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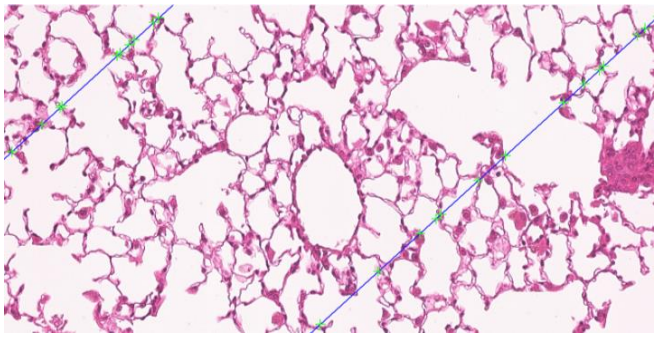
Histopathological and Morphometrical Assessment of Lung, Nose, and Liver of ApoE-Deficient Mice

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Report

16-Dec-2014

Consisting of 117 Pages



Determination of the Mean Chord Length

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Report Structure

The data for the entire project are reported in three parts:

- **in part I**, the data from the dissections performed 1, 2, and 3 months after the experimental start of the study are reported
- **in part II**, the data from the dissections performed 6 months after the experimental start of the study are reported
- **in part III**, the data from all dissection time points (1, 2, 3, 6, and 8 months after the start of exposure) are reported

Part I - II are **interim reports**, part III is the **final report**.

The individual animal data for the histopathological and morphometric al analysis are listed in the Appendix.

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STUDY ORGANISATION

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- study organisation and supervision

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- morphometrical analysis
- statistical analysis
- preparation of the histopathology report

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ABSTRACT

The present study was designed to investigate the influence on histopathological and morphometrical endpoints of switching from a standard cigarette (3R4F) to a test product (THS 2.2) after 2 months. In order to describe the temporal course of histomorphological effects, 4 interim dissection time points (DTs) formed part of the 8-month exposure design. Female ApoE-deficient mice were exposed to mainstream smoke (MSS) from the 3R4F (3R4F_CONT), to aerosol from the THS 2.2 (THS 2.2_CONT), or to fresh air (SHAM) for up to 8 months or to MSS from the 3R4F for 2 months followed by exposure to fresh air (Cessation) or to aerosol from the THS 2.2 (THS 2.2_Switch) for up to 6 months.

The degree of pulmonary emphysema, which is considered to be the key endpoint of the study, was investigated by measuring the morphometric endpoints mean chord length, destructive index, and bronchiolar attachments. In addition, a histopathological evaluation of pulmonary emphysema and other histomorphological alterations was performed on step serial lung sections. The nose was investigated histopathologically at 3 levels imaging the respiratory and olfactory epithelium at defined areas. The liver was investigated histopathologically on HE-stained slides as well as after especial staining for identification of fat and glycogen.

Typical adaptation effects in the nasal epithelium that were associated with 3R4F exposure were not seen after sustained exposure to THS 2.2. The effects of initial 3R4F exposure recovered completely upon cessation and THS 2.2-switch< time course of recovery was very similar.

A complex inflammatory response described by several histopathological endpoints was associated with 3R4F exposure in the lung. Generally, the severity of findings progressed with exposure duration. The amount of intra-alveolar inflammatory cells reversed after cessation. Depending on the cell type, a complete or partial recovery was seen. For the interstitial inflammatory response, a delayed recovery after initial progression can be concluded from the data after discontinuation of 3R4F exposure. In contrast to the significant inflammatory response associated with 3R4F exposure, continuous exposure to THS 2.2 did not result in significant inflammatory effects regardless of the exposure duration. The time course of accumulation and reversal of inflammatory cells in the lung parenchyma was reflected in a very similar way in the Cessation and THS 2.2_Switch groups; differences were numerically low and not statistically significant.

The extent of emphysema seen with sustained 3R4F exposure over 8 months progressed over time based on histopathological and morphometrical endpoints. No significant exposure effects were seen with sustained THS 2.2 exposure of up to 8 months for endpoints that measure the extent of emphysema. Differences between the THS 2.2_Switch and Cessation groups were numerically low and not statistically significant.

In the liver, minimal exposure effects were seen for the 3R4F (not statistically significant). A similar trend was seen for the THS 2.2 for the content of glycogen in hepatocytes, but not for the other endpoints. Differences between the THS 2.2_Switch and Cessation groups were numerically low and generally not statistically significant.

No significant exposure effects were demonstrated for the THS 2.2 and no new exposure effects were found compared to the 3R4F. The effects of switching from conventional cigarettes to the THS 2.2 were essentially the same as the effects of smoking cessation with respect to nose histopathology, lung inflammation, and pulmonary emphysema endpoints.

OBJECTIVE

The aim of the project was to assess exposure effects of aerosol from a test product (THS 2.2) with respect to lung inflammation, emphysema, and histopathological observations in the liver and to compare the influence of switching from a conventional cigarette (3R4F standard reference cigarette) to THS 2.2 with that of complete smoking cessation. The temporal course of exposure effects was tracked over 5 dissection time points, i.e., 1, 2, 3, 6, and 8 months after start of the experimental part of the study including 3 cessation/switching periods of 1, 4, and 6 months after an initial 2 months of exposure to mainstream smoke (MSS) from the 3R4F.

METHODS

STUDY DESIGN

In total 210 female ApoE-deficient mice were allocated to different exposure groups, i.e. a SHAM group, which was exposed to fresh air, a reference group, which was exposed to MSS from the 3R4F, and a test group, which was exposed to aerosol from the "THS 2.2".

The study design included 5 dissection time points, i.e. 1, 2, 3, 6, and 8 months after experimental start of the study. After an initial exposure period of 2 months to MSS from the 3R4F, one group was switched to fresh air (Cessation) and one to aerosol from the THS 2.2 (THS 2.2-Switch), (**Figure 1**). Each study group consisted of 10 animals.

Terminology of study groups:

SHAM:	animals exposed to fresh air
3R4F_CONT:	animals exposed to MSS from the 3R4F
THS 2.2_CONT:	animals exposed to the aerosol from the test item
Cessation:	switching from 3R4F exposure to fresh air exposure after two months (see **Figure 1**)
THS 2.2_Switch:	switching from 3R4F exposure to THS 2.2 exposure after two months (see **Figure 1**)
DT1, 2, 3, 6, and 8:	animals dissected 1, 2, 3, 6, and 8months after start of initial exposure

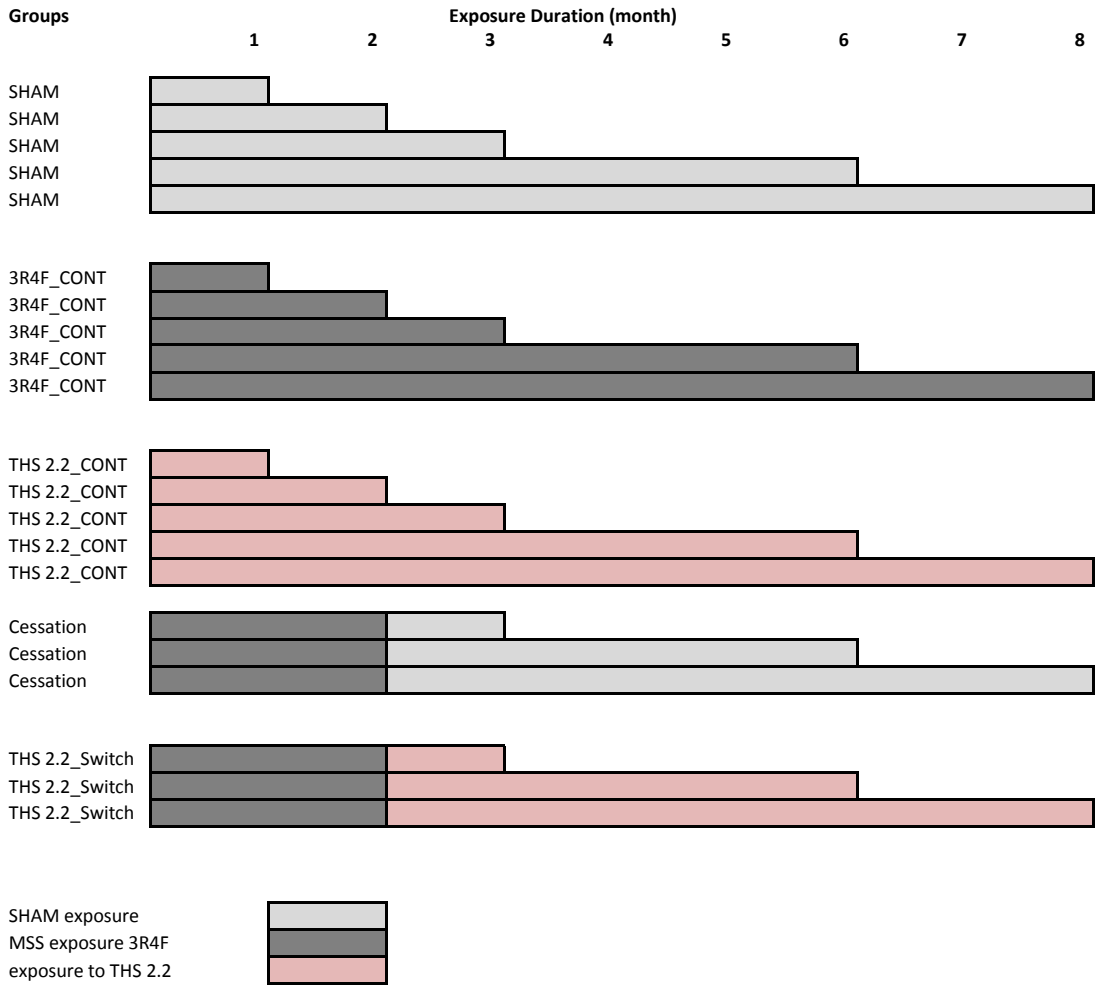


Figure 1 **Study design**

HISTOTECHNICAL PROCESSING

The histotechnical processing was performed by Philip Morris International Research Laboratories Pte Ltd, Singapore and digitalized histological slide images were sent to *Histovia* for morphometrical and histopathological evaluation. Organs, sectioning levels, and staining are specified in **Table 1**.

Table 1 Organs, sectioning levels, and staining for histopathological evaluation

organ	sectioning levels	staining
left lung	step serial sections (distance of 150 µm)	HE, PAS, ResFu
nose	level 1, level 2, level 4	HE, PAS (level 1 only)
liver	one representative level	HE, PAS, PAS-D, Oil Red (frozen tissue)

HE: Hematoxylin and Eosin
PAS: Alcian Blue Periodic Acid Schiff's reagent
ResFu: Resorcin Fuchsin
PAS-D: Alcian Blue Periodic Acid Schiff's reagent, digested

HISTOPATHOLOGICAL ASSESSMENT

Blinded measurement was applied throughout all evaluations using digital imaging. Upon completion of the evaluation, animal numbers were decoded and allocated to the study groups for statistical analysis (see **Statistics**).

The following semi-quantitative severity grading was applied for all histopathological endpoints:

- score 0: equal to the morphology of untreated animals
- score 1: minimal alteration
- score 2: minimal to moderate alteration
- score 3: moderate alteration
- score 4: moderate to severe alteration
- score 5: severe alteration

Nose:
Histopathological evaluation was performed for each endpoint individually at nose level 1 (respiratory epithelium and goblet cells in the nasal septum), nose level 2 (respiratory and olfactory epithelium), and nose level 4 (olfactory epithelium, olfactory bulb of the brain, molar teeth, pharyngeal duct).

Liver:
In addition to the evaluation of HE-stained slides, the content of fat within hepatocytes was estimated on slides stained with Oil Red (frozen tissue).The amount of glycogen within hepatocytes was estimated on slides stained with a combination of PAS and PAS-D (absence of PAS staining after enzymatic digestion of glycogen).

Strategy applied for step serial sectioning levels of the lung:
Five sections of the lung were selected for histopathological evaluation according to the following strategy:

Level 1: taken at approximately 450 µm to 600 µm in front of section 2
Level 2: taken at approximately 450 µm to 600 µm in front of section 3
Level 3: section that best represents the left main bronchus with branching secondary bronchi
Level 4: taken at approximately 450 µm to 600 µm behind section 3
Level 5: taken at approximately 450 µm to 600 µm behind section 4

With this approach, central and peripheral aspects of the lung parenchyma were covered for histopathological investigation.

Evaluation of goblet cells (main bronchus) and bronchus-associated lymphoid tissue (BALT) was performed at lung level 3, because the main bronchus was best represented on this slide. XXL-PAS-positive macrophages were also counted at level 3. XXL-macrophages are a subtype of pulmonary macrophages that are localised in the alveolar lumen. Morphologically, they appear to be significantly enlarged and stain positive after PAS incubation.

All other histopathological endpoints were evaluated separately for each lung section (5 independent data sets, see **Appendix**). For the statistical analysis based on study groups, the arithmetic mean value per animal was calculated from the 5 data sets (lung levels).

MORPHOMETRICAL ASSESSMENT OF THE LUNG

Blinded measurement was applied throughout all evaluations using digital imaging. Upon completion of the evaluation, animal numbers were decoded and allocated to the corresponding study groups for statistical analysis (see **Statistics**).

Lung morphometry was performed on digital images using the *Visiopharm* (Horlsholm, Denmark) stereology software, version 4.2.9.0 (Visiopharm Integrator System).

Morphometric evaluations of the endpoints mean chord length, bronchiolar attachments, and destructive index was performed at lung level 4.

Morphometric measurements of the mean chord length and destructive index were executed using approximately 30% of the total lung slide (randomly selected). For the bronchiolar attachments, 100 % of the slide was evaluated.

The mean chord length was determined using 3 randomised orientated lines with a guard zone of 100 µm per image.

The destructive index was determined using a grid structure of 4 x 5 measurement points per image.

The number of bronchiolar attachments was determined on 4 counting frames per image (equivalent to 30% of tissue section).

Lung volume measurement was performed according to the *Cavalieri method for lung volume estimation.* (published in: Gundersen H.J.G., Jensn E.B.V., Kieu K., and Nielsen J.: The efficiency of systematic sampling in stereology-reconsidered. J. Microsc. 193: 199-210, 1999.)

Individual animal data are shown in the **Appendix.**

STATISTICS

Statistical comparison of the study data was performed according to the following strategies:

1. comparison of SHAM, 3R4F_CONT, and THS 2.2_CONT groups at the same dissection time point in order to investigate a) exposure effects compared to SHAM, and b) differences between the 3R4F_CONT and THS 2.2_CONT groups (Tukey layout); (reported in: **Results**)
2. comparison of different dissection time points for SHAM, 3R4F_CONT, and THS 2.2_CONT groups, respectively, in order to investigate the progression of effects over time (Tukey layout); (reported in: **Statistical data, comparison between different dissection time points**)
3. comparison of SHAM, 3R4F_CONT, Cessation, and THS 2.2_Switch groups at the same dissection time point in order to investigate the influence of cessation/switching on MSS exposure effects in animals of the same age (Tukey layout); (reported in the chapter: Results)
4. comparison of 3R4F_CONT at DT2 with Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8 in order to investigate differences in groups that had been exposed to MSS of the 3R4F for two months only (reported in: **Results**)
5. comparison of Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8 in order to investigate differences between cessation and switching (reported in: **Results**)

For the histopathology lung data, the statistical analysis was based on the mean values per animal which were calculated from the data evaluated at 5 step serial lung sections. A minimum of 2 lung sections per animal were required to be valid in order for histopathological investigation to be performed; otherwise data for this animal were excluded from the final evaluation for that endpoint.

Depending on the data type, the following statistical tests were applied:

- continuous data (mean chord length, bronchiolar attachment, destructive index, number of XXL-macrophages, lung volume): ANOVA followed by Tukey post hoc test
- ordinal data (histopathological scores): non-parametric ANOVA on rank transformed data followed by Tukey post hoc test

All tests were conducted at the nominal level of significance of $\alpha = 0.05$, $\alpha = 0.01$, and $\alpha = 0.001$ (2-tailed). Results are considered to be statistically significant at $p \leq 0.05$.

For each exposure group, the mean values (mean), the standard error of the mean (SEM), the incidence (histopathological endpoints), and the results of the statistical analysis are reported.

Key end points of the study are illustrated graphically, showing mean values and SEM.

RESULTS

HISTOPATHOLOGY DATA, NOSE

For the following endpoints, statistically significant exposure effects were observed after continuous exposure to MSS from the 3R4F, or aerosol from the THS_2.2. Statistical comparisons between the different dissection time points for the SHAM, 3R4F, and THS 2.2 groups are shown in **Table 35**.

- reserve cell hyperplasia of the respiratory epithelium, nose level 1 **(Table 2, Figure 2)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - statistically significant exposure effect for the THS 2.2_CONT group at DT6 but not at the other dissection time points
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- squamous epithelial metaplasia of the respiratory epithelium, nose level 1 **(Table 3, Figure 3)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - finding not observed for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- reserve cell hyperplasia of the respiratory epithelium, nose level 2 **(Table 4)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT8
  - finding not observed for the THS 2.2_CONT group
  - finding not observed for the Cessation and THS 2.2_Switch groups

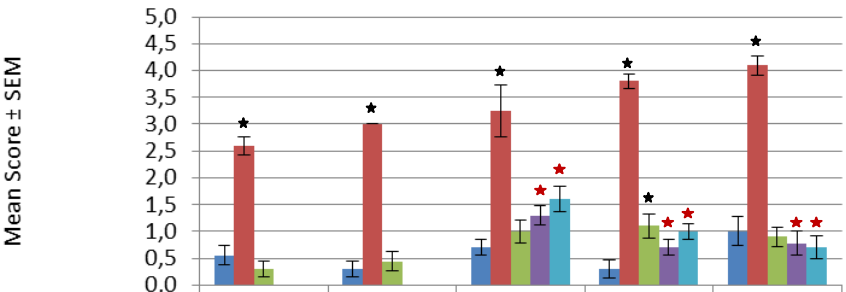
- atrophy of the olfactory epithelium, nose level 2 **(Table 10)** and 4 **(Table 11)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT8
  - finding not observed for the THS 2.2_CONT group
  - finding not observed for the Cessation and THS 2.2_Switch groups

For the endpoint degeneration/atrophy of the respiratory epithelium (nose level 1), the mean value was statistically significantly lower for the 3R4F_CONT group at DT6 compared to SHAM but not at the other dissection time points. The finding is considered to be a background finding in untreated animals from a qualitative perspective. The statistical significance is considered to be a chance finding in the context of the study **(Table 9)**.

Vacuolisation was seen in the respiratory epithelium of nose level 1 (**Table 5, Figure 4)** and nose level 2, (**Table 6, Figure 5**) and in the olfactory epithelium of nose level 2 **(Table 7)** and nose level 4 (**Table 8, Figure 6**). The finding was generally more prominent at the late dissection time points. Generally lower mean values were observed for the 3R4F_CONT group compared to the other study groups, especially in the respiratory epithelium of nose levels 1 and 2 (statistically significant for the 3R4F_CONT group at DT8, nose level 2). For the THS 2.2 groups, epithelial vacuolisation was not statistically significantly different from SHAM.

For the following endpoints, no statistically significant exposure effects were observed after continuous exposure to MSS from the 3R4F or aerosol from the THS_2.2. Descriptive statistics are shown in **Table 32**.

