Animal Ref	Findings	
003103	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Very slight multifocal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNGS, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 9
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Medium Dose THC Treatment: 300mg/m3THC Sex: Males

Animal Ref	Findings	
003104	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia
Very slight focal respiratory epithelial basal-cell hyperplasia
Very slight focal submucosal mineralisation

LARYNX :
Very slight multifocal submucosal mononuclear cell infiltration

LUNGS :
Slight focal neuroendocrine cell hyperplasia
Very slight focal interstitial mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Animal Ref	Findings	
003105	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration
Very slight multifocal mucous (goblet) cell hyperplasia

LARYNX :
Very slight focal epithelial alteration : due to inspissation of plant fibres

TRACHEA :
Very slight focal mucous (goblet) cell hyperplasia : bifurcation

LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight focal alveolar inflammatory cell infiltration
Very slight focal alveolar haemorrhage

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 10
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Medium Dose THC Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings	
003201	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight focal respiratory epithelial basal-cell hyperplasia
Very slight focal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003202	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight focal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia
LARYNX :
Very slight focal submucosal mononuclear cell infiltration
LUNGS :
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003203	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Slight multifocal mucous (goblet) cell hyperplasia
Very slight focal submucosal inflammatory cell infiltration
LUNGS :
Very slight focal interstitial mononuclear cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 11
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : Medium Dose THC Treatment: 300mg/m3THC Sex: Females

Animal Ref	Findings	
003204	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003205	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight multifocal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia
LARYNX :
Very slight focal submucosal mononuclear cell infiltration
LUNGS :
Very slight multifocal alveolar histiocytosis

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

003206	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight multifocal interstitial inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 12
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : High Dose THC Treatment: 1000mg/m3THC Sex: Males

Animal Ref	Findings
004101	Killed Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia
Focal submucosal cyst(s)
Very slight multifocal olfactory epithelial atrophy
LARYNX :
Very slight multifocal submucosal mononuclear cell infiltration
Very slight focal mucous (goblet) cell hyperplasia
TRACHEA :
Very slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar inflammatory cell infiltration
Very slight multifocal alveolar histiocytosis
Slight multifocal interstitial inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

004102	Killed	Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Moderate multifocal mucous (goblet) cell hyperplasia
TRACHEA :
Very slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Slight multifocal alveolar inflammatory cell infiltration
Slight multifocal alveolar histiocytosis
Very slight multifocal bronchiolo-alveolar hyperplasia
Slight multifocal interstitial inflammatory cell infiltration
LUNG ASSOCIATED LYMPH NODES :
Slight lymphoid hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, PHARYNX (LARYNGO-)

Page: 13
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : High Dose THC Treatment: 1000mg/m3THC Sex: Males

Animal Ref	Findings
004103	Killed Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar inflammatory cell infiltration
Slight multifocal alveolar histiocytosis
Very slight multifocal interstitial inflammatory cell infiltration
Very slight focal bronchiolo-alveolar hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

004104 Killed Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Moderate focal submucosal inflammatory cell infiltration
Slight multifocal mucous (goblet) cell hyperplasia
LARYNX :
Very slight multifocal submucosal mononuclear cell infiltration
TRACHEA :
Very slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Very slight multifocal alveolar histiocytosis
Very slight multifocal interstitial mononuclear cell infiltration
Very slight multifocal alveolar inflammatory cell infiltration
Severe diffuse congestion
LUNG ASSOCIATED LYMPH NODES :
Slight lymphoid hyperplasia

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
PHARYNX (LARYNGO-)

Page: 14
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : High Dose THC Treatment: 1000mg/m3THC Sex: Males

Animal Ref	Findings
004105	Killed Necropsied on Day: 14

NASAL and PARANASAL CAVITIES :
Moderate multifocal mucous (goblet) cell hyperplasia
Very slight multifocal olfactory epithelial atrophy
Slight focal respiratory epithelial basal-cell hyperplasia
Very slight multifocal submucosal inflammatory cell infiltration

LUNGS :
Slight multifocal alveolar histiocytosis
Very slight multifocal alveolar inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

Page: 15
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : High Dose THC Treatment: 1000mg/m3THC Sex: Females

Animal Ref	Findings	
004201	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight multifocal olfactory epithelial basal-cell hyperplasia
Slight multifocal mucous (goblet) cell hyperplasia
LARYNX :
Slight focal submucosal mononuclear cell infiltration
LUNGS :
Slight multifocal alveolar histiocytosis
Slight multifocal alveolar inflammatory cell infiltration
Very slight multifocal bronchiolo-alveolar hyperplasia
Slight multifocal interstitial inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

004202	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Very slight multifocal olfactory epithelial atrophy
Moderate multifocal mucous (goblet) cell hyperplasia
TRACHEA :
Very slight multifocal mucous (goblet) cell hyperplasia
LUNGS :
Slight multifocal alveolar histiocytosis
Very slight multifocal alveolar inflammatory cell infiltration
Very slight multifocal bronchiolo-alveolar hyperplasia
Very slight focal interstitial fibrosis
Slight multifocal interstitial inflammatory cell infiltration

NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
LARYNX, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

004203	Killed	Necropsied on Day: 21

NASAL and PARANASAL CAVITIES :
Slight multifocal mucous (goblet) cell hyperplasia
TRACHEA :
Very slight multifocal mucous (goblet) cell hyperplasia