- degeneration/atrophy of the respiratory epithelium (nose level 2)
- vacuolisation of the respiratory epithelium (nose level 1)
- cornification of the respiratory epithelium (nose level 1)
- dilatation of blood vessels in the lamina propria of the respiratory epithelium (nose level 1 and 2)
- lymphocytic cells in the lamina propria of the respiratory epithelium (nose level 1)
- red blood cells, eosinophilic material, and necrotic cells in the lumen of the respiratory epithelium (nose level 1 and 2)
- reserve cell hyperplasia of the respiratory epithelium (nose level 2)
- hyperplasia of epithelial layers of the olfactory epithelium (nose level 2)
- red blood cells and eosinophilic material in the lumen of the olfactory epithelium (nose level 2 and 4)
- vacuolisation of the olfactory epithelium (nose level 2 and 4)
- vacuolisation of pharyngeal duct epithelium (nose level 4)
- fatty changes in the lamina propria of the olfactory epithelium (nose level 4)



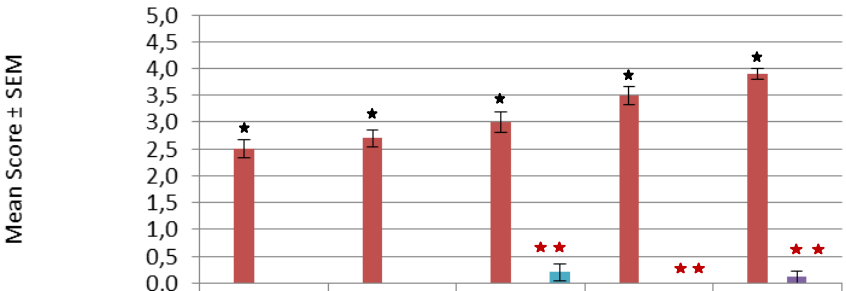
	DT1	DT2	DT3	DT6	DT8
SHAM	0,6	0,3	0,7	0,3	1,0
3R4F_CONT	2,6	3,0	3,3	3,8	4,1
THS 2.2_CONT	0,3	0,4	1,0	1,1	0,9
Cessation			1,3	0,7	0,8
THS 2.2_Switch			1,6	1,0	0,7

Figure 2 **Reserve cell hyperplasia of the respiratory epithelium, nose level 1**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



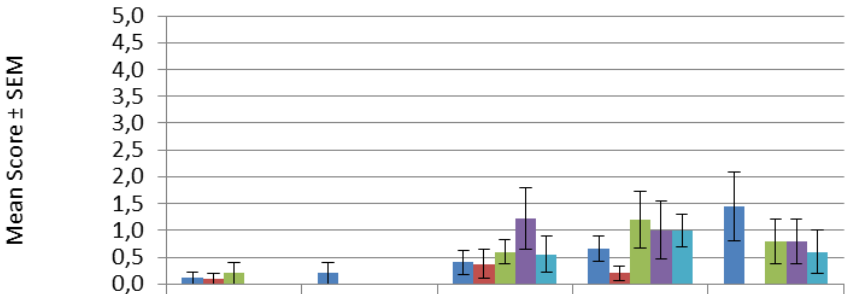
	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,0	0,0	0,0	0,0
3R4F_CONT	2,5	2,7	3,0	3,5	3,9
THS 2.2_CONT	0,0	0,0	0,0	0,0	0,0
Cessation			0,0	0,0	0,1
THS 2.2_Switch			0,2	0,0	0,0

Figure 3 **Squamous epithelial metaplasia of the respiratory epithelium, nose level 1**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



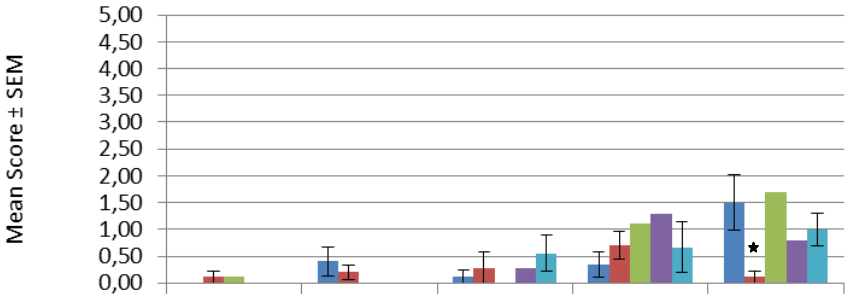
	DT1	DT2	DT3	DT6	DT8
SHAM	0,1	0,2	0,4	0,7	1,4
3R4F_CONT	0,1	0,0	0,4	0,2	0,0
ZRH_CONT	0,2	0,0	0,6	1,2	0,8
Cessation			1,2	1,0	0,8
ZRH_Switch			0,6	1,0	0,6

Figure 4 **Vacuolisation of the respiratory epithelium, nose level 1**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



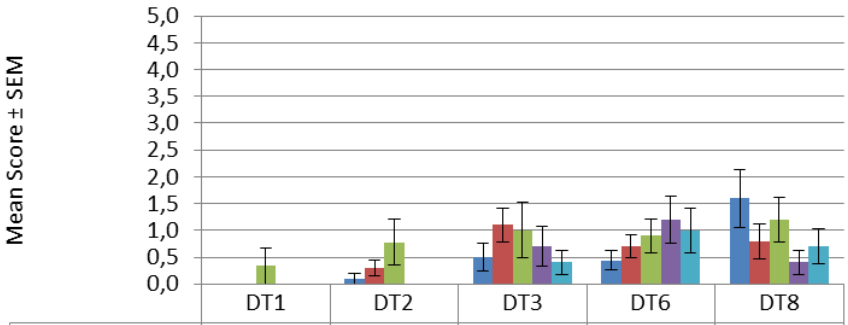
	DT1	DT2	DT3	DT6	DT8
SHAM	0,00	0,40	0,13	0,33	1,50
3R4F_CONT	0,11	0,20	0,29	0,70	0,11
ZRH_CONT	0,13	0,00	0,00	1,10	1,70
Cessation			0,29	1,30	0,80
ZRH_Switch			0,56	0,67	1,00

Figure 5 **Vacuolisation of the respiratory epithelium, nose level 2**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,1	0,5	0,4	1,6
3R4F_CONT	0,0	0,3	1,1	0,7	0,8
THS 2.2_CONT	0,3	0,8	1,0	0,9	1,2
Cessation			0,7	1,2	0,4
THS 2.2_Switch			0,4	1,0	0,7

Figure 6 **Vacuolisation of the olfactory epithelium, nose level 4**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups

Table 2 Histopathological evaluation, nose level 1, reserve cell hyperplasia of respiratory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.56 / 0.18 5/9	0.30 / 0.15 3/10	0.70 / 0.15 7/10	0.33 / 0.17 3/9	1.00 / 0.27 6/8
3R4F_CONT	Mean/SEM INC	2.60 / 0.16 10/10	3.00 / 0.00 10/10	3.25 / 0.49 7/8	3.80 / 0.13 10/10	4.10 / 0.18 10/10
THS 2.2_CONT	Mean/SEM INC	0.30 / 0.15 3/10	0.44 / 0.18 4/9	1.00 / 0.21 8/10	1.10 / 0.23 8/10	0.90 / 0.18 10/10
Cessation	Mean/SEM INC			1.33 / 0.17 9/9	0.70 / 0.15 7/10	0.78 / 0.22 6/9
THS 2.2_Switch	Mean/SEM INC			1.56 / 0.24 8/9	1.00 / 0.15 9/10	0.70 /0.21 6/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.424)	= (0.724)	= (0.638)	+ (0.014)	= (0.936)
Cessation			= (0.257)	= (0.439)	= (0.948)
THS 2.2_Switch			+ (0.047)	+ (0.034)	= (0.836)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+++ (≤0.001)	+++ (≤0.001)	++ (0.006)	+++ (≤0.001)	+++ (≤0.001)
Cessation			+ (0.033)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			= (0.182)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.311)	= (0.184)	= (0.794)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 3 Histopathological evaluation, nose level 1, squamous epithelial metaplasia of respiratory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.00 / 0.00 0/8
3R4F_CONT	Mean/SEM INC	2.50 / 0.17 10/10	2.70 / 0.15 10/10	3.00 / 0.19 8/8	3.50 / 0.17 10/10	3.90 / 0.10 10/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.11 / 0.11 1/9
THS 2.2_Switch	Mean/SEM INC			0.22 / 0.15 2/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (1.000)	= (1.000)	= (1.000)	= (1.000)	= (1.000)
Cessation			= (1.000)	= (1.000)	= (0.558)
THS 2.2_Switch			= (0.128)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.150)	= (1.000)	= (0.305)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 4 Histopathological evaluation, nose level 2, reserve cell hyperplasia of respiratory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/8	0.00 / 0.00 0/9	0.00 / 0.00 0/9
3R4F_CONT	Mean/SEM INC	0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.29 / 0.18 2/7	0.00 / 0.00 0/10	0.78 / 0.15 7/9
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/8	0.00 / 0.00 0/9	0.00 / 0.00 0/8	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.00 / 0.00 0/7	0.00 / 0.00 0/10	0.00 / 0.00 0/10
THS 2.2_Switch	Mean/SEM INC			0.00 / 0.00 0/9	0.00 / 0.00 0/9	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (1.000)	= (1.000)	= (0.123)	= (1.000)	+++ (≤0.001)
THS 2.2_CONT	= (1.000)	= (1.000)	= (1.000)	= (1.000)	= (1.000)
Cessation			= (1.000)	= (1.000)	= (1.000)
THS 2.2_Switch			= (1.000)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (1.000)	= (1.000)	= (0.123)	= (1.000)	+++ (≤0.001)
Cessation			= (1.000)	= (1.000)	+++ (≤0.001)
THS 2.2_Switch			= (1.000)	= (1.000)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	-	-	-
THS 2.2_Switch	-	-	-

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
-	-	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

Table 5 Histopathological evaluation, nose level 1, vacuolisation of the respiratory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.11 / 0.11 1/9	0.20 / 0.20 1/10	0.40 / 0.22 3/10	0.67 / 0.24 5/9	1.44 / 0.65 4/9
3R4F_CONT	Mean/SEM INC	0.10 / 0.10 1/10	0.00 / 0.00 0/10	0.38 / 0.26 2/8	0.20/ 0.13 2/10	0.00 / 0.00 0/10
THS 2.2_CONT	Mean/SEM INC	0.20 / 0.20 1/10	0.00 / 0.00 0/9	0.60 / 0.22 5/10	1.20 / 0.53 4/10	0.80 / 0.42 4/10
Cessation	Mean/SEM INC			1.22 / 0.57 4/9	1.00 / 0.54 3/10	0.80 / 0.42 3/10
THS 2.2_Switch	Mean/SEM INC			0.56 / 0.34 3/9	1.00 / 0.30 7/10	0.60 / 0.40 3/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.997)	= (0.463)	= (0.988)	= (0.343)	= (0.055)
THS 2.2_CONT	= (1.000)	= (0.481)	= (0.715)	= (1.000)	= (0.843)
Cessation			= (0.862)	= (0.994)	= (0.920)
THS 2.2_Switch			= (1.000)	= (0.965)	= (0.857)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.997)	= (1.000)	= (0.652)	= (0.334)	= (0.151)
Cessation			= (0.822)	= (0.872)	= (0.546)
THS 2.2_Switch			= (0.998)	= (0.260)	= (0.653)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.145)	= (0.374)	= (0.463)
THS 2.2_Switch	= (0.348)	++ (0.006)	= (0.394)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.467)	= (0.384)	= (0.893)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 6 Histopathological evaluation, nose level 2, vacuolisation of the respiratory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/10	0.40 / 0.27 2/10	0.13 / 0.13 1/8	0.33 / 0.24 2/9	1.50 / 0.52 8/10
3R4F_CONT	Mean/SEM INC	0.11 / 0.11 1/9	0.20 / 0.13 2/10	0.29 / 0.29 1/7	0.70/ 0.26 5/10	0.11 / 0.11 1/9
THS 2.2_CONT	Mean/SEM INC	0.13 / 0.13 1/8	0.00 / 0.00 0/9	0.00 / 0.00 0/8	1.10 / 0.46 5/10	1.70 / 0.42 8/10
Cessation	Mean/SEM INC			0.29 / 0.18 2/7	1.30 / 0.56 6/10	0.80 / 0.29 5/10
THS 2.2_Switch	Mean/SEM INC			0.56 / 0.34 3/9	0.67 / 0.47 2/9	1.00 / 0.30 7/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.650)	= (0.983)	= (0.980)	= (0.554)	++ (0.008)
THS 2.2_CONT	= (0.601)	= (0.395)	= (0.700)	= (0.373)	= (0.838)
Cessation			= (0.942)	= (0.521)	= (0.809)
THS 2.2_Switch			= (0.774)	= (0.999)	= (0.982)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.994)	= (0.491)	= (0.599)	= (0.943)	++ (0.002)
Cessation			= (0.982)	= (0.981)	= (0.330)
THS 2.2_Switch			= (0.887)	= (0.931)	= (0.123)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.990)	= (0.211)	= (0.370)
THS 2.2_Switch	= (0.888)	= (0.965)	= (0.110)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.757)	= (0.193)	= (0.643)

=: $p > 0.05$ (not statistically significant) +: $p \leq 0.05$ ++: $p \leq 0.01$ +++: $p \leq 0.001$ INC: incidence SEM: standard error of the mean

Table 7 Histopathological evaluation, nose level 2, vacuolisation of the olfactory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.40 / 0.40 1/10
3R4F_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.11 / 0.11 1/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.20 / 0.13 2/10	0.40 / 0.22 3/10	0.10 / 0.10 1/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.00 / 0.00 0/9	0.20 / 0.20 1/10	0.00 / 0.00 0/10
THS 2.2_Switch	Mean/SEM INC			0.10 / 0.10 1/10	0.00 / 0.00 0/9	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (1.000)	= (1.000)	= (0.772)	= (1.000)	= (0.449)
THS 2.2_CONT	= (1.000)	= (0.177)	= (0.132)	= (0.481)	= (0.449)
Cessation			= (0.942)	= (0.813)	= (0.517)
THS 2.2_Switch			= (0.774)	= (1.000)	= (0.517)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (1.000)	= (0.177)	= (0.430)	= (0.463)	= (1.000)
Cessation			= (0.982)	= (0.798)	= (1.000)
THS 2.2_Switch			= (0.887)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (1.000)	= (0.511)	= (1.000)
THS 2.2_Switch	= (0.511)	= (1.000)	= (1.000)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.357)	= (0.357)	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

Table 8 Histopathological evaluation, nose level 4, vacuolisation of the olfactory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/10	0.10 / 0.10 1/10	0.50/ 0.27 3/10	0.44 / 0.18 4/9	1.60 / 0.54 7/10
3R4F_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.30 / 0.15 3/10	1.10 / 0.31 7/10	0.70 / 0.21 6/10	0.80 / 0.33 5/10
THS 2.2_CONT	Mean/SEM INC	0.33 / 0.33 1/9	0.78 / 0.43 4/9	1.00 / 0.52 4/10	0.90 / 0.31 6/10	1.20 / 0.42 6/10
Cessation	Mean/SEM INC			0.67 / 0.37 3/9	1.20 / 0.44 6/10	0.40 / 0.22 3/10
THS 2.2_Switch	Mean/SEM INC			0.40 / 0.22 3/10	1.00 / 0.42 5/10	0.70 / 0.33 4/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (1.000)	= (0.604)	= (0.301)	= (0.724)	= (0.520)
THS 2.2_CONT	= (0.404)	= (0.202)	= (0.850)	= (0.571)	= (0.902)
Cessation			= (1.000)	= (0.754)	= (0.282)
THS 2.2_Switch			= (1.000)	= (0.924)	= (0.606)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.404)	= (0.691)	= (0.605)	= (0.964)	= (0.783)
Cessation			= (0.676)	= (0.984)	= (0.906)
THS 2.2_Switch			= (0.427)	= (1.000)	= (0.998)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.963)	= (0.348)	= (0.999)
THS 2.2_Switch	= (0.999)	= (0.602)	= (0.892)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.739)	= (0.729)	= (0.576)

=: $p > 0.05$ (not statistically significant) +: $p \leq 0.05$ ++: $p \leq 0.01$ +++: $p \leq 0.001$ INC: incidence SEM: standard error of the mean

Table 9 Histopathological evaluation, nose level 1, degeneration/atrophy of the respiratory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.56 / 0.24 4/9	0.60 / 0.27 4/10	0.80/ 0.25 6/10	0.67 / 0.24 5/9	0.13 / 0.13 1/8
3R4F_CONT	Mean/SEM INC	0.30 / 0.15 3/10	0.20 / 0.13 2/10	0.13 / 0.13 1/8	0.00 / 0.00 0/10	0.30 / 0.30 1/10
THS 2.2_CONT	Mean/SEM INC	0.70 / 0.26 5/10	0.56 / 0.29 3/9	0.70 / 0.26 5/10	0.40 / 0.16 4/10	0.40 / 0.16 4/10
Cessation	Mean/SEM INC			0.44 / 0.18 4/9	0.20 / 0.13 2/10	0.90 / 0.43 4/10
THS 2.2_Switch	Mean/SEM INC			0.22 / 0.15 2/9	0.20 / 0.13 2/10	0.30 / 0.21 2/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0,747)	= (0.534)	= (0.111)	+ (0.018)	= (1.000)
THS 2.2_CONT	= (0.931)	= (0.972)	= (0.850)	= (0.921)	= (0.382)
Cessation			= (0.861)	= (0.305)	= (0.547)
THS 2.2_Switch			= (0.339)	= (0.306)	= (0.993)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.508)	= (0.691)	= (0.214)	= (0.123)	= (0.334)
Cessation			= (0.733)	= (0.835)	= (0.510)
THS 2.2_Switch			= (0.996)	= (0.835)	= (0.994)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.731)	= (1.000)	= (0.567)
THS 2.2_Switch	= (1.000)	= (1.000)	= (1.000)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.346)	= (1.000)	= (0.295)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 10 Histopathological evaluation, nose level 2, atrophy of the olfactory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.00 / 0.00 0/10
3R4F_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.20 / 0.20 1/10	1.10 / 0.18 9/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
THS 2.2_Switch	Mean/SEM INC			0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (1.000)	= (1.000)	= (1.000)	= (0.481)	+++ (≤0.001)
THS 2.2_CONT	= (1.000)	= (1.000)	= (1.000)	= (1.000)	= (1.000)
Cessation			= (1.000)	= (1.000)	= (1.000)
THS 2.2_Switch			= (1.000)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (1.000)	= (1.000)	= (1.000)	= (0.463)	+++ (≤0.001)
Cessation			= (1.000)	= (0.539)	+++ (≤0.001)
THS 2.2_Switch			= (1.000)	= (0.565)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	-	-	-
THS 2.2_Switch	-	-	-

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
-	-	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

Table 11 Histopathological evaluation, nose level 4, atrophy of the olfactory epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/9	0.00 / 0.00 0/10
3R4F_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.30 / 0.21 2/10	0.10 / 0.10 1/10	0.60 / 0.16 6/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/9	0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.00 / 0.00 0/9	0.00 / 0.00 0/10	0.00 / 0.00 0/10
THS 2.2_Switch	Mean/SEM INC			0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (1.000)	= (1.000)	= (0.177)	= (0.481)	+++ (≤0.001)
THS 2.2_CONT	= (1.000)	= (1.000)	= (1.000)	= (1.000)	= (1.000)
Cessation			= (1.000)	= (1.000)	= (1.000)
THS 2.2_Switch			= (1.000)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (1.000)	= (1.000)	= (0.177)	= (0.463)	+++ (≤0.001)
Cessation			= (0.170)	= (0.528)	+++ (≤0.001)
THS 2.2_Switch			= (0.150)	= (0.528)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	-	-	-
THS 2.2_Switch	-	-	-

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
-	-	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

HISTOPATHOLOGY DATA, LUNG

For the following endpoints, statistically significant exposure effects were observed after continuous exposure to MSS from the 3R4F or aerosol from the THS_2.2. Statistical comparisons between the different dissection time points for the SHAM, 3R4F, and THS 2.2 groups are shown in **Table 36.**

- neutrophilic granulocytes in the alveolar lumen **(Table 12, Figure 7)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- lymphocytes/plasma cells in the alveolar lumen **(Table 13, Figure 8)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- XXL-PAS-positive macrophages in the alveolar lumen **(Table 14, Figure 9)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - finding not observed for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

- unpigmented macrophages in the alveolar lumen **(Table 15, Figure 10)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - statistically significantly lower mean value for the THS 2.2_Switch group compared to the Cessation group at DT 8 but not at DT3 and DT6
- yellow pigmented macrophages in the alveolar lumen **(Table 16, Figure 11)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - finding not observed for the THS 2.2_CONT group
  - no statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3 (stable)
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- pigmented macrophage nests in the alveolar lumen **(Table 17, Figure 12)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT2 and DT8)
  - finding not observed for the THS 2.2_CONT group
  - no statistically significant differences after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (stable)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

- lymphocytic cells in the alveolar interstitium **(Table 18, Figure 13)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT3, DT6, and DT8 (increase in mean values between DT2 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - higher mean values (statistically significant for the cessation group) after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3 (initial progression)
  - no statistically significant differences after cessation/switching (compared to 3R4F_CONT group, DT2) at DT6, and DT8 (stable)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- lymphocytic cells in the peri-vascular area **(Table 19, Figure 14)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - higher mean values (not statistically significant[a]) after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (progression)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

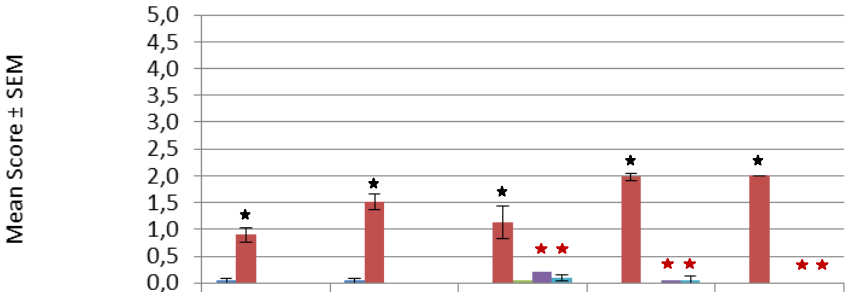
[a] missing statistical significance based on high variation of individual data within groups

- alveolar emphysema **(Table 20, Figure 15)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (stepwise increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - no statistically significant differences after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (stable)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- hypertrophy/hyperplasia of the alveolar epithelium **(Table 21, Figure 16)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- reserve cell hyperplasia of the bronchial epithelium **(Table 22, Figure 17)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT6, and DT8, but not at DT3
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly lower mean values after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

Goblet cell hyperplasia of the main bronchus (**Table 23**) was statistically significantly lower for the THS 2.2_CONT group at DT2 compared to SHAM (no statistically significant differences were seen at DT1, DT3, DT6 and DT8). For the 3R4F_CONT groups, no statistical significance compared to SHAM was observed. Based on missing time-dependency and on the low difference in mean severity scores, the statistical significance at DT2 is considered to be a chance finding**.**

For the following endpoints, no statistically significant exposure effects were observed after continuous exposure to MSS from the 3R4F or aerosol from the THS_2.2. Descriptive statistics are shown in **Table 33**.

- transudate/exudate in the alveolar lumen
- brownish deposits in the alveolar lumen
- thickened and cell-rich alveolar interstitium



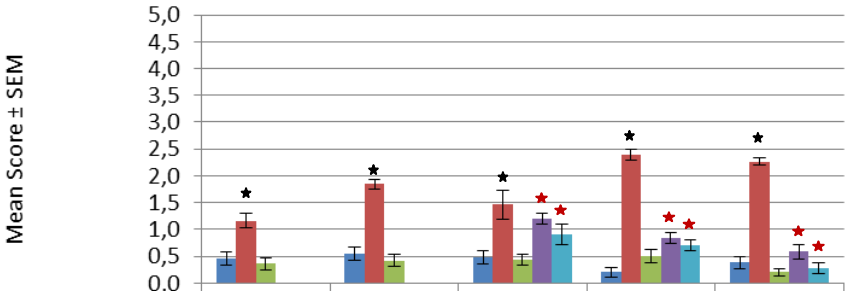
	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,0	0,0	0,0	0,0
3R4F_CONT	0,9	1,5	1,1	2,0	2,0
THS 2.2_CONT	0,0	0,0	0,0	0,0	0,0
Cessation			0,2	0,1	0,0
THS 2.2_Switch			0,1	0,1	0,0

Figure 7 **Neutrophilic granulocytes in the alveolar lumen**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



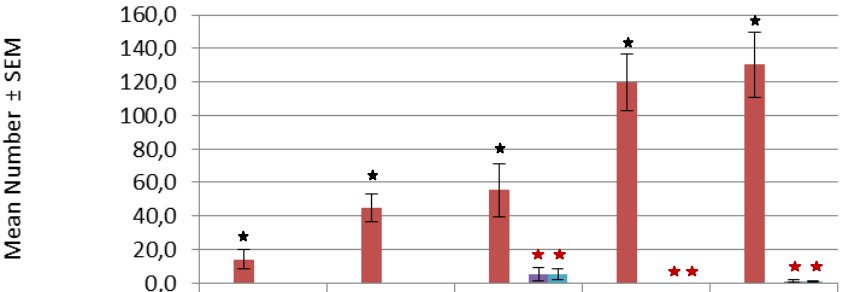
	DT1	DT2	DT3	DT6	DT8
SHAM	0,5	0,5	0,5	0,2	0,4
3R4F_CONT	1,2	1,8	1,5	2,4	2,3
THS 2.2_CONT	0,4	0,4	0,4	0,5	0,2
Cessation			1,2	0,8	0,6
THS 2.2_Switch			0,9	0,7	0,3

Figure 8 **Lymphocytes plasma-cells in the alveolar lumen**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



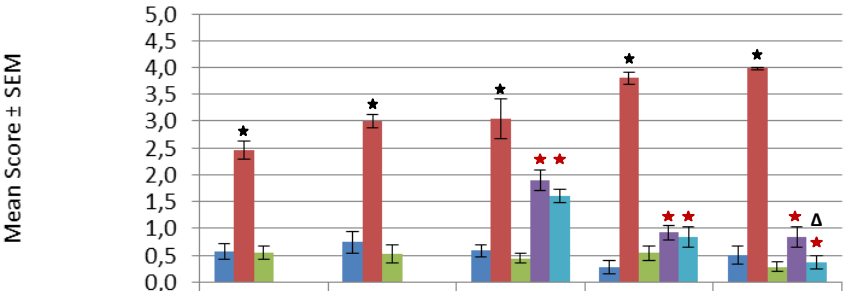
	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,0	0,0	0,0	0,0
3R4F_CONT	14,1	44,9	55,3	119,7	130,2
THS 2.2._CONT	0,0	0,0	0,0	0,0	0,0
Cessation			5,2	0	1,1
THS 2.2_Switch			5,2	0	0,9

Figure 9 **XXL-PAS-positive macrophages in the alveolar lumen**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



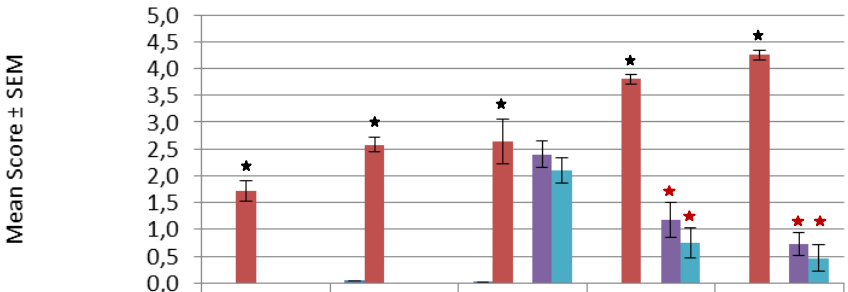
	DT1	DT2	DT3	DT6	DT8
SHAM	0,6	0,7	0,6	0,3	0,5
3R4F_CONT	2,5	3,0	3,0	3,8	4,0
THS 2.2_CONT	0,5	0,5	0,4	0,5	0,3
Cessation			1,9	0,9	0,8
THS 2.2_Switch			1,6	0,8	0,4

Figure 10 **Unpigmented macrophages in the alveolar lumen**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



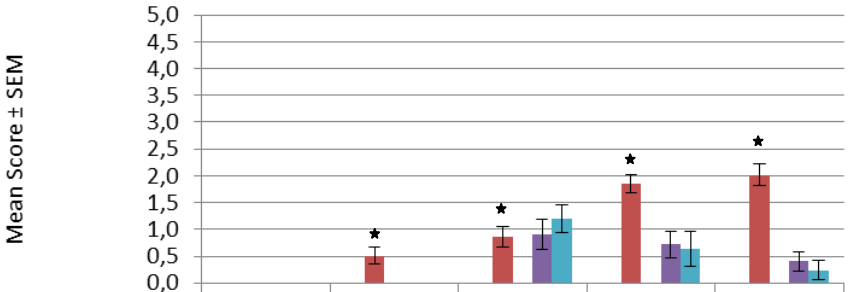
	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,0	0,0	0,0	0,0
3R4F_CONT	1,7	2,6	2,6	3,8	4,3
THS 2.2_CONT	0,0	0,0	0,0	0,0	0,0
Cessation			2,4	1,2	0,7
THS 2.2_Switch			2,1	0,7	0,5

Figure 11 Yellow pigmented macrophages in the alveolar lumen

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



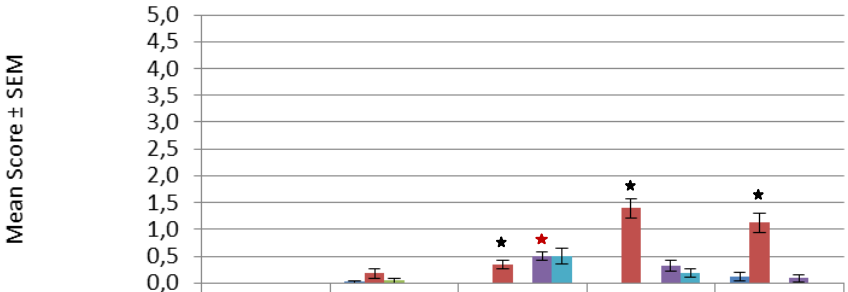
	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,0	0,0	0,0	0,0
3R4F_CONT	0,0	0,5	0,9	1,9	2,0
THS 2.2_CONT	0,0	0,0	0,0	0,0	0,0
Cessation			0,9	0,7	0,4
THS 2.2_Switch			1,2	0,6	0,2

Figure 12 Pigmented macrophage nests in the alveolar lumen

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



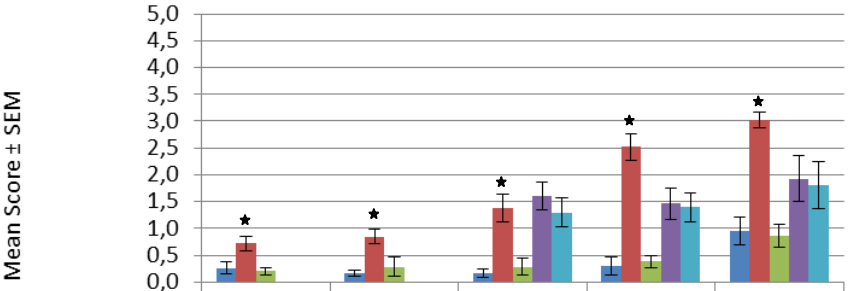
	DT1	DT2	DT3	DT6	DT8
SHAM	0,0	0,0	0,0	0,0	0,1
3R4F_CONT	0,0	0,2	0,3	1,4	1,1
THS 2.2_CONT	0,0	0,0	0,0	0,0	0,0
Cessation			0,5	0,3	0,1
THS 2.2_Switch			0,5	0,2	0,0

Figure 13 Lymphocytic cells in the alveolar interstitium

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



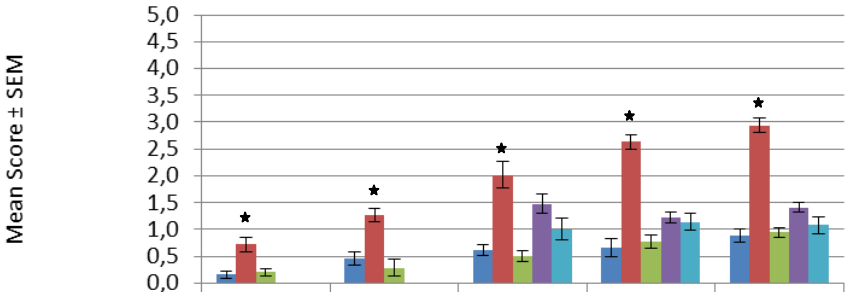
	DT1	DT2	DT3	DT6	DT8
SHAM	0,3	0,2	0,2	0,3	1,0
3R4F_CONT	0,7	0,8	1,4	2,5	3,0
THS 2.2_CONT	0,2	0,3	0,3	0,4	0,9
Cessation			1,6	1,5	1,9
THS 2.2_Switch			1,3	1,4	1,8

Figure 14 Lymphocytic cells in the peri-vascular area

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



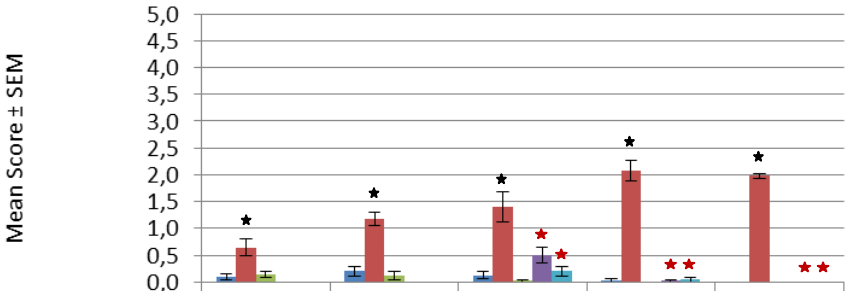
	DT1	DT2	DT3	DT6	DT8
SHAM	0,2	0,5	0,6	0,7	0,9
3R4F_CONT	0,7	1,3	2,0	2,6	2,9
THS 2.2_CONT	0,2	0,3	0,5	0,8	0,9
Cessation			1,5	1,2	1,4
THS 2.2_Switch			1,0	1,1	1,1

Figure 15 Alveolar emphysema

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



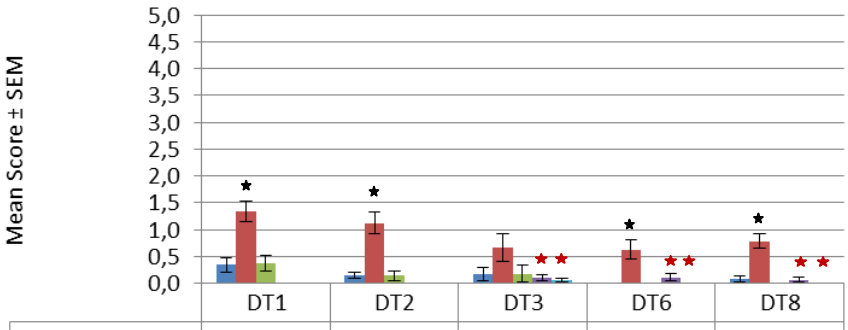
	DT1	DT2	DT3	DT6	DT8
SHAM	0,1	0,2	0,1	0,03	0,0
3R4F_CONT	0,6	1,2	1,4	2,1	2,0
THS 2.2_CONT	0,1	0,1	0,0	0,00	0,0
Cessation			0,5	0,02	0,0
THS 2.2_Switch			0,2	0,04	0,0

Figure 16 Hyperplasia of alveolar epithelium

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



	DT1	DT2	DT3	DT6	DT8
SHAM	0,3	0,1	0,2	0,0	0,1
3R4F_CONT	1,3	1,1	0,7	0,6	0,8
THS 2.2_CONT	0,4	0,1	0,2	0,0	0,0
Cessation			0,1	0,1	0,1
THS 2.2_Switch			0,1	0,0	0,0

Figure 17 Reserve cell hyperplasia of bronchial epithelium

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups

Table 12 Histopathological evaluation, neutrophilic granulocytes in the alveolar lumen (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.04 / 0.04 1/10	0.04 / 0.04 1/10	0.00 / 0.00 0/10	0.00 / 0.00 0/8	0.00 / 0.00 0/10
3R4F_CONT	Mean/SEM INC	0.90 / 0.13 9/10	1.51 / 0.15 9/9	1.14 / 0.30 7/10	1.98 / 0.07 10/10	2.00 / 0.00 10/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.04 / 0.04 1/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.24 / 0.17 2/10	0.06 / 0.06 1/10	0.00 / 0.00 0/9
THS 2.2_Switch	Mean/SEM INC			0.10 / 0.05 3/10	0.06 / 0.06 1/10	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.792)	= (0.620)	= (0.841)	= (1.000)	= (1.000)
Cessation			= (0.760)	= (0.864)	= (1.000)
THS 2.2_Switch			= (0.565)	= (0.864)	= (1.000)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			+ (0.015)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			+ (0.035)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.849)	= (1.000)	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

Table 13 Histopathological evaluation, lymphocytes/plasma cells in the alveolar lumen (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.46 / 0.13 7/10	0.54 / 0.13 8/10	0.48 / 0.12 8/10	0.20 / 0.09 4/8	0.38 / 0.12 7/10
3R4F_CONT	Mean/SEM INC	1.16 / 0.14 10/10	1.84 / 0.09 9/9	1.46 / 0.27 9/10	2.39 / 0.10 10/10	2.26 / 0.07 10/10
THS 2.2_CONT	Mean/SEM INC	0.36 / 0.11 7/10	0.42 / 0.11 7/10	0.44 / 0.10 8/10	0.50 / 0.12 8/10	0.20 / 0.06 7/10
Cessation	Mean/SEM INC			1.18 / 0.11 10/10	0.84 / 0.10 10/10	0.58 / 0.13 8/9
THS 2.2_Switch	Mean/SEM INC			0.86 / 0.19 10/10	0.70 / 0.10 9/10	0.28 / 0.10 7/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	++ (0.002)	+++ (≤0.001)	+ (0.022)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.816)	= (0.737)	= (0.988)	= (0.109)	= (0.399)
Cessation			+ (0.012)	+++ (≤0.001)	= (0.735)
THS 2.2_Switch			= (0.415)	++ (0.009)	= (0.926)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+++ (≤0.001)	+++ (≤0.001)	+ (0.016)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.999)	+++ (≤0.001)	++ (0.002)
THS 2.2_Switch			= (0.352)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	++ (0.005)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	++ (0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.163)	= (0.498)	= (0.094)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 14 Histopathological evaluation, number of XXL-PAS-positive macrophages in the alveolar lumen (Mean / SEM / N)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM N	0.0 / 0.00 10	0.0 / 0.00 10	0.0 / 0.00 10	0.0 / 0.00 8	0.0 / 0.00 10
3R4F_CONT	Mean/SEM N	14.1 / 5.61 10	44.9 / 8.44 9	55.3 / 15.95 10	119.7 / 17.06 9	130.2 / 19.48 9
THS 2.2_CONT	Mean/SEM N	0.0 / 0.00 10	0.0 / 0.00 10	0.0 / 0.00 10	0.0 / 0.00 10	0.0 / 0.00 10
Cessation	Mean/SEM N			5.2 / 4.14 10	0.0 / 0.00 10	1.1 / 0.59 9
THS 2.2_Switch	Mean/SEM N			5.2 / 3.47 10	0.0 / 0.00 10	0.9 / 0.60 10

Statistical comparison to SHAM group

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+ (0.013)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (1.000)	= (1.000)	= (1.000)	= (1.000)	= (1.000)
Cessation			= (0.988)	= (1.000)	= (1.000)
THS 2.2_Switch			= (0.988)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+ (0.013)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.988)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			= (0.988)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (1.000)	-	= (0.806)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

Table 15 Histopathological evaluation, unpigmented macrophages in the alveolar lumen (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.56 / 0.15 8/10	0.74 / 0.20 8/10	0.58 / 0.12 9/10	0.28 / 0.13 5/8	0.50 / 0.16 7/10
3R4F_CONT	Mean/SEM INC	2.46 / 0.16 10/10	3.00 / 0.13 9/9	3.04 / 0.37 10/10	3.80 / 0.11 10/10	3.98 / 0.02 10/10
THS 2.2_CONT	Mean/SEM INC	0.54 / 0.12 8/10	0.52 / 0.16 8/10	0.44 / 0.09 8/10	0.54 / 0.14 8/10	0.28 / 0.09 7/10
Cessation	Mean/SEM INC			1.92 / 0.19 10/10	0.92 / 0.14 10/10	0.84 / 0.20 8/9
THS 2.2_Switch	Mean/SEM INC			1.58 / 0.13 10/10	0.84 / 0.20 9/10	0.36 / 0.12 7/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.996)	= (0.412)	= (0.310)	= (0.265)	= (0.542)
Cessation			+++ (≤0.001)	++ (0.007)	= (0.481)
THS 2.2_Switch			+++ (≤0.001)	= (0.052)	= (0.952)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.161)	+++ (≤0.001)	++ (0.003)
THS 2.2_Switch			++ (0.009)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+ (≤0.011)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.259)	= (0.527)	+ (0.049)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 16 Histopathological evaluation, yellow pigmented macrophages in the alveolar lumen (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00/ 0.00 0/10	0.04 / 0.03 2/10	0.02 / 0.02 1/10	0.00 / 0.00 0/8	0.00 / 0.00 0/10
3R4F_CONT	Mean/SEM INC	1.72 / 0.20 9/10	2.58 / 0.14 9/9	2.64 / 0.42 10/10	3.80 / 0.09 10/10	4.26 / 0.09 10/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			2.38 / 0.25 10/10	1.18 / 0.32 9/10	0.73 / 0.21 7/9
THS 2.2_Switch	Mean/SEM INC			2.06 / 0.23 10/10	0.74 / 0.28 6/10	0.46 / 025 5/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (1.000)	= (0.286)	= (0.645)	= (1.000)	= (1.000)
Cessation			+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			+++ (≤0.001)	++ (0.002)	+ (0.012)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.882)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			= (0.341)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.864)	++ (0.001)	+++ (≤0.001)
THS 2.2_Switch	= (0.427)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.439)	= (0.245)	= (0.217)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 17 Histopathological evaluation, pigmented macrophage nests in the alveolar lumen (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00/ 0.00 0/10	0.00/ 0.00 0/10	0.00/ 0.00 0/10	0.00/ 0.00 0/8	0.00/ 0.00 0/10
THS 2.2_CONT	Mean/SEM INC	0.00/ 0.00 0/10	0.51 / 0.16 7/9	0.86 / 0.18 9/10	1.85 / 0.17 10/10	2.02 / 0.20 10/10
ZRH_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.92 / 0.28 9/10	0.72 / 0.25 7/10	0.40 / 0.18 4/9
THS 2.2_Switch	Mean/SEM INC			1.16 / 0.25 10/10	0.64 / 0.32 4/10	0.24 / 0.18 3/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	-	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	-	= (1.000)	= (1.000)	= (1.000)	= (1.000)
Cessation			+++ (≤0.001)	++ (0.007)	+ (0.038)
THS 2.2_Switch			+++ (≤0.001)	= (0.103)	= (0.280)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	-	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (1.000)	+ (0.011)	+++ (≤0.001)
THS 2.2_Switch			= (0.621)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.772)	= (0.988)	= (0.892)
THS 2.2_Switch	= (0.329)	= (0.912)	= (0.346)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.438)	= (0.467)	= (0.466)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 18 Histopathological evaluation, lymphocytic cells in the alveolar interstitium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.00/ 0.00 0/10	0.02/ 0.02 1/10	0.00/ 0.00 0/10	0.00/ 0.00 0/8	0.12 / 0.07 3/10
3R4F_CONT	Mean/SEM INC	0.00/ 0.00 0/10	0.18 / 0.10 3/9	0.34 / 0.08 7/10	1.40 / 0.18 10/10	1.12 / 0.17 9/10
THS 2.2_CONT	Mean/SEM INC	0.00 / 0.00 0/10	0.04 / 0.03 2/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.50 / 0.08 10/10	0.32 / 0.11 6/10	0.09 / 0.07 2/9
THS 2.2_Switch	Mean/SEM INC			0.46 / 0.15 8/10	0.18 / 0.08 5/10	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	-	= (0.325)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	-	= (0.879)	= (1.000)	= (1.000)	= (0.269)
Cessation			+++ (≤0.001)	++ (0.005)	= (0.989)
THS 2.2_Switch			+++ (≤0.001)	= (0.068)	= (0.330)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	-	= (0.589)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.393)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			= (0.982)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+ (0.030)	= (0.632)	= (0.898)
THS 2.2_Switch	= (0.132)	= (0.974)	= (0.294)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.433)	= (0.437)	= (0.129)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 19 Histopathological evaluation, lymphocytic cells in the peri-vascular area (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.26/ 0.11 5/10	0.16/ 0.05 6/10	0.16/ 0.08 4/10	0.30 / 0.17 4/8	0.96 / 0.26 9/10
3R4F_CONT	Mean/SEM INC	0.72/ 0.13 9/10	0.84 / 0.14 8/9	1.38 / 0.25 10/10	2.52 / 0.25 10/10	3.02 / 0.15 10/10
THS 2.2_CONT	Mean/SEM INC	0.20 / 0.07 6/10	0.28 / 0.18 4/10	0.28 / 0.16 4/10	0.38 / 0.11 7/10	0.86 / 0.22 9/10
Cessation	Mean/SEM INC			1.60 / 0.26 10/10	1.46 / 0.30 10/10	1.93 / 0.42 9/9
THS 2.2_Switch	Mean/SEM INC			1.32 / 0.27 10/10	1.40 / 0.27 9/10	1.80 / 0.44 9/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+ (0.023)	++ (0.007)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.964)	= (0.990)	= (0.907)	= (0.566)	= (0.951)
Cessation			+++ (≤0.001)	++ (0.003)	= (0.164)
THS 2.2_Switch			+++ (≤0.001)	++ (0.007)	= (0.363)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+ (0.012)	++ (0.005)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.971)	= (0.096)	= (0.125)
THS 2.2_Switch			= (1.000)	+ (0.044)	+ (0.032)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.236)	= (0.529)	= (0.149)
THS 2.2_Switch	= (0.762)	= (0.495)	= (0.349)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.583)	= (0.913)	= (0.753)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 20 Histopathological evaluation, alveolar emphysema (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.16 / 0.07 5/10	0.46/ 0.12 7/10	0.62/ 0.10 10/10	0.65 / 0.17 7/8	0.88 / 0.13 9/10
3R4F_CONT	Mean/SEM INC	0.72 / 0.13 9/10	1.27 / 0.13 9/9	2.02 / 0.25 10/10	2.63 / 0.13 10/10	2.94 / 0.14 10/10
THS 2.2_CONT	Mean/SEM INC	0.20 / 0.06 7/10	0.28 / 0.16 4/10	0.50 / 0.11 9/10	0.77 / 0.13 10/10	0.94 / 0.09 10/10
Cessation	Mean/SEM INC			1.48 / 0.17 10/10	1.22 / 0.11 10/10	1.41 / 0.09 9/9
THS 2.2_Switch	Mean/SEM INC			1.00 / 0.20 9/10	1.14 / 0.15 10/10	1.08 / 0.16 10/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	++ (0.003)	++ (0.002)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
ZRH_CONT	= (0.835)	= (0.435)	= (0.732)	= (0.787)	= (0.950)
Cessation			++ (0.004)	+ (0.031)	+ (0.025)
THS 2.2_Switch			= (0.400)	= (0.099)	= (0.930)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+ (0.011)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.776)	+++ (≤0.001)	++ (0.009)
THS 2.2_Switch			+ (0.021)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.715)	= (1.000)	= (0.746)
THS 2.2_Switch	= (0.738)	= (0.964)	= (0.820)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.095)	= (0.741)	= (0.168)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 21 Histopathological evaluation, hypertrophy/hyperplasia of the alveolar epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.10 / 0.06 3/10	0.20 / 0.08 5/10	0.12/ 0.07 3/10	0.03 / 0.03 1/8	0.00 / 0.00 0/10
3R4F_CONT	Mean/SEM INC	0.64 / 0.16 7/10	1.18 / 0.13 9/9	1.40 / 0.29 8/10	2.07 / 0.19 10/10	1.98 / 0.04 9/9
THS 2.2_CONT	Mean/SEM INC	0.14 / 0.06 5/10	0.12 / 0.08 3/10	0.02 / 0.02 1/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.54 / 0.15 9/10	0.02 / 0.02 1/10	0.00 / 0.00 0/9
THS 2.2_Switch	Mean/SEM INC			0.22 / 0.09 4/10	0.04 / 0.04 1/10	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+ (0.020)	+++ (≤0.001)	++ (0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.800)	= (0.582)	= (0.606)	= (0.607)	= (1.000)
Cessation			+ (0.039)	= (1.000)	= (1.000)
THS 2.2_Switch			= (0.950)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.083)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.654)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			++ (0.007)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	++ (0.003)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.079)	= (0.944)	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