004203 Continued on the next page ....

Page: 16
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : High Dose THC Treatment: 1000mg/m3THC Sex: Females

Animal Ref	Findings
004203	Continued from previous page
	LUNGS :
	Slight multifocal alveolar histiocytosis
	Very slight multifocal alveolar inflammatory cell infiltration
	Very slight multifocal interstitial mononuclear cell infiltration
	Very slight multifocal bronchiolo-alveolar hyperplasia
	NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
	LARYNX, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)
004204	Killed Necropsied on Day: 21
	NASAL and PARANASAL CAVITIES :
	Moderate multifocal mucous (goblet) cell hyperplasia
	Very slight multifocal submucosal inflammatory cell infiltration
	LUNGS :
	Very slight multifocal alveolar inflammatory cell infiltration
	Very slight multifocal alveolar histiocytosis
	Very slight multifocal interstitial mononuclear cell infiltration
	NO MICROSCOPIC ABNORMALITIES DETECTED IN :-
	LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)
004205	Killed Necropsied on Day: 21
	NASAL and PARANASAL CAVITIES :
	Very slight multifocal olfactory epithelial atrophy
	Moderate multifocal mucous (goblet) cell hyperplasia
	Very slight multifocal submucosal inflammatory cell infiltration
	LUNGS :
	Slight multifocal alveolar inflammatory cell infiltration
	Slight multifocal alveolar histiocytosis
	Very slight multifocal bronchiolo-alveolar hyperplasia
	Slight multifocal interstitial inflammatory cell infiltration

004205 Continued on the next page ....

Page: 17
Date: 9-APR-2008 Time:09:16

FRAUNHOFER INSTITUTE OF
TOXICOLOGY AND EXPERIMENTAL MEDICINE
Individual Animal Listing

STUDY : 02N07533

Dose Group : High Dose THC Treatment: 1000mg/m3THC Sex: Females

Animal Ref	Findings
004205	Continued from previous page
	NO MICROSCOPIC ABNORMALITIES DETECTED IN :- LARYNX, TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)
004206	Killed Necropsied on Day: 21
	NASAL and PARANASAL CAVITIES : Slight multifocal mucous (goblet) cell hyperplasia Very slight multifocal olfactory epithelial atrophy Very slight focal olfactory epithelial mineralisation
	LARYNX : Very slight focal submucosal mononuclear cell infiltration
	LUNGS : Very slight multifocal alveolar inflammatory cell infiltration Slight multifocal alveolar histiocytosis Very slight multifocal interstitial mononuclear cell infiltration
	NO MICROSCOPIC ABNORMALITIES DETECTED IN :- TRACHEA, LUNG ASSOCIATED LYMPH NODES, PHARYNX (LARYNGO-)

*** Listing Complete ***

Appendix K

Blood Formation
Individual Data

Blood Formation

Study No: **02N07533**

Negative Control: **Clean Air**

Bone Marrow Preparation: **24 hours from beginning of last exposure**

Sex	Animal No.	PCE / 400 RBC	NCE / 400 RBC	PCE : NCE
Males	1101	116	284	0.41
	1102	134	266	0.50
	1103	133	267	0.50
	1104	135	265	0.51
	1105	148	252	0.59
	Mean ± SD	**133 ± 11.4**	**267 ± 11.4**	**0.50 ± 0.063**
Females	1201	134	266	0.50
	1202	134	266	0.50
	1203	141	259	0.54
	1204	138	262	0.53
	1205	163	237	0.69
	Mean ± SD	**142 ± 12.1**	**258 ± 12.1**	**0.55 ± 0.077**

PCE: Polychromatic Erythrocytes
NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation

Blood Formation

Study No: **02N07533**

Roofing Asphalt Fume Condensate: **300 mg/m³**

Bone Marrow Preparation: **24 hours from beginning of last exposure**

Sex	Animal No.	PCE / 400 RBC	NCE / 400 RBC	PCE : NCE
Females	3203	144	256	0.56
	3204	160	240	0.67
	3205	108	292	0.37
	3206	127	273	0,47
	Mean ± SD	**135 ± 22.4**	**265 ± 22.4**	**0.52 ± 0.128**

PCE: Polychromatic Erythrocytes
NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation

Blood Formation

Study No: **02N07533**

Roofing Asphalt Fume Condensate: **1000 mg/m³**

Bone Marrow Preparation: **24 hours after last exposure**

Sex	Animal No.	PCE / 400 RBC	NCE / 400 RBC	PCE : NCE
Males	4101	140	260	0.54
	4102	105	295	0.36
	4103	124	276	0.45
	4104	118	282	0.42
	4105	113	287	0.39
	Mean ± SD	**120 ± 13.2**	**280 ± 13.2**	**0.43 ± 0.069**
Females	4201	92	308	0.30
	4202	130	270	0.48
	4203	96	304	0.32
	4204	104	296	0.35
	4205	127	273	0.47
	4206[a]	273	127	2.15
	Mean ± SD	**110 ± 17.6****	**290 ± 17.6****	**0.38 ± 0.085****

PCE: Polychromatic Erythrocytes
NCE: Normochromatic Erythrocytes
RBC: Red Blood Cells
MN: Micronuclei
SD: Standard Deviation
**: $P < 0.01$
[a]: This additional animal was excluded from statistical analysis due to an abnormally high number of PCE.