Table 22 Histopathological evaluation, reserve cell hyperplasia of bronchial epithelium (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.35/ 0.14 6/10	0.15/ 0.05 5/10	0.18/ 0.13 2/10	0.00 / 0.00 0/8	0.08 / 0.05 2/10
3R4F_CONT	Mean/SEM INC	1.35/ 0.19 10/10	1.13 / 0.20 9/9	0.67 / 0.25 5/10	0.63 / 0.18 7/10	0.79 / 0.14 10/10
THS 2.2_CONT	Mean/SEM INC	0.38 / 0.15 6/10	0.15 / 0.09 3/10	0.18 / 0.16 2/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10
Cessation	Mean/SEM INC			0.11 / 0.05 4/10	0.11 / 0.07 2/10	0.07 / 0.05 2/9
THS 2.2_Switch	Mean/SEM INC			0.06 / 0.03 3/10	0.00 / 0.00 0/10	0.00 / 0.00 0/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+++ (≤0.001)	+++ (≤0.001)	= (0.226)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.984)	= (0.904)	= (0.999)	= (1.000)	= (0.311)
Cessation			= (0.960)	= (0.661)	= (1.000)
THS 2.2_Switch			= (1.000)	= (1.000)	= (0.485)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	++ (0.001)	+++ (≤0.001)	= (0.245)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.833)	++ (0.002)	+++ (≤0.001)
THS 2.2_Switch			= (0.480)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.411)	= (0.152)	= (0.129)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 23 Histopathological evaluation, goblet cell hyperplasia of bronchial epithelium (main bronchus), (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.20/ 0.13 2/10	0.50/ 0.17 5/10	0.00/ 0.00 0/6	0.00/ 0.00 0/8	0.30 / 0.15 3/10
3R4F_CONT	Mean/SEM INC	0.11/ 0.11 1/9	0.33 / 0.17 3/9	0.10 / 0.10 1/10	0.38 / 0.18 3/8	0.75 / 0.25 5/8
THS 2.2_CONT	Mean/SEM INC	0.33 / 0.17 3/9	0.00 / 0.00 0/10	0.22 / 0.15 2/9	0.20 / 0.20 1/10	0.30 / 0.21 2/10
Cessation	Mean/SEM INC			0.22 / 0.15 2/9	0.00/ 0.00 0/9	0.00 / 0.00 0/8
THS 2.2_Switch	Mean/SEM INC			0.33 / 0.24 2/9	0.10 / 0.10 1/10	0.00 / 0.00 0/9

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.892)	= (0.662)	= (0.832)	= (0.124)	= (0.301)
THS 2.2_CONT	= (0.774)	+ (0.032)	= (0.431)	= (0.784)	= (0.962)
Cessation			= (0.818)	= (1.000)	= (0.504)
THS 2.2_Switch			= (0.771)	= (0.961)	= (0.472)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.515)	= (0.208)	= (0.709)	= (0.314)	= (0.202)
Cessation			= (0.960)	= (0.117)	+ (0.016)
THS 2.2_Switch			= (0.935)	= (0.356)	+ (0.012)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.898)	= (0.179)	= (0.201)
THS 2.2_Switch	= (0.954)	= (0.545)	= (0.262)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.907)	= (0.357)	-

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

-: not applicable

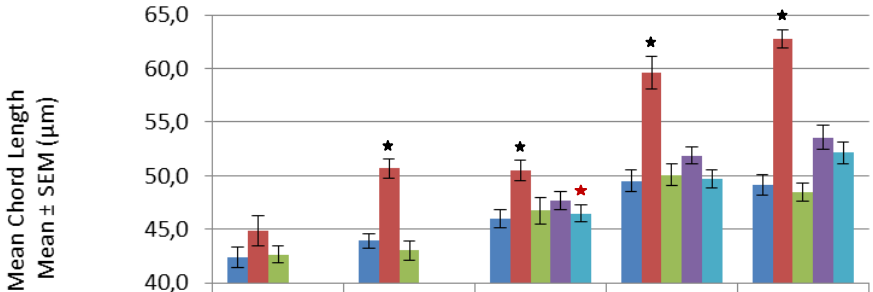
MORPHOMETRY DATA, LUNG

For the following endpoints, statistically significant exposure effects were observed after continuous exposure to MSS from the 3R4F or aerosol from the THS_2.2. Statistical comparisons between the different dissection time points for the SHAM, 3R4F, and THS 2.2 groups are shown in **Table 38.**

- mean chord length **(Table 24, Figure 18)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT2, DT3, DT6, and DT8 (increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - no statistically significant differences after cessation (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (stable)
  - statistically significantly lower mean value after THS 2.2-switch (compared to 3R4F_CONT group, DT2) at DT3 but not at DT6, and DT8 (overall stable)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- destructive index **(Table 25, Figure 19)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT1, DT2, DT3, DT6, and DT8 (increase in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly lower mean value after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (recovery)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

- bronchiolar attachments **(Table 26, Figure 20)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT3, DT6, and DT8 (decrease[a] in mean values between DT1 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - statistically significantly higher[a] mean value after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3
  - no statistically significant differences after cessation/switching (compared to 3R4F_CONT group, DT2) at DT6, and DT8 (overall stable)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- lung volume **(Table 27, Figure 21)**
  - statistically significant exposure effect for the 3R4F_CONT group at DT3 and DT8 (increase in mean values between DT1 and DT6, no further increase between DT6 and DT8)
  - no statistically significant exposure effect for the THS 2.2_CONT group
  - no statistically significant differences after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 (stable)
  - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

[a] consider negative correlation with 3R4F exposure



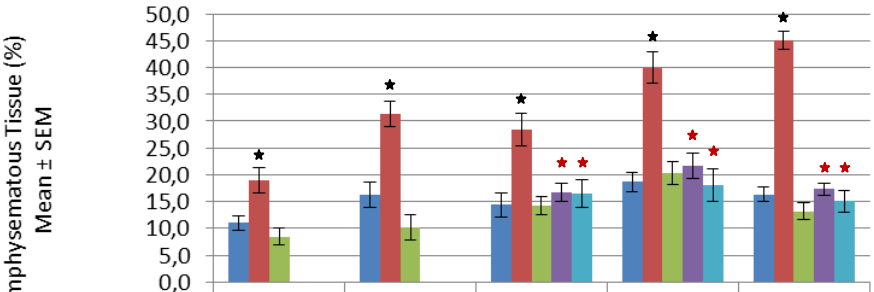
	DT1	DT2	DT3	DT6	DT8
SHAM	42,4	43,9	46,0	49,5	49,2
3R4F_CONT	44,9	50,7	50,5	59,6	62,7
THS 2.2._CONT	42,6	43,1	46,7	50,1	48,5
Cessation			47,7	51,9	53,6
THS 2.2_Switch			46,5	49,7	52,1

Figure 18 **Mean chord length**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



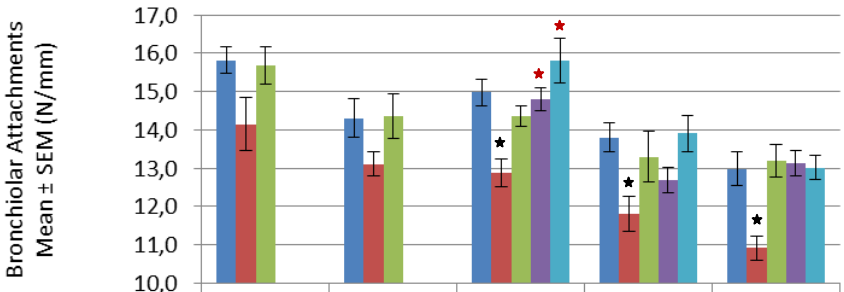
	DT1	DT2	DT3	DT6	DT8
SHAM	11,0	16,3	14,4	18,7	16,4
3R4F_CONT	18,9	31,3	28,5	40,0	45,1
THS 2.2._CONT	8,5	10,1	14,3	20,3	13,2
Cessation			16,8	21,7	17,3
THS 2.2_Switch			16,4	18,1	15,1

Figure 19 **Destructive index**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



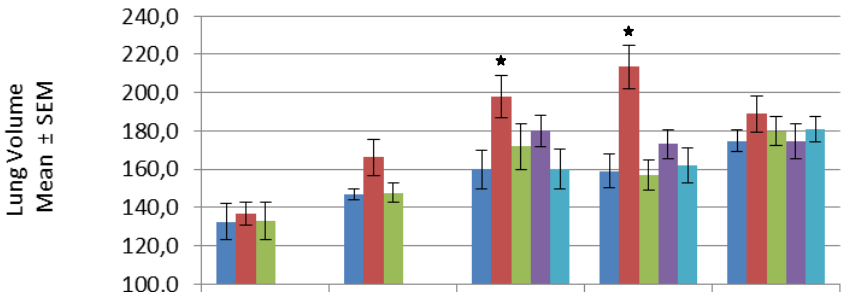
	DT1	DT2	DT3	DT6	DT8
SHAM	15,8	14,3	15,0	13,8	13,0
3R4F_CONT	14,2	13,1	12,9	11,8	10,9
THS 2.2._CONT	15,7	14,4	14,4	13,3	13,2
Cessation			14,8	12,7	13,1
THS 2.2_Switch			15,8	13,9	13,0

Figure 20 **Bronchiolar attachments**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



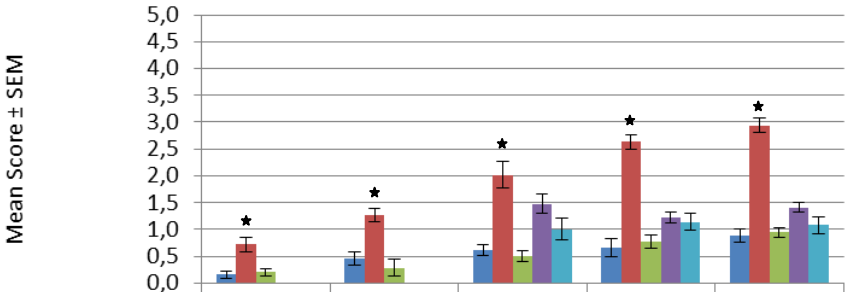
	DT1	DT2	DT3	DT6	DT8
SHAM	132,6	146,9	159,8	158,8	174,8
3R4F_CONT	136,7	166,1	198,1	213,3	188,8
THS 2.2._CONT	133,0	147,6	171,8	156,8	179,8
Cessation			180,0	173,0	174,6
THS 2.2_Switch			160,0	162,0	180,8

Figure 21 **Lung volume**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



	DT1	DT2	DT3	DT6	DT8
SHAM	0,2	0,5	0,6	0,7	0,9
3R4F_CONT	0,7	1,3	2,0	2,6	2,9
THS 2.2_CONT	0,2	0,3	0,5	0,8	0,9
Cessation			1,5	1,2	1,4
THS 2.2_Switch			1,0	1,1	1,1

Figure 22 (identical to Figure 16, section: Histopathology data lung)

alveolar emphysema, histopathology score (for 3R4F_CONT and THS 2.2_CONT)
***: statistical significance compared to SHAM**
***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**
Δ: statistical significance between Cessation and THS_2.2_Switch groups

Table 24 Morphometrical evaluation, mean chord length (Mean / SEM / N)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM N	42.4 / 0.97 9	43.9 / 0.68 8	46.0 / 0.80 10	49.5 / 1.02 8	49.2 / 0.95 10
3R4F_CONT	Mean/SEM N	44.9 / 1.41 10	50.7 / 0.95 9	50.5 / 0.93 10	59.6 / 1.51 10	62.7 / 0.86 9
THS 2.2_CONT	Mean/SEM N	42.6 / 0.78 9	43.1 / 0.90 9	46.7 / 1.23 9	50.1 / 1.00 10	48.5 / 0.87 10
Cessation	Mean/SEM N			47.7 / 0.87 10	51.9 / 0.78 10	53.6 / 1.12 9
THS 2.2_Switch	Mean/SEM N			46.5 / 0.77 10	49.7 / 0.81 10	52.1 / 1.04 10

Statistical comparison to SHAM group

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.275)	+++ (≤0.001)	++ (0.008)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.989)	= (0.759)	= (0.859)	= (0.936)	= (0.850)
Cessation			= (0.668)	= (0.538)	+ (0.229)
THS 2.2_Switch			= (0.996)	= (1.000)	= (0.202)

Statistical comparison to 3R4F_CONT group

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.341)	+++ (≤0.001)	+ (0.034)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.226)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			+ (0.026)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.134)	= (0.777)	= (0.162)
THS 2.2_Switch	+ (0.013)	= (0.886)	= (0.671)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.292)	= (0.068)	= (0.365)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 N: number of animals SEM: standard error of the mean

Table 25 Morphometrical evaluation, destructive index (Mean / SEM / N)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM N	11.0 / 1.40 9	16.3 / 2.41 8	14.4 / 2.23 10	18.7 / 1.80 8	14.4 / 1.28 10
3R4F_CONT	Mean/SEM N	18.9 / 2.34 10	31.3 / 2.38 9	28.5 / 3.08 10	40.0 / 2.87 10	45.1 / 1.65 9
THS 2.2_CONT	Mean/SEM N	8.5 / 1.50 9	10.1 / 2.40 9	14.3 / 1.63 9	20.3 / 2.12 10	13.2 / 1.63 10
Cessation	Mean/SEM N			16.8 / 1.70 10	21.7 / 2.35 10	17.3 / 1.15 9
THS 2.2_Switch	Mean/SEM N			16.4 / 2.59 10	18.1 / 3.08 10	15.1 / 2.02 10

Statistical comparison to SHAM group

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	+ (0.014)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.610)	= (0.199)	= (0.999)	= (0.884)	= (0.853)
Cessation			= (0.949)	= (0.929)	= (0.697)
THS 2.2_Switch			= (0.975)	= (1.000)	= (0.998)

Statistical comparison to 3R4F_CONT group

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	++ (0.001)	+++ (≤0.001)	++ (0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			++ (0.007)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_Switch			++ (0.005)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	+++ (≤0.001)	++ (0.008)	+++ (≤0.001)
THS 2.2_Switch	++ (0.001)	++ (0.005)	+++ (≤0.001)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.894)	= (0.367)	= (0.366)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 N: number of animals SEM: standard error of the mean

Table 26 Morphometrical evaluation, bronchiolar attachments (Mean / SEM / N)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM N	15.8 / 0.34 9	14.3 / 0.50 8	15.0 / 0.35 10	13.8 / 0.37 8	13.0 / 0.44 10
3R4F_CONT	Mean/SEM N	14.2 / 0.70 10	13.1 / 0.31 9	12.9 / 0.36 10	11.8 / 0.45 10	10.9 / 0.32 9
THS 2.2_CONT	Mean/SEM N	15.7 /0.49 9	14.4 / 0.57 9	14.4 / 0.27 9	13.3 / 0.67 10	13.2 / 0.43 10
Cessation	Mean/SEM N			14.8 / 0.31 10	12.7 / 0.33 10	13.1 / 0.34 9
THS 2.2_Switch	Mean/SEM N			15.8 / 0.58 10	13.9 / 0.47 10	13.0 / 0.31 10

Statistical comparison to SHAM group

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.097)	= (0.200)	+++ (≤0.001)	+ (0.048)	++ (0.004)
THS 2.2_CONT	= (0.997)	= (0.996)	= (0.399)	= (0.846)	= (0.927)
Cessation			= (0.998)	= (0.609)	= (0.998)
THS 2.2_Switch			= (0.635)	= (1.000)	= (1.000)

Statistical comparison to 3R4F_CONT group

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.132)	= (0.157)	+ (0.012)	= (0.116)	++ (0.002)
Cessation			++ (0.009)	= (0.641)	++ (0.002)
THS 2.2_Switch			+++ (≤0.001)	+ (0.025)	++ (0.003)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	++ (0.004)	= (0.850)	= (1.000)
THS 2.2_Switch	+++ (≤0.001)	= (0.589)	= (0.999)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.173)	= (0.056)	= (0.801)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 N: number of animals SEM: standard error of the mean

Table 27 Morphometrical evaluation, lung volume (Mean / SEM / N)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM N	132.6 / 9.35 9	146.9 / 2.95 8	159.8 / 10.16 10	158.8 / 8.84 8	174.8 / 5.41 10
3R4F_CONT	Mean/SEM N	136.7 / 5.79 10	166.1 / 9.57 9	198.1 / 11.07 10	213.3 / 11.53 9	188.8 / 9.47 9
THS 2.2_CONT	Mean/SEM N	133.0 / 9.89 9	147.6 / 4.87 9	171.8 / 12.06 9	156.8 / 7.83 10	179.8 / 7.59 10
Cessation	Mean/SEM N			179.9 / 8.33 10	173.0 / 7.47 10	174.6 / 9.25 9
THS 2.2_Switch	Mean/SEM N			160.0 / 10.55 9	162.0 / 8.93 10	180.8 / 6.71 10

Statistical comparison to SHAM group

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.934)	= (0.128)	+ (0.050)	++ (0.002)	= (0.411)
THS 2.2_CONT	= (0.999)	= (0.997)	= (0.733)	= (0.988)	= (0.882)
Cessation			= (0.641)	= (0.808)	= (1.000)
THS 2.2_Switch			= (1.000)	= (1.000)	= (0.980)

Statistical comparison to 3R4F_CONT group

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.947)	= (0.132)	= (0.238)	+++ (≤0.001)	= (0.689)
Cessation			= (0.717)	+ (0.021)	= (0.718)
THS 2.2_Switch			= (0.096)	++ (0.002)	= (0.950)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.678)	= (0.941)	= (0.905)
THS 2.2_Switch	= (0.964)	= (0.987)	= (0.655)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.154)	= (0.354)	= (0.587)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 N: number of animals SEM: standard error of the mean

Table 28 (identical with Table 20, section: Histopathology data lung)

Histopathological evaluation, alveolar emphysema (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.16 / 0.07 5/10	0.46/ 0.12 7/10	0.62/ 0.10 10/10	0.65 / 0.17 7/8	0.88 / 0.13 9/10
3R4F_CONT	Mean/SEM INC	0.72 / 0.13 9/10	1.27 / 0.13 9/9	2.02 / 0.25 10/10	2.63 / 0.13 10/10	2.94 / 0.14 10/10
THS 2.2_CONT	Mean/SEM INC	0.20 / 0.06 7/10	0.28 / 0.16 4/10	0.50 / 0.11 9/10	0.77 / 0.13 10/10	0.94 / 0.09 10/10
Cessation	Mean/SEM INC			1.48 / 0.17 10/10	1.22 / 0.11 10/10	1.41 / 0.09 9/9
THS 2.2_Switch	Mean/SEM INC			1.00 / 0.20 9/10	1.14 / 0.15 10/10	1.08 / 0.16 10/10

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	++ (0.003)	++ (0.002)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
THS 2.2_CONT	= (0.835)	= (0.435)	= (0.732)	= (0.787)	= (0.950)
Cessation			++ (0.004)	+ (0.031)	+ (0.025)
THS 2.2_Switch			= (0.400)	= (0.099)	= (0.930)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	+ (0.011)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)	+++ (≤0.001)
Cessation			= (0.776)	+++ (≤0.001)	++ (0.009)
THS 2.2_Switch			+ (0.021)	+++ (≤0.001)	+++ (≤0.001)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.715)	= (1.000)	= (0.746)
THS 2.2_Switch	= (0.738)	= (0.964)	= (0.820)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.095)	= (0.741)	= (0.168)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 N: number of animals SEM: standard error of the mean

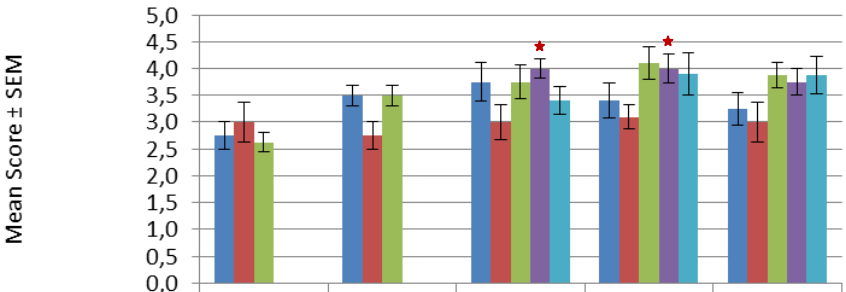
HISTOPATHOLOGY DATA, LIVER

For the content of fat in hepatocytes (evaluated after Oil Red staining, frozen section), the content of glycogen in hepatocytes (evaluated after PAS and PAS-D staining), and the endpoint micro-granuloma with micro-hemorrhage, the following trends were seen. Statistical comparisons between the different dissection time points for the SHAM, 3R4F, and THS 2.2 groups are shown in **Table 37.**

- content of fat **(Figure 23, Table 29)**:
    - lower mean values for the 3R4F_CONT group compared to SHAM (DT2, DT3, DT6, and DT8, not statistically significant)
    - higher mean values for the THS 2.2_CONT group compared to SHAM (DT6 and DT8, not statistically significant)
    - higher mean value after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8 respectively (statistically significant for the Cessation group at DT3 and DT6)
    - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8
- content of glycogen **(Figure 24, Table 30)**:
    - lower mean values for the 3R4F_CONT and THS 2.2_CONT groups compared to SHAM (DT1, DT2, DT3, DT6, and DT8; statistically significant for THS 2.2_CONT at DT6)
    - no statistically significant differences after cessation/switching (compared to 3R4F_CONT group, DT2) at DT3, DT6, and DT8
    - statistically significantly lower mean value for the Cessation group compared to the THS 2.2_Switch group at DT3 but not at DT6 and DT8
- micro-granuloma with micro-hemorrhage **(Figure 25, Table 31)**:
    - lower mean values for the 3R4F_CONT compared to SHAM at DT1, DT2, DT5 and DT6 (statistically significant at DT6), **(Figure 25)**
    - higher mean value after cessation/switching (compared to 3R4F_CONT group, DT2) at DT8 (statistically significant for the THS 2.2_Switch group)
    - no statistically significant differences for the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8

For the following endpoints, no statistically significant exposure effects (compared to SHAM) were observed for the 3R4F_CONT, the THS 2.2_CONT, the Cessation and the THS 2.2_Switch groups at DT1, DT2, DT3, DT6 and DT8. Mean values were similar for all exposure groups without any obvious trends compared to SHAM. The findings are considered to be typical in ApoE deficient mice from qualitative perspective. Descriptive statistics are shown in **Table 34.**

- cytoplasmatic vacuolisation of hepatocytes
- mono-nuclear inflammatory cells, parenchyma
- haemorrhage, parenchyma
- degeneration/necrosis of hepatocytes
- mono-nuclear inflammatory cells, peri-portal/interstitial
- bile duct hyperplasia
- increase of collagen fibres, peri-portal/interstitial
- peri-portal/interstitial brownish pigment
- hyper-chromatic nuclei



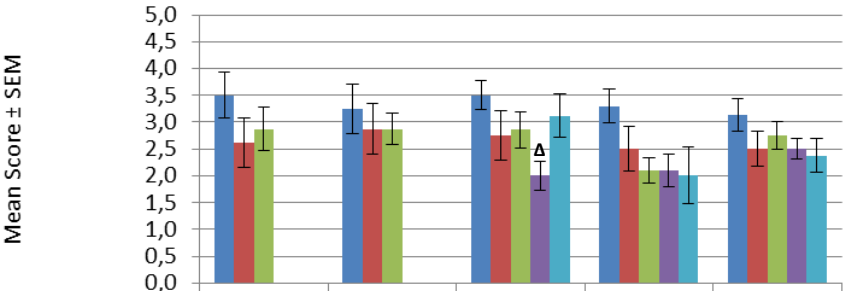
	DT1	DT2	DT3	DT6	DT8
SHAM	2,8	3,5	3,8	3,4	3,25
3R4F_CONT	3,0	2,8	3,0	3,1	3,00
THS 2.2_CONT	2,6	3,5	3,8	4,1	3,88
Cessation			4,0	4,0	3,75
THS 2.2_Switch			3,4	3,9	3,88

Figure 23 **Content of fat in hepatocytes**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



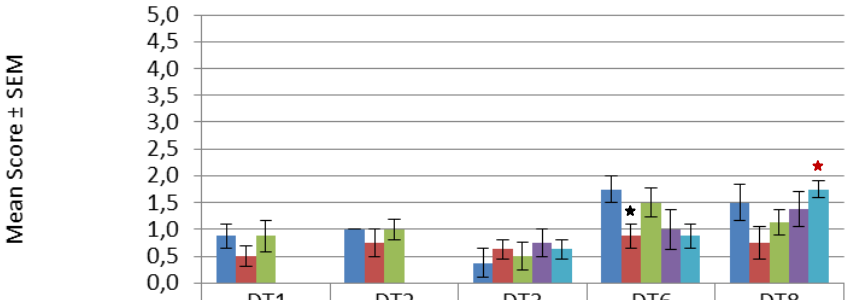
	DT1	DT2	DT3	DT6	DT8
SHAM	3,5	3,3	3,5	3,3	3,1
3R4F_CONT	2,6	2,9	2,8	2,5	2,5
THS 2.2_CONT	2,9	2,9	2,9	2,1	2,8
Cessation			2,0	2,1	2,5
THS 2.2_Switch			3,1	2,0	2,4

Figure 24 **Content of glycogen in hepatocytes**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups



	DT1	DT2	DT3	DT6	DT8
SHAM	0,9	1,0	0,4	1,8	1,5
3R4F_CONT	0,5	0,8	0,6	0,9	0,8
THS 2.2_CONT	0,9	1,0	0,5	1,5	1,1
Cessation			0,8	1,0	1,4
THS 2.2_Switch			0,6	0,9	1,8

Figure 25 **Micro-granuloma with micro-hemorrhage**

***: statistical significance compared to SHAM (for 3R4F_CONT and THS 2.2_CONT)**

***: statistical significance compared to 3R4F_CONT at DT2 (same initial 3R4F exposure)**

Δ: statistical significance between Cessation and THS_2.2_Switch groups

Table 29 Histopathological evaluation, content of fat in hepatocytes (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	2.75 / 0.25 8/8	3.50 / 0.19 8/8	3.75 / 0.37 8/8	3.38 / 0.32 8/8	3.25 / 0.31 8/8
3R4F_CONT	Mean/SEM INC	3.00 / 0.38 8/8	2.75 / 0.25 8/8	3.00 / 0.33 8/8	3.13 / 0.23 8/8	3.00 / 0.38 8/8
THS 2.2_CONT	Mean/SEM INC	2.63 / 0.18 8/8	3.50 / 0.19 8/8	3.75 / 0.31 8/8	4.13 / 0.30 8/8	3.88 / 0.23 8/8
Cessation	Mean/SEM INC			4.00 / 0.19 8/8	4.00 / 0.27 8/8	3.75 / 0.25 8/8
THS 2.2_Switch	Mean/SEM INC			3.38 / 0.26 8/8	3.88 / 0.40 8/8	3.88 / 0.35 8/8

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.699)	= (0.071)	= (0.310)	= (0.822)	= (0.785)
THS 2.2_CONT	= (0.951)	= (1.000)	= (0.997)	= (0.182)	= (0.373)
Cessation			= (0.969)	= (0.590)	= (0.846)
THS 2.2_Switch			= (0.899)	= (0.761)	= (0.770)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.514)	= (0.073)	= (0.345)	= (0.059)	= (0.127)
Cessation			= (0.178)	= (0.261)	= (0.469)
THS 2.2_Switch			= (0.943)	= (0.404)	= (0.382)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	++ (0.007)	++ (0.008)	= (0.051)
THS 2.2_Switch	= (0.458)	= (0.094)	= (0.103)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.076)	= (0.917)	= (0.873)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

Table 30 Histopathological evaluation, content of glycogen in hepatocytes (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	3.50 / 0.42 8/8	3.25 / 0.45 8/8	3.50 / 0.27 8/8	3.25 / 0.31 8/8	3.13 / 0.30 8/8
3R4F_CONT	Mean/SEM INC	2.63 / 0.46 8/8	2.88 / 0.48 8/8	2.75 / 0.45 8/8	2.50 / 0.42 7/8	2.50 / 0.33 8/8
THS 2.2_CONT	Mean/SEM INC	2.88 / 0.40 8/8	2.88 / 0.30 8/8	2.86 / 0.34 7/7	2.13 / 0.23 8/8	2.75 / 0.25 8/8
Cessation	Mean/SEM INC			2.00 / 0.27 8/8	2.13 / 0.30 8/8	2.50 / 0.19 8/8
THS 2.2_Switch	Mean/SEM INC			3.13 / 0.40 8/8	2.00 / 0.53 6/8	2.38 / 0.32 8/8

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.297)	= (0.771)	= (0.271)	= (0.359)	= (0.353)
THS 2.2_CONT	= (0.543)	= (0.771)	= (0.411)	+ (0.036)	= (0.644)
Cessation			+ (0.029)	= (0.174)	= (0.530)
THS 2.2_Switch			= (0.967)	= (0.244)	= (0.530)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.890)	= (1.000)	= (0.969	= (0.423)	= (0.868)
Cessation			= (0.593)	= (0.861)	= (1.000)
THS 2.2_Switch			= (0.852)	= (0.930)	= (1.000)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (0.448)	= (0.654)	= (0.992)
THS 2.2_Switch	= (0.928)	= (0.686)	= (0.864)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
+ (0.034)	= (1.000)	= (1.000)

=: $p > 0.05$ (not statistically significant) +: $p \leq 0.05$ ++: $p \leq 0.01$ +++: $p \leq 0.001$ INC: incidence SEM: standard error of the mean

Table 31 Histopathological evaluation, micro-granuloma with micro-hemorrhage (severity scores, Mean / SEM / INC)

		DT1	DT2	DT3	DT6	DT8
SHAM	Mean/SEM INC	0.88 / 0.23 6/8	1.00 / 0.00 8/8	0.38 / 0.26 2/8	1.75 /0.25 8/8	1.50 / 0.33 7/8
3R4F_CONT	Mean/SEM INC	0.50 / 0.19 4/8	0.75 / 0.25 5/8	0.63 / 0.18 5/8	0.88 / 0.23 6/8	0.75 / 0.31 4/8
THS 2.2_CONT	Mean/SEM INC	0.88 / 0.30 5/8	1.00 / 0.19 7/8	0.50 / 0.27 3/8	1.50 / 0.27 8/8	1.13 / 0.23 7/8
Cessation	Mean/SEM INC			0.75 / 0.25 5/8	1.00 / 0.38 5/8	1.38 / 0.23 7/8
THS 2.2_Switch	Mean/SEM INC			0.63 / 0.18 5/8	0.88 / 0.23 6/8	1.75 / 0.16 8/8

Statistical comparison to SHAM group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
3R4F_CONT	= (0.526)	= (0.548)	= (0.517)	+ (0.046)	= (0.220)
THS 2.2_CONT	= (0.993)	= (0.999)	= (0.900)	= (0.671)	= (0.705)
Cessation			= (0.693)	= (0.216)	= (0.996)
THS 2.2_Switch			= (0.823)	= (0.156)	= (0.926)

Statistical comparison to 3R4F_CONT group (same dissection time point)

	DT1	DT2	DT3	DT6	DT8
THS 2.2_CONT	= (0.596)	= (0.576)	= (0.780	= (0.229)	= (0.635)
Cessation			= (0.999)	= (1.000)	= (0.636)
THS 2.2_Switch			= (1.000)	= (1.000)	= (0.098)

Statistical comparison to 3R4F_CONT_DT2 group

	DT3	DT6	DT8
Cessation	= (1.000)	= (0.980)	= (0.521)
THS 2.2_Switch	= (0.974)	= (0.974)	+ (0.011)

Statistical comparison between Cessation group and THS 2.2_Switch group

DT3	DT6	DT8
= (0.776)	= (1.000)	= (0.261)

=: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001 INC: incidence SEM: standard error of the mean

STATISTICAL DATA, ENDPOINTS WITHOUT STATISTICAL SIGNIFICANCE

Table 32 nose, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
nose level 1, respiratory epithelium, vacuolization	3R4F_CONT_DT1	10	0,10	0,10	1
nose level 1, respiratory epithelium, vacuolization	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, vacuolization	3R4F_CONT_DT3	8	0,38	0,26	2
nose level 1, respiratory epithelium, vacuolization	3R4F_CONT_DT6	10	0,20	0,13	2
nose level 1, respiratory epithelium, vacuolization	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, vacuolization	Cessation_DT3	9	1,22	0,57	4
nose level 1, respiratory epithelium, vacuolization	Cessation_DT6	10	1,00	0,54	3
nose level 1, respiratory epithelium, vacuolization	Cessation_DT8	10	0,80	0,42	3
nose level 1, respiratory epithelium, vacuolization	THS 2.2_CONT_DT1	10	0,20	0,20	1
nose level 1, respiratory epithelium, vacuolization	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 1, respiratory epithelium, vacuolization	THS 2.2_CONT_DT3	10	0,60	0,22	5
nose level 1, respiratory epithelium, vacuolization	THS 2.2_CONT_DT6	10	1,20	0,53	4
nose level 1, respiratory epithelium, vacuolization	THS 2.2_CONT_DT8	10	0,80	0,42	4
nose level 1, respiratory epithelium, vacuolization	THS 2.2_Switch_DT3	9	0,56	0,34	3
nose level 1, respiratory epithelium, vacuolization	THS 2.2_Switch_DT6	10	1,00	0,30	7
nose level 1, respiratory epithelium, vacuolization	THS 2.2_Switch_DT8	10	0,60	0,40	3
nose level 1, respiratory epithelium, vacuolization	SHAM_DT1	9	0,11	0,11	1
nose level 1, respiratory epithelium, vacuolization	SHAM_DT2	10	0,20	0,20	1
nose level 1, respiratory epithelium, vacuolization	SHAM_DT3	10	0,40	0,22	3
nose level 1, respiratory epithelium, vacuolization	SHAM_DT6	9	0,67	0,24	5
nose level 1, respiratory epithelium, vacuolization	SHAM_DT8	9	1,44	0,65	4
nose level 1, respiratory epithelium, amount of cornification	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	3R4F_CONT_DT3	8	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	3R4F_CONT_DT8	10	0,30	0,15	3
nose level 1, respiratory epithelium, amount of cornification	Cessation_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	Cessation_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	Cessation_DT8	9	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_Switch_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	SHAM_DT1	9	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	SHAM_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	SHAM_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	SHAM_DT6	9	0,00	0,00	0
nose level 1, respiratory epithelium, amount of cornification	SHAM_DT8	8	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT1	10	0,10	0,10	1
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT3	8	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT8	10	0,20	0,20	1
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	Cessation_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	Cessation_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	Cessation_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT6	10	0,40	0,27	2
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT8	10	0,50	0,34	2
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_Switch_DT6	10	0,30	0,30	1
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_Switch_DT8	10	0,40	0,27	2
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT1	10	0,50	0,34	2
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT6	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT8	9	0,00	0,00	0

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 32 cont. nose, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	3R4F_CONT_DT3	8	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	Cessation_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	Cessation_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	Cessation_DT8	10	0,40	0,40	1
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_CONT_DT1	10	0,10	0,10	1
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_CONT_DT6	10	0,20	0,20	1
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_Switch_DT6	10	0,10	0,10	1
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	THS 2.2_Switch_DT8	10	0,20	0,20	1
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	SHAM_DT1	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	SHAM_DT2	10	0,10	0,10	1
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	SHAM_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	SHAM_DT6	9	0,00	0,00	0
nose level 1, respiratory epithelium, lamina propria, lymphocytis cells	SHAM_DT8	9	0,11	0,11	1
nose level 1, respiratory epithelium, lumen, red blood cells	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	3R4F_CONT_DT3	8	0,25	0,25	1
nose level 1, respiratory epithelium, lumen, red blood cells	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	Cessation_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	Cessation_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	Cessation_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_CONT_DT3	10	0,10	0,10	1
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_Switch_DT3	9	0,11	0,11	1
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_Switch_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	SHAM_DT1	10	0,10	0,10	1
nose level 1, respiratory epithelium, lumen, red blood cells	SHAM_DT2	10	0,20	0,20	1
nose level 1, respiratory epithelium, lumen, red blood cells	SHAM_DT3	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	SHAM_DT6	9	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, red blood cells	SHAM_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT1	10	1,10	0,23	8
nose level 1, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT2	10	0,70	0,42	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT3	8	0,50	0,27	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT6	10	0,30	0,15	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT8	10	0,60	0,40	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	Cessation_DT3	9	0,44	0,18	4
nose level 1, respiratory epithelium, lumen, eosinophilic material	Cessation_DT6	10	0,70	0,21	6
nose level 1, respiratory epithelium, lumen, eosinophilic material	Cessation_DT8	10	0,60	0,22	5
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT1	10	0,80	0,20	7
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT2	9	0,78	0,22	6
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT3	10	0,30	0,15	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT6	10	0,60	0,22	5
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT8	10	0,30	0,15	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_Switch_DT3	9	1,00	0,29	6
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_Switch_DT6	10	0,70	0,26	5
nose level 1, respiratory epithelium, lumen, eosinophilic material	THS 2.2_Switch_DT8	10	0,30	0,15	3
nose level 1, respiratory epithelium, lumen, eosinophilic material	SHAM_DT1	10	0,50	0,22	4
nose level 1, respiratory epithelium, lumen, eosinophilic material	SHAM_DT2	10	0,50	0,22	4
nose level 1, respiratory epithelium, lumen, eosinophilic material	SHAM_DT3	10	0,90	0,23	7
nose level 1, respiratory epithelium, lumen, eosinophilic material	SHAM_DT6	9	0,78	0,22	6
nose level 1, respiratory epithelium, lumen, eosinophilic material	SHAM_DT8	10	0,60	0,16	6

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 32 cont. nose, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
nose level 1, respiratory epithelium, lumen, necrotic cells	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	3R4F_CONT_DT2	10	0,30	0,30	1
nose level 1, respiratory epithelium, lumen, necrotic cells	3R4F_CONT_DT3	8	0,13	0,13	1
nose level 1, respiratory epithelium, lumen, necrotic cells	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	3R4F_CONT_DT8	10	0,10	0,10	1
nose level 1, respiratory epithelium, lumen, necrotic cells	Cessation_DT3	9	0,22	0,22	1
nose level 1, respiratory epithelium, lumen, necrotic cells	Cessation_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	Cessation_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_CONT_DT2	9	0,11	0,11	1
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_CONT_DT3	10	0,40	0,27	2
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_CONT_DT6	10	0,50	0,27	3
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_CONT_DT8	10	0,20	0,20	1
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_Switch_DT6	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	SHAM_DT1	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	SHAM_DT2	10	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	SHAM_DT3	10	0,10	0,10	1
nose level 1, respiratory epithelium, lumen, necrotic cells	SHAM_DT6	9	0,00	0,00	0
nose level 1, respiratory epithelium, lumen, necrotic cells	SHAM_DT8	10	0,60	0,43	2
nose level 2, respiratory epithelium, degeneration	3R4F_CONT_DT1	9	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	3R4F_CONT_DT3	7	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	3R4F_CONT_DT8	9	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	Cessation_DT3	7	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	Cessation_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	Cessation_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_CONT_DT1	8	0,13	0,13	1
nose level 2, respiratory epithelium, degeneration	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_CONT_DT3	8	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_Switch_DT6	9	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	SHAM_DT1	10	0,10	0,10	1
nose level 2, respiratory epithelium, degeneration	SHAM_DT2	10	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	SHAM_DT3	8	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	SHAM_DT6	9	0,00	0,00	0
nose level 2, respiratory epithelium, degeneration	SHAM_DT8	9	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT1	9	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT3	7	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT6	10	0,20	0,20	1
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	3R4F_CONT_DT8	9	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	Cessation_DT3	7	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	Cessation_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	Cessation_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT1	8	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT2	9	0,33	0,33	1
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT3	8	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_CONT_DT8	10	0,30	0,30	1
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_Switch_DT6	9	0,33	0,33	1
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT1	10	0,10	0,10	1
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT2	10	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT3	8	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT6	9	0,00	0,00	0
nose level 2, respiratory epithelium, lamina propria, dilatation of blood vessels	SHAM_DT8	10	0,00	0,00	0

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 32 cont. nose, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
nose level 2, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT1	9	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT3	7	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	3R4F_CONT_DT8	9	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	Cessation_DT3	7	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	Cessation_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	Cessation_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT1	8	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT3	8	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_Switch_DT3	9	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_Switch_DT6	9	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	THS 2.2_Switch_DT8	10	0,10	0,10	1
nose level 2, respiratory epithelium, lumen, eosinophilic material	SHAM_DT1	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	SHAM_DT2	10	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	SHAM_DT3	8	0,00	0,00	0
nose level 2, respiratory epithelium, lumen, eosinophilic material	SHAM_DT6	9	0,11	0,11	1
nose level 2, respiratory epithelium, lumen, eosinophilic material	SHAM_DT8	10	0,10	0,10	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	3R4F_CONT_DT1	10	0,10	0,10	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	3R4F_CONT_DT2	10	0,20	0,13	2
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	3R4F_CONT_DT3	9	0,11	0,11	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	3R4F_CONT_DT6	10	0,20	0,20	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	3R4F_CONT_DT8	10	0,20	0,20	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	Cessation_DT3	9	0,11	0,11	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	Cessation_DT6	10	0,30	0,21	2
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	Cessation_DT8	10	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_CONT_DT2	10	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_CONT_DT3	10	0,30	0,21	2
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_CONT_DT6	10	0,20	0,13	2
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_CONT_DT8	10	0,30	0,21	2
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_Switch_DT3	10	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_Switch_DT6	9	0,22	0,22	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	THS 2.2_Switch_DT8	10	0,40	0,22	3
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	SHAM_DT1	10	0,10	0,10	1
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	SHAM_DT2	9	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	SHAM_DT3	10	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	SHAM_DT6	9	0,00	0,00	0
nose level 2, olfactory epithelium, hyperplasia, epithelial layers	SHAM_DT8	10	0,10	0,10	1
nose level 2, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT1	10	0,20	0,20	1
nose level 2, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT3	9	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	Cessation_DT3	9	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	Cessation_DT6	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	Cessation_DT8	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT2	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_Switch_DT3	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_Switch_DT6	9	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	SHAM_DT1	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	SHAM_DT2	9	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	SHAM_DT3	10	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	SHAM_DT6	9	0,00	0,00	0
nose level 2, olfactory epithelium, lumen, red blood cells	SHAM_DT8	10	0,00	0,00	0

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 32 cont. nose, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
nose level 4, olfactory epithelium, vacuolization	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, vacuolization	3R4F_CONT_DT2	10	0,30	0,15	3
nose level 4, olfactory epithelium, vacuolization	3R4F_CONT_DT3	10	1,10	0,31	7
nose level 4, olfactory epithelium, vacuolization	3R4F_CONT_DT6	10	0,70	0,21	6
nose level 4, olfactory epithelium, vacuolization	3R4F_CONT_DT8	10	0,80	0,33	5
nose level 4, olfactory epithelium, vacuolization	Cessation_DT3	9	0,67	0,37	3
nose level 4, olfactory epithelium, vacuolization	Cessation_DT6	10	1,20	0,44	6
nose level 4, olfactory epithelium, vacuolization	Cessation_DT8	10	0,40	0,22	3
nose level 4, olfactory epithelium, vacuolization	THS 2.2_CONT_DT1	9	0,33	0,33	1
nose level 4, olfactory epithelium, vacuolization	THS 2.2_CONT_DT2	9	0,78	0,43	4
nose level 4, olfactory epithelium, vacuolization	THS 2.2_CONT_DT3	10	1,00	0,52	4
nose level 4, olfactory epithelium, vacuolization	THS 2.2_CONT_DT6	10	0,90	0,31	6
nose level 4, olfactory epithelium, vacuolization	THS 2.2_CONT_DT8	10	1,20	0,42	6
nose level 4, olfactory epithelium, vacuolization	THS 2.2_Switch_DT3	10	0,40	0,22	3
nose level 4, olfactory epithelium, vacuolization	THS 2.2_Switch_DT6	10	1,00	0,42	5
nose level 4, olfactory epithelium, vacuolization	THS 2.2_Switch_DT8	10	0,70	0,33	4
nose level 4, olfactory epithelium, vacuolization	SHAM_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, vacuolization	SHAM_DT2	10	0,10	0,10	1
nose level 4, olfactory epithelium, vacuolization	SHAM_DT3	10	0,50	0,27	3
nose level 4, olfactory epithelium, vacuolization	SHAM_DT6	9	0,44	0,18	4
nose level 4, olfactory epithelium, vacuolization	SHAM_DT8	10	1,60	0,54	7
nose level 4, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	Cessation_DT3	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	Cessation_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	Cessation_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT1	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_Switch_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_Switch_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	SHAM_DT1	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	SHAM_DT2	10	0,10	0,10	1
nose level 4, olfactory epithelium, lumen, red blood cells	SHAM_DT3	10	0,20	0,20	1
nose level 4, olfactory epithelium, lumen, red blood cells	SHAM_DT6	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, red blood cells	SHAM_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	3R4F_CONT_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	3R4F_CONT_DT8	10	0,30	0,30	1
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	Cessation_DT3	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	Cessation_DT6	10	0,20	0,20	1
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	Cessation_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_CONT_DT1	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_Switch_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_Switch_DT6	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	SHAM_DT1	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	SHAM_DT2	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	SHAM_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	SHAM_DT6	9	0,00	0,00	0
nose level 4, olfactory epithelium, lumen, amorphous eosinophilic material	SHAM_DT8	10	0,00	0,00	0

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 32 cont. nose, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
nose level 4, olfactory epithelium, lamina propria, fatty changes	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	3R4F_CONT_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	3R4F_CONT_DT6	10	0,20	0,13	2
nose level 4, olfactory epithelium, lamina propria, fatty changes	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	Cessation_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	Cessation_DT6	10	0,50	0,17	5
nose level 4, olfactory epithelium, lamina propria, fatty changes	Cessation_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_CONT_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_CONT_DT2	9	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_CONT_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_CONT_DT6	10	0,10	0,10	1
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_CONT_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_Switch_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_Switch_DT6	10	0,40	0,16	4
nose level 4, olfactory epithelium, lamina propria, fatty changes	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	SHAM_DT1	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	SHAM_DT2	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	SHAM_DT3	10	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	SHAM_DT6	9	0,00	0,00	0
nose level 4, olfactory epithelium, lamina propria, fatty changes	SHAM_DT8	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	3R4F_CONT_DT1	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	3R4F_CONT_DT2	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	3R4F_CONT_DT3	10	0,60	0,43	2
nose level 4, pharyngeal duct epithelium, vacuolization	3R4F_CONT_DT6	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	3R4F_CONT_DT8	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	Cessation_DT3	10	0,30	0,21	2
nose level 4, pharyngeal duct epithelium, vacuolization	Cessation_DT6	10	0,50	0,50	1
nose level 4, pharyngeal duct epithelium, vacuolization	Cessation_DT8	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_CONT_DT1	9	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_CONT_DT2	9	0,22	0,22	1
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_CONT_DT3	10	0,40	0,31	2
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_CONT_DT6	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_CONT_DT8	10	0,20	0,20	1
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_Switch_DT3	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_Switch_DT6	10	0,10	0,10	1
nose level 4, pharyngeal duct epithelium, vacuolization	THS 2.2_Switch_DT8	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	SHAM_DT1	9	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	SHAM_DT2	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	SHAM_DT3	10	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	SHAM_DT6	9	0,00	0,00	0
nose level 4, pharyngeal duct epithelium, vacuolization	SHAM_DT8	10	0,40	0,40	1

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 33 left lung, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
left lung, alveoli, lumen, transudate / exudate	3R4F_CONT_DT1	10	0,48	0,13	8
left lung, alveoli, lumen, transudate / exudate	3R4F_CONT_DT2	9	0,16	0,16	1
left lung, alveoli, lumen, transudate / exudate	3R4F_CONT_DT3	10	0,68	0,28	5
left lung, alveoli, lumen, transudate / exudate	3R4F_CONT_DT6	10	0,23	0,10	5
left lung, alveoli, lumen, transudate / exudate	3R4F_CONT_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, transudate / exudate	Cessation_DT3	10	0,30	0,22	3
left lung, alveoli, lumen, transudate / exudate	Cessation_DT6	10	0,04	0,04	1
left lung, alveoli, lumen, transudate / exudate	Cessation_DT8	9	0,04	0,04	1
left lung, alveoli, lumen, transudate / exudate	THS 2.2_CONT_DT1	10	0,14	0,08	3
left lung, alveoli, lumen, transudate / exudate	THS 2.2_CONT_DT2	10	0,04	0,03	2
left lung, alveoli, lumen, transudate / exudate	THS 2.2_CONT_DT3	10	0,28	0,24	2
left lung, alveoli, lumen, transudate / exudate	THS 2.2_CONT_DT6	10	0,06	0,04	2
left lung, alveoli, lumen, transudate / exudate	THS 2.2_CONT_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, transudate / exudate	THS 2.2_Switch_DT3	10	0,02	0,02	1
left lung, alveoli, lumen, transudate / exudate	THS 2.2_Switch_DT6	10	0,00	0,00	0
left lung, alveoli, lumen, transudate / exudate	THS 2.2_Switch_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, transudate / exudate	SHAM_DT1	10	0,14	0,08	4
left lung, alveoli, lumen, transudate / exudate	SHAM_DT2	10	0,20	0,08	5
left lung, alveoli, lumen, transudate / exudate	SHAM_DT3	10	0,24	0,12	5
left lung, alveoli, lumen, transudate / exudate	SHAM_DT6	8	0,08	0,05	2
left lung, alveoli, lumen, transudate / exudate	SHAM_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	3R4F_CONT_DT1	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	3R4F_CONT_DT2	9	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	3R4F_CONT_DT3	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	3R4F_CONT_DT6	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	3R4F_CONT_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	Cessation_DT3	10	0,04	0,04	1
left lung, alveoli, lumen, brownisch deposits	Cessation_DT6	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	Cessation_DT8	9	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_CONT_DT1	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_CONT_DT2	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_CONT_DT3	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_CONT_DT6	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_CONT_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_Switch_DT3	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_Switch_DT6	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	THS 2.2_Switch_DT8	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	SHAM_DT1	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	SHAM_DT2	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	SHAM_DT3	10	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	SHAM_DT6	8	0,00	0,00	0
left lung, alveoli, lumen, brownisch deposits	SHAM_DT8	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	3R4F_CONT_DT1	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	3R4F_CONT_DT2	9	0,00	0,00	0
left lung, interstitium, thickened and cell rich	3R4F_CONT_DT3	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	3R4F_CONT_DT6	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	3R4F_CONT_DT8	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	Cessation_DT3	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	Cessation_DT6	10	0,08	0,08	1
left lung, interstitium, thickened and cell rich	Cessation_DT8	9	0,02	0,02	1
left lung, interstitium, thickened and cell rich	THS 2.2_CONT_DT1	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	THS 2.2_CONT_DT2	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	THS 2.2_CONT_DT3	10	0,04	0,04	1
left lung, interstitium, thickened and cell rich	THS 2.2_CONT_DT6	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	THS 2.2_CONT_DT8	10	0,02	0,02	1
left lung, interstitium, thickened and cell rich	THS 2.2_Switch_DT3	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	THS 2.2_Switch_DT6	10	0,12	0,12	1
left lung, interstitium, thickened and cell rich	THS 2.2_Switch_DT8	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	SHAM_DT1	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	SHAM_DT2	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	SHAM_DT3	10	0,00	0,00	0
left lung, interstitium, thickened and cell rich	SHAM_DT6	8	0,00	0,00	0
left lung, interstitium, thickened and cell rich	SHAM_DT8	10	0,08	0,08	1

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 34 liver, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	3R4F_CONT_DT1	8	2,00	0,57	6
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	3R4F_CONT_DT2	7	1,14	0,40	5
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	3R4F_CONT_DT3	8	2,13	0,40	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	3R4F_CONT_DT6	8	2,13	0,40	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	3R4F_CONT_DT8	8	2,25	0,62	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	Cessation_DT3	8	1,75	0,59	5
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	Cessation_DT6	8	2,50	0,42	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	Cessation_DT8	8	2,88	0,30	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_CONT_DT1	8	1,75	0,41	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_CONT_DT2	8	2,00	0,33	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_CONT_DT3	8	2,13	0,44	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_CONT_DT6	8	2,88	0,55	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_CONT_DT8	8	3,25	0,25	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_Switch_DT3	8	1,75	0,31	7
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_Switch_DT6	8	2,75	0,25	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	THS 2.2_Switch_DT8	8	3,13	0,30	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	SHAM_DT1	8	1,75	0,41	6
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	SHAM_DT2	8	1,38	0,46	6
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	SHAM_DT3	8	2,50	0,42	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	SHAM_DT6	8	2,50	0,33	8
liver, parenchyma, cytoplasmatic vacuolisation, hepatocytes	SHAM_DT8	8	3,25	0,31	8
liver, parenchyma, hyperchromasia, hepatocytes	3R4F_CONT_DT1	8	1,50	0,50	5
liver, parenchyma, hyperchromasia, hepatocytes	3R4F_CONT_DT2	7	1,57	0,53	5
liver, parenchyma, hyperchromasia, hepatocytes	3R4F_CONT_DT3	8	1,63	0,38	7
liver, parenchyma, hyperchromasia, hepatocytes	3R4F_CONT_DT6	8	0,75	0,31	4
liver, parenchyma, hyperchromasia, hepatocytes	3R4F_CONT_DT8	8	0,88	0,44	3
liver, parenchyma, hyperchromasia, hepatocytes	Cessation_DT3	8	1,38	0,46	5
liver, parenchyma, hyperchromasia, hepatocytes	Cessation_DT6	8	0,13	0,13	1
liver, parenchyma, hyperchromasia, hepatocytes	Cessation_DT8	8	0,75	0,37	3
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_CONT_DT1	8	0,75	0,37	3
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_CONT_DT2	8	0,88	0,48	3
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_CONT_DT3	8	1,00	0,42	4
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_CONT_DT6	8	0,25	0,16	2
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_CONT_DT8	8	0,50	0,33	2
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_Switch_DT3	8	1,13	0,48	4
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_Switch_DT6	8	0,25	0,25	1
liver, parenchyma, hyperchromasia, hepatocytes	THS 2.2_Switch_DT8	8	0,75	0,49	2
liver, parenchyma, hyperchromasia, hepatocytes	SHAM_DT1	8	0,75	0,49	2
liver, parenchyma, hyperchromasia, hepatocytes	SHAM_DT2	8	1,13	0,40	5
liver, parenchyma, hyperchromasia, hepatocytes	SHAM_DT3	8	0,88	0,40	4
liver, parenchyma, hyperchromasia, hepatocytes	SHAM_DT6	8	0,38	0,26	2
liver, parenchyma, hyperchromasia, hepatocytes	SHAM_DT8	8	1,13	0,44	4
liver, parenchyma, mono-nuclear inflammatory cells	3R4F_CONT_DT1	8	0,38	0,18	3
liver, parenchyma, mono-nuclear inflammatory cells	3R4F_CONT_DT2	8	0,75	0,16	6
liver, parenchyma, mono-nuclear inflammatory cells	3R4F_CONT_DT3	8	1,38	0,18	8
liver, parenchyma, mono-nuclear inflammatory cells	3R4F_CONT_DT6	8	0,50	0,27	3
liver, parenchyma, mono-nuclear inflammatory cells	3R4F_CONT_DT8	8	0,38	0,26	2
liver, parenchyma, mono-nuclear inflammatory cells	Cessation_DT3	8	1,13	0,30	6
liver, parenchyma, mono-nuclear inflammatory cells	Cessation_DT6	8	0,63	0,18	5
liver, parenchyma, mono-nuclear inflammatory cells	Cessation_DT8	8	0,38	0,26	2
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_CONT_DT1	8	1,00	0,19	7
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_CONT_DT2	8	0,88	0,13	7
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_CONT_DT3	8	1,00	0,19	7
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_CONT_DT6	8	0,75	0,16	6
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_CONT_DT8	8	0,25	0,16	2
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_Switch_DT3	8	1,00	0,19	7
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_Switch_DT6	8	0,63	0,18	5
liver, parenchyma, mono-nuclear inflammatory cells	THS 2.2_Switch_DT8	8	0,25	0,16	2
liver, parenchyma, mono-nuclear inflammatory cells	SHAM_DT1	8	0,88	0,13	7
liver, parenchyma, mono-nuclear inflammatory cells	SHAM_DT2	8	0,88	0,13	7
liver, parenchyma, mono-nuclear inflammatory cells	SHAM_DT3	8	0,75	0,25	5
liver, parenchyma, mono-nuclear inflammatory cells	SHAM_DT6	8	0,88	0,23	6
liver, parenchyma, mono-nuclear inflammatory cells	SHAM_DT8	8	0,38	0,18	3

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 34 cont. liver, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
liver, parenchyma, neutrophlic granulocytes	3R4F_CONT_DT1	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	3R4F_CONT_DT2	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	3R4F_CONT_DT3	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	3R4F_CONT_DT6	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	3R4F_CONT_DT8	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	Cessation_DT3	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	Cessation_DT6	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	Cessation_DT8	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_CONT_DT1	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_CONT_DT2	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_CONT_DT3	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_CONT_DT6	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_CONT_DT8	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_Switch_DT3	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_Switch_DT6	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	THS 2.2_Switch_DT8	8	0,13	0,13	1
liver, parenchyma, neutrophlic granulocytes	SHAM_DT1	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	SHAM_DT2	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	SHAM_DT3	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	SHAM_DT6	8	0,00	0,00	0
liver, parenchyma, neutrophlic granulocytes	SHAM_DT8	8	0,00	0,00	0
liver, parenchyma, hemorrhage	3R4F_CONT_DT1	8	0,38	0,38	1
liver, parenchyma, hemorrhage	3R4F_CONT_DT2	8	0,00	0,00	0
liver, parenchyma, hemorrhage	3R4F_CONT_DT3	8	0,00	0,00	0
liver, parenchyma, hemorrhage	3R4F_CONT_DT6	8	0,00	0,00	0
liver, parenchyma, hemorrhage	3R4F_CONT_DT8	8	0,00	0,00	0
liver, parenchyma, hemorrhage	Cessation_DT3	8	0,00	0,00	0
liver, parenchyma, hemorrhage	Cessation_DT6	8	0,00	0,00	0
liver, parenchyma, hemorrhage	Cessation_DT8	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_CONT_DT1	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_CONT_DT2	8	0,13	0,13	1
liver, parenchyma, hemorrhage	THS 2.2_CONT_DT3	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_CONT_DT6	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_CONT_DT8	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_Switch_DT3	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_Switch_DT6	8	0,00	0,00	0
liver, parenchyma, hemorrhage	THS 2.2_Switch_DT8	8	0,00	0,00	0
liver, parenchyma, hemorrhage	SHAM_DT1	8	0,00	0,00	0
liver, parenchyma, hemorrhage	SHAM_DT2	8	0,00	0,00	0
liver, parenchyma, hemorrhage	SHAM_DT3	8	0,00	0,00	0
liver, parenchyma, hemorrhage	SHAM_DT6	8	0,38	0,38	1
liver, parenchyma, hemorrhage	SHAM_DT8	8	0,25	0,25	1
liver, parenchyma, degeneration/necrosis, hepatocytes	3R4F_CONT_DT1	8	0,75	0,25	5
liver, parenchyma, degeneration/necrosis, hepatocytes	3R4F_CONT_DT2	8	0,50	0,19	4
liver, parenchyma, degeneration/necrosis, hepatocytes	3R4F_CONT_DT3	8	0,88	0,13	7
liver, parenchyma, degeneration/necrosis, hepatocytes	3R4F_CONT_DT6	8	0,88	0,35	4
liver, parenchyma, degeneration/necrosis, hepatocytes	3R4F_CONT_DT8	8	0,88	0,35	4
liver, parenchyma, degeneration/necrosis, hepatocytes	Cessation_DT3	8	0,75	0,31	4
liver, parenchyma, degeneration/necrosis, hepatocytes	Cessation_DT6	8	1,00	0,38	4
liver, parenchyma, degeneration/necrosis, hepatocytes	Cessation_DT8	8	1,50	0,38	6
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_CONT_DT1	8	0,50	0,19	4
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_CONT_DT2	8	1,00	0,27	6
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_CONT_DT3	8	0,75	0,37	3
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_CONT_DT6	8	1,00	0,33	5
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_CONT_DT8	8	1,25	0,41	5
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_Switch_DT3	8	0,25	0,25	1
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_Switch_DT6	8	0,75	0,31	4
liver, parenchyma, degeneration/necrosis, hepatocytes	THS 2.2_Switch_DT8	8	0,88	0,44	3
liver, parenchyma, degeneration/necrosis, hepatocytes	SHAM_DT1	8	0,50	0,27	3
liver, parenchyma, degeneration/necrosis, hepatocytes	SHAM_DT2	8	0,88	0,23	6
liver, parenchyma, degeneration/necrosis, hepatocytes	SHAM_DT3	8	0,63	0,38	3
liver, parenchyma, degeneration/necrosis, hepatocytes	SHAM_DT6	8	1,25	0,31	6
liver, parenchyma, degeneration/necrosis, hepatocytes	SHAM_DT8	8	1,75	0,41	6

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 34 cont. liver, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
liver, periportal/interstitial, mono-nuclear inflammatory cells	3R4F_CONT_DT1	8	1,00	0,27	6
liver, periportal/interstitial, mono-nuclear inflammatory cells	3R4F_CONT_DT2	8	1,63	0,18	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	3R4F_CONT_DT3	8	1,13	0,30	6
liver, periportal/interstitial, mono-nuclear inflammatory cells	3R4F_CONT_DT6	8	1,63	0,26	7
liver, periportal/interstitial, mono-nuclear inflammatory cells	3R4F_CONT_DT8	8	2,38	0,18	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	Cessation_DT3	8	0,88	0,23	6
liver, periportal/interstitial, mono-nuclear inflammatory cells	Cessation_DT6	8	2,00	0,19	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	Cessation_DT8	8	2,38	0,18	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_CONT_DT1	8	1,13	0,23	7
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_CONT_DT2	8	1,63	0,18	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_CONT_DT3	8	1,13	0,23	7
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_CONT_DT6	8	2,13	0,23	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_CONT_DT8	8	2,63	0,46	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_Switch_DT3	8	1,50	0,27	7
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_Switch_DT6	8	2,00	0,19	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	THS 2.2_Switch_DT8	8	2,63	0,26	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	SHAM_DT1	8	1,00	0,27	6
liver, periportal/interstitial, mono-nuclear inflammatory cells	SHAM_DT2	8	1,50	0,27	7
liver, periportal/interstitial, mono-nuclear inflammatory cells	SHAM_DT3	8	1,00	0,38	5
liver, periportal/interstitial, mono-nuclear inflammatory cells	SHAM_DT6	8	1,50	0,19	8
liver, periportal/interstitial, mono-nuclear inflammatory cells	SHAM_DT8	8	2,63	0,38	8
liver, periportal/interstitial, bile duct hyperplasia	3R4F_CONT_DT1	8	0,63	0,32	3
liver, periportal/interstitial, bile duct hyperplasia	3R4F_CONT_DT2	8	0,63	0,18	5
liver, periportal/interstitial, bile duct hyperplasia	3R4F_CONT_DT3	8	1,00	0,38	4
liver, periportal/interstitial, bile duct hyperplasia	3R4F_CONT_DT6	8	1,63	0,18	8
liver, periportal/interstitial, bile duct hyperplasia	3R4F_CONT_DT8	8	1,88	0,13	8
liver, periportal/interstitial, bile duct hyperplasia	Cessation_DT3	8	0,50	0,27	3
liver, periportal/interstitial, bile duct hyperplasia	Cessation_DT6	8	1,25	0,25	7
liver, periportal/interstitial, bile duct hyperplasia	Cessation_DT8	8	1,63	0,18	8
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_CONT_DT1	8	0,38	0,18	3
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_CONT_DT2	8	0,88	0,30	5
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_CONT_DT3	8	0,63	0,32	3
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_CONT_DT6	8	1,88	0,35	7
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_CONT_DT8	8	1,63	0,18	8
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_Switch_DT3	8	1,13	0,35	5
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_Switch_DT6	8	1,38	0,32	7
liver, periportal/interstitial, bile duct hyperplasia	THS 2.2_Switch_DT8	8	2,25	0,16	8
liver, periportal/interstitial, bile duct hyperplasia	SHAM_DT1	8	0,50	0,27	3
liver, periportal/interstitial, bile duct hyperplasia	SHAM_DT2	8	0,50	0,19	4
liver, periportal/interstitial, bile duct hyperplasia	SHAM_DT3	8	0,63	0,32	3
liver, periportal/interstitial, bile duct hyperplasia	SHAM_DT6	8	1,00	0,27	6
liver, periportal/interstitial, bile duct hyperplasia	SHAM_DT8	8	1,88	0,23	8
liver, periportal/interstitial, increase of collagen fibers	3R4F_CONT_DT1	8	0,88	0,35	4
liver, periportal/interstitial, increase of collagen fibers	3R4F_CONT_DT2	8	1,38	0,26	7
liver, periportal/interstitial, increase of collagen fibers	3R4F_CONT_DT3	8	0,63	0,26	4
liver, periportal/interstitial, increase of collagen fibers	3R4F_CONT_DT6	8	2,00	0,19	8
liver, periportal/interstitial, increase of collagen fibers	3R4F_CONT_DT8	8	2,38	0,26	8
liver, periportal/interstitial, increase of collagen fibers	Cessation_DT3	8	0,88	0,30	5
liver, periportal/interstitial, increase of collagen fibers	Cessation_DT6	8	1,88	0,13	8
liver, periportal/interstitial, increase of collagen fibers	Cessation_DT8	8	2,38	0,18	8
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_CONT_DT1	8	0,75	0,31	4
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_CONT_DT2	8	1,50	0,19	8
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_CONT_DT3	8	0,25	0,16	2
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_CONT_DT6	8	2,00	0,19	8
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_CONT_DT8	8	2,25	0,16	8
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_Switch_DT3	8	0,88	0,30	5
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_Switch_DT6	8	1,63	0,26	8
liver, periportal/interstitial, increase of collagen fibers	THS 2.2_Switch_DT8	8	2,38	0,26	8
liver, periportal/interstitial, increase of collagen fibers	SHAM_DT1	8	0,88	0,40	4
liver, periportal/interstitial, increase of collagen fibers	SHAM_DT2	8	0,88	0,30	5
liver, periportal/interstitial, increase of collagen fibers	SHAM_DT3	8	0,63	0,26	4
liver, periportal/interstitial, increase of collagen fibers	SHAM_DT6	8	1,38	0,18	8
liver, periportal/interstitial, increase of collagen fibers	SHAM_DT8	8	2,25	0,25	8

N: number of valid animals per group Mean: mean value SEM: standard error of the mean
Incidence: number of animals with finding (≠ score 0) per group

Table 34 cont. liver, findings without statistical significance (N, Mean, SEM, Incidence)

FINDING_TEXT	SHORTNAME	N	Mean	SEM	Incidence
liver, periportal/interstitial, brownish pigment	3R4F_CONT_DT1	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	3R4F_CONT_DT2	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	3R4F_CONT_DT3	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	3R4F_CONT_DT6	8	0,25	0,16	2
liver, periportal/interstitial, brownish pigment	3R4F_CONT_DT8	8	0,75	0,31	4
liver, periportal/interstitial, brownish pigment	Cessation_DT3	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	Cessation_DT6	8	0,25	0,16	2
liver, periportal/interstitial, brownish pigment	Cessation_DT8	8	0,63	0,26	4
liver, periportal/interstitial, brownish pigment	THS 2.2_CONT_DT1	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	THS 2.2_CONT_DT2	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	THS 2.2_CONT_DT3	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	THS 2.2_CONT_DT6	8	0,38	0,26	2
liver, periportal/interstitial, brownish pigment	THS 2.2_CONT_DT8	8	0,25	0,16	2
liver, periportal/interstitial, brownish pigment	THS 2.2_Switch_DT3	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	THS 2.2_Switch_DT6	8	0,13	0,13	1
liver, periportal/interstitial, brownish pigment	THS 2.2_Switch_DT8	8	0,25	0,16	2
liver, periportal/interstitial, brownish pigment	SHAM_DT1	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	SHAM_DT2	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	SHAM_DT3	8	0,00	0,00	0
liver, periportal/interstitial, brownish pigment	SHAM_DT6	8	0,25	0,25	1
liver, periportal/interstitial, brownish pigment	SHAM_DT8	8	0,63	0,42	2

STATISTICAL DATA, COMPARISON BETWEEN DIFFERENT DISSECTION TIME POINTS

In the following tables, data of the statistical comparison between the different dissection time points (Tukey layout) are shown for the SHAM, 3R4F_CONT, and the THS_2.2 groups. The group comparison is reported for all findings with statistically significant effects after exposure to MSS from the 3R4F or aerosol from the THS 2.2 (see **Statistics**).

Table 35 Nose, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
nose level 1, respiratory epithelium, degeneration/atrophy	3R4F	DT1		0,972618	0,850387	0,368883	0,789517	DT1		=	=	=	=
nose level 1, respiratory epithelium, degeneration/atrophy	3R4F	DT2	0,972618		0,992492	0,738983	0,984888	DT2	=		=	=	=
nose level 1, respiratory epithelium, degeneration/atrophy	3R4F	DT3	0,850387	0,992492		0,950782	0,999997	DT3	=	=		=	=
nose level 1, respiratory epithelium, degeneration/atrophy	3R4F	DT6	0,368883	0,738983	0,950782		0,954984	DT6	=	=	=		=
nose level 1, respiratory epithelium, degeneration/atrophy	3R4F	DT8	0,789517	0,984888	0,999997	0,954984		DT8	=	=	=	=	
nose level 1, respiratory epithelium, degeneration/atrophy	THS 2.2	DT1		0,980216	1	0,948662	0,948662	DT1		=	=	=	=
nose level 1, respiratory epithelium, degeneration/atrophy	THS 2.2	DT2	0,980216		0,980216	0,999881	0,999881	DT2	=		=	=	=
nose level 1, respiratory epithelium, degeneration/atrophy	THS 2.2	DT3	1	0,980216		0,948662	0,948662	DT3	=	=		=	=
nose level 1, respiratory epithelium, degeneration/atrophy	THS 2.2	DT6	0,948662	0,999881	0,948662		1	DT6	=	=	=		=
nose level 1, respiratory epithelium, degeneration/atrophy	THS 2.2	DT8	0,948662	0,999881	0,948662	1		DT8	=	=	=	=	
nose level 1, respiratory epithelium, degeneration/atrophy	SHAM	DT1		1	0,9469	0,994487	0,690352	DT1		=	=	=	=
nose level 1, respiratory epithelium, degeneration/atrophy	SHAM	DT2	1		0,941688	0,993917	0,670983	DT2	=		=	=	=
nose level 1, respiratory epithelium, degeneration/atrophy	SHAM	DT3	0,9469	0,941688		0,997432	0,262158	DT3	=	=		=	=
nose level 1, respiratory epithelium, degeneration/atrophy	SHAM	DT6	0,994487	0,993917	0,997432		0,451058	DT6	=	=	=		=
nose level 1, respiratory epithelium, degeneration/atrophy	SHAM	DT8	0,690352	0,670983	0,262158	0,451058		DT8	=	=	=	=	
nose level 1, respiratory epithelium, vacuolisation	3R4F	DT1		0,951196	0,80268	0,951196	0,951196	DT1		=	=	=	=
nose level 1, respiratory epithelium, vacuolisation	3R4F	DT2	0,951196		0,396653	0,608294	1	DT2	=		=	=	=
nose level 1, respiratory epithelium, vacuolisation	3R4F	DT3	0,80268	0,396653		0,992712	0,396653	DT3	=	=		=	=
nose level 1, respiratory epithelium, vacuolisation	3R4F	DT6	0,951196	0,608294	0,992712		0,608294	DT6	=	=	=		=
nose level 1, respiratory epithelium, vacuolisation	3R4F	DT8	0,951196	1	0,396653	0,608294		DT8	=	=	=	=	
nose level 1, respiratory epithelium, vacuolisation	THS 2.2	DT1		0,98467	0,449741	0,40145	0,590481	DT1		=	=	=	=
nose level 1, respiratory epithelium, vacuolisation	THS 2.2	DT2	0,98467		0,210907	0,181492	0,308529	DT2	=		=	=	=
nose level 1, respiratory epithelium, vacuolisation	THS 2.2	DT3	0,449741	0,210907		0,999989	0,999389	DT3	=	=		=	=
nose level 1, respiratory epithelium, vacuolisation	THS 2.2	DT6	0,40145	0,181492	0,999989		0,997933	DT6	=	=	=		=
nose level 1, respiratory epithelium, vacuolisation	THS 2.2	DT8	0,590481	0,308529	0,999389	0,997933		DT8	=	=	=	=	
nose level 1, respiratory epithelium, vacuolisation	SHAM	DT1		0,999992	0,897009	0,330652	0,276442	DT1		=	=	=	=
nose level 1, respiratory epithelium, vacuolisation	SHAM	DT2	0,999992		0,916343	0,345149	0,288117	DT2	=		=	=	=
nose level 1, respiratory epithelium, vacuolisation	SHAM	DT3	0,897009	0,916343		0,826124	0,766673	DT3	=	=		=	=
nose level 1, respiratory epithelium, vacuolisation	SHAM	DT6	0,330652	0,345149	0,826124		0,999965	DT6	=	=	=		=
nose level 1, respiratory epithelium, vacuolisation	SHAM	DT8	0,276442	0,288117	0,766673	0,999965		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 35 cont **Nose, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
nose level 1, respiratory epithelium, reserve cell hyperplasia	3R4F	DT1		0,679659	0,002371	1,11E-05	2,64E-07	DT1		=	++	+++	+++
nose level 1, respiratory epithelium, reserve cell hyperplasia	3R4F	DT2	0,679659		0,066533	0,000788	2,14E-05	DT2	=		=	+++	+++
nose level 1, respiratory epithelium, reserve cell hyperplasia	3R4F	DT3	0,002371	0,066533		0,655268	0,129495	DT3	++	=		=	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	3R4F	DT6	1,11E-05	0,000788	0,655268		0,793489	DT6	+++	+++	=		=
nose level 1, respiratory epithelium, reserve cell hyperplasia	3R4F	DT8	2,64E-07	2,14E-05	0,129495	0,793489		DT8	+++	+++	=	=	
nose level 1, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT1		0,978332	0,082945	0,041661	0,154272	DT1		=	=	+	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT2	0,978332		0,291269	0,174581	0,446541	DT2	=		=	=	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT3	0,082945	0,291269		0,99831	0,99831	DT3	=	=		=	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT6	0,041661	0,174581	0,99831		0,976229	DT6	+	=	=		=
nose level 1, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT8	0,154272	0,446541	0,99831	0,976229		DT8	=	=	=	=	
nose level 1, respiratory epithelium, reserve cell hyperplasia	SHAM	DT1		0,816665	0,972818	0,890005	0,680839	DT1		=	=	=	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	SHAM	DT2	0,816665		0,425431	0,999908	0,136929	DT2	=		=	=	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	SHAM	DT3	0,972818	0,425431		0,539042	0,940094	DT3	=	=		=	=
nose level 1, respiratory epithelium, reserve cell hyperplasia	SHAM	DT6	0,890005	0,999908	0,539042		0,197958	DT6	=	=	=		=
nose level 1, respiratory epithelium, reserve cell hyperplasia	SHAM	DT8	0,680839	0,136929	0,940094	0,197958		DT8	=	=	=	=	
nose level 1, respiratory epithelium, squamous epithelial metaplasia	3R4F	DT1		0,911217	0,23503	0,000276	3,53E-07	DT1		=	=	+++	+++
nose level 1, respiratory epithelium, squamous epithelial metaplasia	3R4F	DT2	0,911217		0,691386	0,00378	6,12E-06	DT2	=		=	++	+++
nose level 1, respiratory epithelium, squamous epithelial metaplasia	3R4F	DT3	0,23503	0,691386		0,167155	0,001191	DT3	=	=		=	++
nose level 1, respiratory epithelium, squamous epithelial metaplasia	3R4F	DT6	0,000276	0,00378	0,167155		0,272698	DT6	+++	++	=		=
nose level 1, respiratory epithelium, squamous epithelial metaplasia	3R4F	DT8	3,53E-07	6,12E-06	0,001191	0,272698		DT8	+++	+++	++	=	
nose level 1, respiratory epithelium, squamous epithelial metaplasia	THS 2.2	DT1		0	0	0	0	DT1					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	THS 2.2	DT2	0		0	0	0	DT2					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	THS 2.2	DT3	0	0		0	0	DT3					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	THS 2.2	DT6	0	0	0		0	DT6					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	THS 2.2	DT8	0	0	0	0		DT8					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	SHAM	DT1		0	0	0	0	DT1					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	SHAM	DT2	0		0	0	0	DT2					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	SHAM	DT3	0	0		0	0	DT3					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	SHAM	DT6	0	0	0		0	DT6					
nose level 1, respiratory epithelium, squamous epithelial metaplasia	SHAM	DT8	0	0	0	0		DT8					

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 35 cont **Nose, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
nose level 2, respiratory epithelium, vacuolisation	3R4F	DT1		0,99197	0,998247	0,216945	1	DT1		=	=	=	=
nose level 2, respiratory epithelium, vacuolisation	3R4F	DT2	0,99197		0,999969	0,407619	0,99197	DT2	=		=	=	=
nose level 2, respiratory epithelium, vacuolisation	3R4F	DT3	0,998247	0,999969		0,440615	0,998247	DT3	=	=		=	=
nose level 2, respiratory epithelium, vacuolisation	3R4F	DT6	0,216945	0,407619	0,440615		0,216945	DT6	=	=	=		=
nose level 2, respiratory epithelium, vacuolisation	3R4F	DT8	1	0,99197	0,998247	0,216945		DT8	=	=	=	=	
nose level 2, respiratory epithelium, vacuolisation	THS 2.2	DT1		0,976218	0,978584	0,142721	0,001584	DT1		=	=	=	++
nose level 2, respiratory epithelium, vacuolisation	THS 2.2	DT2	0,976218		1	0,02933	0,000158	DT2	=		=	+	+++
nose level 2, respiratory epithelium, vacuolisation	THS 2.2	DT3	0,978584	1		0,03723	0,000254	DT3	=	=		+	+++
nose level 2, respiratory epithelium, vacuolisation	THS 2.2	DT6	0,142721	0,02933	0,03723		0,35361	DT6	=	+	+		=
nose level 2, respiratory epithelium, vacuolisation	THS 2.2	DT8	0,001584	0,000158	0,000254	0,35361		DT8	++	+++	+++	=	
nose level 2, respiratory epithelium, vacuolisation	SHAM	DT1		0,675636	0,971052	0,700387	0,000345	DT1		=	=	=	+++
nose level 2, respiratory epithelium, vacuolisation	SHAM	DT2	0,675636		0,969008	1	0,016814	DT2	=		=	=	+
nose level 2, respiratory epithelium, vacuolisation	SHAM	DT3	0,971052	0,969008		0,972443	0,004939	DT3	=	=		=	++
nose level 2, respiratory epithelium, vacuolisation	SHAM	DT6	0,700387	1	0,972443		0,020859	DT6	=	=	=		+
nose level 2, respiratory epithelium, vacuolisation	SHAM	DT8	0,000345	0,016814	0,004939	0,020859		DT8	+++	+	++	+	
nose level 2, respiratory epithelium, reserve cell hyperplasia	3R4F	DT1		1	0,25046	1	4E-06	DT1		=	=	=	+++
nose level 2, respiratory epithelium, reserve cell hyperplasia	3R4F	DT2	1		0,230729	1	2,41E-06	DT2	=		=	=	+++
nose level 2, respiratory epithelium, reserve cell hyperplasia	3R4F	DT3	0,25046	0,230729		0,230729	0,007853	DT3	=	=		=	++
nose level 2, respiratory epithelium, reserve cell hyperplasia	3R4F	DT6	1	1	0,230729		2,41E-06	DT6	=	=	=		+++
nose level 2, respiratory epithelium, reserve cell hyperplasia	3R4F	DT8	4E-06	2,41E-06	0,007853	2,41E-06		DT8	+++	+++	++	+++	
nose level 2, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT1		0	0	0	0	DT1					
nose level 2, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT2	0		0	0	0	DT2					
nose level 2, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT3	0	0		0	0	DT3					
nose level 2, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT6	0	0	0		0	DT6					
nose level 2, respiratory epithelium, reserve cell hyperplasia	THS 2.2	DT8	0	0	0	0		DT8					
nose level 2, respiratory epithelium, reserve cell hyperplasia	SHAM	DT1		0	0	0	0	DT1					
nose level 2, respiratory epithelium, reserve cell hyperplasia	SHAM	DT2	0		0	0	0	DT2					
nose level 2, respiratory epithelium, reserve cell hyperplasia	SHAM	DT3	0	0		0	0	DT3					
nose level 2, respiratory epithelium, reserve cell hyperplasia	SHAM	DT6	0	0	0		0	DT6					
nose level 2, respiratory epithelium, reserve cell hyperplasia	SHAM	DT8	0	0	0	0		DT8					

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 35 cont **Nose, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
nose level 2, olfactory epithelium, vacuolisation	3R4F	DT1		1	0,44364	1	1	DT1		=	=	=	=
nose level 2, olfactory epithelium, vacuolisation	3R4F	DT2	1		0,44364	1	1	DT2	=		=	=	=
nose level 2, olfactory epithelium, vacuolisation	3R4F	DT3	0,44364	0,44364		0,44364	0,44364	DT3	=	=		=	=
nose level 2, olfactory epithelium, vacuolisation	3R4F	DT6	1	1	0,44364		1	DT6	=	=	=		=
nose level 2, olfactory epithelium, vacuolisation	3R4F	DT8	1	1	0,44364	1		DT8	=	=	=	=	
nose level 2, olfactory epithelium, vacuolisation	THS 2.2	DT1		0,648654	0,221056	0,958561	1	DT1		=	=	=	=
nose level 2, olfactory epithelium, vacuolisation	THS 2.2	DT2	0,648654		0,937977	0,958561	0,648654	DT2	=		=	=	=
nose level 2, olfactory epithelium, vacuolisation	THS 2.2	DT3	0,221056	0,937977		0,595981	0,221056	DT3	=	=		=	=
nose level 2, olfactory epithelium, vacuolisation	THS 2.2	DT6	0,958561	0,958561	0,595981		0,958561	DT6	=	=	=		=
nose level 2, olfactory epithelium, vacuolisation	THS 2.2	DT8	1	0,648654	0,221056	0,958561		DT8	=	=	=	=	
nose level 2, olfactory epithelium, vacuolisation	SHAM	DT1		1	1	1	0,528092	DT1		=	=	=	=
nose level 2, olfactory epithelium, vacuolisation	SHAM	DT2	1		1	1	0,528092	DT2	=		=	=	=
nose level 2, olfactory epithelium, vacuolisation	SHAM	DT3	1	1		1	0,528092	DT3	=	=		=	=
nose level 2, olfactory epithelium, vacuolisation	SHAM	DT6	1	1	1		0,554258	DT6	=	=	=		=
nose level 2, olfactory epithelium, vacuolisation	SHAM	DT8	0,528092	0,528092	0,528092	0,554258		DT8	=	=	=	=	
nose level 2, olfactory epithelium, atrophy	3R4F	DT1		1	1	0,770112	1,56E-10	DT1		=	=	=	+++
nose level 2, olfactory epithelium, atrophy	3R4F	DT2	1		1	0,770112	1,56E-10	DT2	=		=	=	+++
nose level 2, olfactory epithelium, atrophy	3R4F	DT3	1	1		0,787019	3,14E-10	DT3	=	=		=	+++
nose level 2, olfactory epithelium, atrophy	3R4F	DT6	0,770112	0,770112	0,787019		6,08E-09	DT6	=	=	=		+++
nose level 2, olfactory epithelium, atrophy	3R4F	DT8	1,56E-10	1,56E-10	3,14E-10	6,08E-09		DT8	+++	+++	+++	+++	
nose level 2, olfactory epithelium, atrophy	THS 2.2	DT1		0	0	0	0	DT1					
nose level 2, olfactory epithelium, atrophy	THS 2.2	DT2	0		0	0	0	DT2					
nose level 2, olfactory epithelium, atrophy	THS 2.2	DT3	0	0		0	0	DT3					
nose level 2, olfactory epithelium, atrophy	THS 2.2	DT6	0	0	0		0	DT6					
nose level 2, olfactory epithelium, atrophy	THS 2.2	DT8	0	0	0	0		DT8					
nose level 2, olfactory epithelium, atrophy	SHAM	DT1		0	0	0	0	DT1					
nose level 2, olfactory epithelium, atrophy	SHAM	DT2	0		0	0	0	DT2					
nose level 2, olfactory epithelium, atrophy	SHAM	DT3	0	0		0	0	DT3					
nose level 2, olfactory epithelium, atrophy	SHAM	DT6	0	0	0		0	DT6					
nose level 2, olfactory epithelium, atrophy	SHAM	DT8	0	0	0	0		DT8					

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 35 cont **Nose, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
nose level 4, olfactory epithelium, atrophy	3R4F	DT1		1	0,610072	0,964565	0,002506	DT1		=	=	=	++
nose level 4, olfactory epithelium, atrophy	3R4F	DT2	1		0,610072	0,964565	0,002506	DT2	=		=	=	++
nose level 4, olfactory epithelium, atrophy	3R4F	DT3	0,610072	0,610072		0,935992	0,107649	DT3	=	=		=	=
nose level 4, olfactory epithelium, atrophy	3R4F	DT6	0,964565	0,964565	0,935992		0,016286	DT6	=	=	=		+
nose level 4, olfactory epithelium, atrophy	3R4F	DT8	0,002506	0,002506	0,107649	0,016286		DT8	++	++	=	+	
nose level 4, olfactory epithelium, atrophy	THS 2.2	DT1		0	0	0	0	DT1					
nose level 4, olfactory epithelium, atrophy	THS 2.2	DT2	0		0	0	0	DT2					
nose level 4, olfactory epithelium, atrophy	THS 2.2	DT3	0	0		0	0	DT3					
nose level 4, olfactory epithelium, atrophy	THS 2.2	DT6	0	0	0		0	DT6					
nose level 4, olfactory epithelium, atrophy	THS 2.2	DT8	0	0	0	0		DT8					
nose level 4, olfactory epithelium, atrophy	SHAM	DT1		0	0	0	0	DT1					
nose level 4, olfactory epithelium, atrophy	SHAM	DT2	0		0	0	0	DT2					
nose level 4, olfactory epithelium, atrophy	SHAM	DT3	0	0		0	0	DT3					
nose level 4, olfactory epithelium, atrophy	SHAM	DT6	0	0	0		0	DT6					
nose level 4, olfactory epithelium, atrophy	SHAM	DT8	0	0	0	0		DT8					
nose level 4, olfactory epithelium, vacuolisation	3R4F	DT1		0,7050	0,006816	0,063152	0,095745	DT1		=	++	=	=
nose level 4, olfactory epithelium, vacuolisation	3R4F	DT2	0,70499		0,158614	0,590898	0,70499	DT2	=		=	=	=
nose level 4, olfactory epithelium, vacuolisation	3R4F	DT3	0,006816	0,158614		0,912295	0,836813	DT3	++	=		=	=
nose level 4, olfactory epithelium, vacuolisation	3R4F	DT6	0,063152	0,590898	0,912295		0,999733	DT6	=	=	=		=
nose level 4, olfactory epithelium, vacuolisation	3R4F	DT8	0,095745	0,70499	0,836813	0,999733		DT8	=	=	=	=	
nose level 4, olfactory epithelium, vacuolisation	THS 2.2	DT1		0,788518	0,737659	0,42739	0,263547	DT1		=	=	=	=
nose level 4, olfactory epithelium, vacuolisation	THS 2.2	DT2	0,788518		0,999997	0,97909	0,902296	DT2	=		=	=	=
nose level 4, olfactory epithelium, vacuolisation	THS 2.2	DT3	0,737659	0,999997		0,984946	0,916027	DT3	=	=		=	=
nose level 4, olfactory epithelium, vacuolisation	THS 2.2	DT6	0,42739	0,97909	0,984946		0,997573	DT6	=	=	=		=
nose level 4, olfactory epithelium, vacuolisation	THS 2.2	DT8	0,263547	0,902296	0,916027	0,997573		DT8	=	=	=	=	
nose level 4, olfactory epithelium, vacuolisation	SHAM	DT1		0,988829	0,427245	0,248986	0,00171	DT1		=	=	=	++
nose level 4, olfactory epithelium, vacuolisation	SHAM	DT2	0,988829		0,722755	0,500267	0,006994	DT2	=		=	=	++
nose level 4, olfactory epithelium, vacuolisation	SHAM	DT3	0,427245	0,722755		0,99482	0,150948	DT3	=	=		=	=
nose level 4, olfactory epithelium, vacuolisation	SHAM	DT6	0,248986	0,500267	0,99482		0,338687	DT6	=	=	=		=
nose level 4, olfactory epithelium, vacuolisation	SHAM	DT8	0,00171	0,006994	0,150948	0,338687		DT8	++	++	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 36 Lung, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
left lung, bronchi, reserve cell hyperplasia	3R4F	DT1		0,914767	0,116238	0,090449	0,330132	DT1		=	=	=	=
left lung, bronchi, reserve cell hyperplasia	3R4F	DT2	0,914767		0,531057	0,461228	0,850184	DT2	=		=	=	=
left lung, bronchi, reserve cell hyperplasia	3R4F	DT3	0,116238	0,531057		0,999957	0,979356	DT3	=	=		=	=
left lung, bronchi, reserve cell hyperplasia	3R4F	DT6	0,090449	0,461228	0,999957		0,959337	DT6	=	=	=		=
left lung, bronchi, reserve cell hyperplasia	3R4F	DT8	0,330132	0,850184	0,979356	0,959337		DT8	=	=	=	=	
left lung, bronchi, reserve cell hyperplasia	THS 2.2	DT1		0,389564	0,146476	0,007204	0,007204	DT1		=	=	++	++
left lung, bronchi, reserve cell hyperplasia	THS 2.2	DT2	0,389564		0,979821	0,396337	0,396337	DT2	=		=	=	=
left lung, bronchi, reserve cell hyperplasia	THS 2.2	DT3	0,146476	0,979821		0,739881	0,739881	DT3	=	=		=	=
left lung, bronchi, reserve cell hyperplasia	THS 2.2	DT6	0,007204	0,396337	0,739881		1	DT6	++	=	=		=
left lung, bronchi, reserve cell hyperplasia	THS 2.2	DT8	0,007204	0,396337	0,739881	1		DT8	++	=	=	=	
left lung, bronchi, reserve cell hyperplasia	SHAM	DT1		0,933784	0,377716	0,050691	0,272762	DT1		=	=	=	=
left lung, bronchi, reserve cell hyperplasia	SHAM	DT2	0,933784		0,839133	0,238063	0,729219	DT2	=		=	=	=
left lung, bronchi, reserve cell hyperplasia	SHAM	DT3	0,377716	0,839133		0,790551	0,999579	DT3	=	=		=	=
left lung, bronchi, reserve cell hyperplasia	SHAM	DT6	0,050691	0,238063	0,790551		0,882029	DT6	=	=	=		=
left lung, bronchi, reserve cell hyperplasia	SHAM	DT8	0,272762	0,729219	0,999579	0,882029		DT8	=	=	=	=	
left lung, bronchi, main bronchus, goblet cell hyperplasia	3R4F	DT1		0,829907	0,999998	0,745171	0,10431	DT1		=	=	=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	3R4F	DT2	0,829907		0,788573	0,999688	0,56133	DT2	=		=	=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	3R4F	DT3	0,999998	0,788573		0,697214	0,08152	DT3	=	=		=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	3R4F	DT6	0,745171	0,999688	0,697214		0,702784	DT6	=	=	=		=
left lung, bronchi, main bronchus, goblet cell hyperplasia	3R4F	DT8	0,10431	0,56133	0,08152	0,702784		DT8	=	=	=	=	
left lung, bronchi, main bronchus, goblet cell hyperplasia	THS 2.2	DT1		0,365965	0,974794	0,756686	0,967723	DT1		=	=	=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	THS 2.2	DT2	0,365965		0,736928	0,962818	0,733332	DT2	=		=	=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	THS 2.2	DT3	0,974794	0,736928		0,977624	1	DT3	=	=		=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	THS 2.2	DT6	0,756686	0,962818	0,977624		0,979222	DT6	=	=	=		=
left lung, bronchi, main bronchus, goblet cell hyperplasia	THS 2.2	DT8	0,967723	0,733332	1	0,979222		DT8	=	=	=	=	
left lung, bronchi, main bronchus, goblet cell hyperplasia	SHAM	DT1		0,456212	0,866342	0,826765	0,979905	DT1		=	=	=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	SHAM	DT2	0,456212		0,129184	0,081804	0,794191	DT2	=		=	=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	SHAM	DT3	0,866342	0,129184		1	0,595619	DT3	=	=		=	=
left lung, bronchi, main bronchus, goblet cell hyperplasia	SHAM	DT6	0,826765	0,081804	1		0,51484	DT6	=	=	=		=
left lung, bronchi, main bronchus, goblet cell hyperplasia	SHAM	DT8	0,979905	0,794191	0,595619	0,51484		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 36 cont **Lung, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
left lung, alveoli, epithelium, emphysema	3R4F	DT1		0,311999	0,0002	4,5E-08	3,72E-10	DT1		=	+++	+++	+++
left lung, alveoli, epithelium, emphysema	3R4F	DT2	0,311999		0,071791	5,79E-05	4,78E-07	DT2	=		=	+++	+++
left lung, alveoli, epithelium, emphysema	3R4F	DT3	0,0002	0,071791		0,105481	0,00221	DT3	+++	=		=	++
left lung, alveoli, epithelium, emphysema	3R4F	DT6	4,5E-08	5,79E-05	0,105481		0,586275	DT6	+++	+++	=		=
left lung, alveoli, epithelium, emphysema	3R4F	DT8	3,72E-10	4,78E-07	0,00221	0,586275		DT8	+++	+++	++	=	
left lung, alveoli, epithelium, emphysema	THS 2.2	DT1		0,999989	0,172505	0,00279	0,0001	DT1		=	=	++	+++
left lung, alveoli, epithelium, emphysema	THS 2.2	DT2	0,999989		0,201533	0,003557	0,000131	DT2	=		=	++	+++
left lung, alveoli, epithelium, emphysema	THS 2.2	DT3	0,172505	0,201533		0,487698	0,072486	DT3	=	=		=	=
left lung, alveoli, epithelium, emphysema	THS 2.2	DT6	0,00279	0,003557	0,487698		0,828257	DT6	++	++	=		=
left lung, alveoli, epithelium, emphysema	THS 2.2	DT8	0,0001	0,000131	0,072486	0,828257		DT8	+++	+++	=	=	
left lung, alveoli, epithelium, emphysema	SHAM	DT1		0,291072	0,035302	0,055176	0,000788	DT1		=	+	=	+++
left lung, alveoli, epithelium, emphysema	SHAM	DT2	0,291072		0,851203	0,881602	0,149084	DT2	=		=	=	=
left lung, alveoli, epithelium, emphysema	SHAM	DT3	0,035302	0,851203		1	0,665502	DT3	+	=		=	=
left lung, alveoli, epithelium, emphysema	SHAM	DT6	0,055176	0,881602	1		0,704148	DT6	=	=	=		=
left lung, alveoli, epithelium, emphysema	SHAM	DT8	0,000788	0,149084	0,665502	0,704148		DT8	+++	=	=	=	
left lung, alveoli, epithelium, hypertrophy, hyperplasia	3R4F	DT1		0,446651	0,022397	2,24E-05	1,56E-05	DT1		=	+	+++	+++
left lung, alveoli, epithelium, hypertrophy, hyperplasia	3R4F	DT2	0,446651		0,638807	0,006927	0,004412	DT2	=		=	++	++
left lung, alveoli, epithelium, hypertrophy, hyperplasia	3R4F	DT3	0,022397	0,638807		0,173044	0,116863	DT3	+	=		=	=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	3R4F	DT6	2,24E-05	0,006927	0,173044		0,999022	DT6	+++	++	=		=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	3R4F	DT8	1,56E-05	0,004412	0,116863	0,999022		DT8	+++	++	=	=	
left lung, alveoli, epithelium, hypertrophy, hyperplasia	THS 2.2	DT1		0,753033	0,098257	0,022579	0,022579	DT1		=	=	+	+
left lung, alveoli, epithelium, hypertrophy, hyperplasia	THS 2.2	DT2	0,753033		0,662079	0,301339	0,301339	DT2	=		=	=	=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	THS 2.2	DT3	0,098257	0,662079		0,972583	0,972583	DT3	=	=		=	=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	THS 2.2	DT6	0,022579	0,301339	0,972583		1	DT6	+	=	=		=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	THS 2.2	DT8	0,022579	0,301339	0,972583	1		DT8	+	=	=	=	
left lung, alveoli, epithelium, hypertrophy, hyperplasia	SHAM	DT1		0,775811	0,999977	0,892171	0,542083	DT1		=	=	=	=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	SHAM	DT2	0,775811		0,82716	0,284199	0,070889	DT2	=		=	=	=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	SHAM	DT3	0,999977	0,82716		0,853139	0,480633	DT3	=	=		=	=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	SHAM	DT6	0,892171	0,284199	0,853139		0,981986	DT6	=	=	=		=
left lung, alveoli, epithelium, hypertrophy, hyperplasia	SHAM	DT8	0,542083	0,070889	0,480633	0,981986		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 36 cont **Lung, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
left lung, alveoli, lumen, unpigmented macrophages	3R4F	DT1		0,397303	0,023992	2,37E-05	2,91E-07	DT1		=	+	+++	+++
left lung, alveoli, lumen, unpigmented macrophages	3R4F	DT2	0,397303		0,708373	0,009501	0,0002	DT2	=		=	++	+++
left lung, alveoli, lumen, unpigmented macrophages	3R4F	DT3	0,023992	0,708373		0,174149	0,00727	DT3	+	=		=	++
left lung, alveoli, lumen, unpigmented macrophages	3R4F	DT6	2,37E-05	0,009501	0,174149		0,687359	DT6	+++	++	=		=
left lung, alveoli, lumen, unpigmented macrophages	3R4F	DT8	2,91E-07	0,0002	0,00727	0,687359		DT8	+++	+++	++	=	
left lung, alveoli, lumen, unpigmented macrophages	THS 2.2	DT1		0,984759	0,990554	0,999718	0,532708	DT1		=	=	=	=
left lung, alveoli, lumen, unpigmented macrophages	THS 2.2	DT2	0,984759		0,999996	0,9972	0,83795	DT2	=		=	=	=
left lung, alveoli, lumen, unpigmented macrophages	THS 2.2	DT3	0,990554	0,999996		0,998747	0,807201	DT3	=	=		=	=
left lung, alveoli, lumen, unpigmented macrophages	THS 2.2	DT6	0,999718	0,9972	0,998747		0,650088	DT6	=	=	=		=
left lung, alveoli, lumen, unpigmented macrophages	THS 2.2	DT8	0,532708	0,83795	0,807201	0,650088		DT8	=	=	=	=	
left lung, alveoli, lumen, unpigmented macrophages	SHAM	DT1		0,982937	0,995664	0,692389	0,989486	DT1		=	=	=	=
left lung, alveoli, lumen, unpigmented macrophages	SHAM	DT2	0,982937		0,999836	0,383076	0,849815	DT2	=		=	=	=
left lung, alveoli, lumen, unpigmented macrophages	SHAM	DT3	0,995664	0,999836		0,472826	0,914467	DT3	=	=		=	=
left lung, alveoli, lumen, unpigmented macrophages	SHAM	DT6	0,692389	0,383076	0,472826		0,911365	DT6	=	=	=		=
left lung, alveoli, lumen, unpigmented macrophages	SHAM	DT8	0,989486	0,849815	0,914467	0,911365		DT8	=	=	=	=	
left lung, alveoli, lumen, pigmented macrophages	3R4F	DT1		0,099068	0,04018	9,19E-08	3,62E-11	DT1		=	+	+++	+++
left lung, alveoli, lumen, pigmented macrophages	3R4F	DT2	0,099068		0,997889	0,000783	1,5E-07	DT2	=		=	+++	+++
left lung, alveoli, lumen, pigmented macrophages	3R4F	DT3	0,04018	0,997889		0,001454	2,33E-07	DT3	+	=		++	+++
left lung, alveoli, lumen, pigmented macrophages	3R4F	DT6	9,19E-08	0,000783	0,001454		0,077088	DT6	+++	+++	++		=
left lung, alveoli, lumen, pigmented macrophages	3R4F	DT8	3,62E-11	1,5E-07	2,33E-07	0,077088		DT8	+++	+++	+++	=	
left lung, alveoli, lumen, pigmented macrophages	THS 2.2	DT1		0	0	0	0	DT1					
left lung, alveoli, lumen, pigmented macrophages	THS 2.2	DT2	0		0	0	0	DT2					
left lung, alveoli, lumen, pigmented macrophages	THS 2.2	DT3	0	0		0	0	DT3					
left lung, alveoli, lumen, pigmented macrophages	THS 2.2	DT6	0	0	0		0	DT6					
left lung, alveoli, lumen, pigmented macrophages	THS 2.2	DT8	0	0	0	0		DT8					
left lung, alveoli, lumen, pigmented macrophages	SHAM	DT1		0,356747	0,884714	1	1	DT1		=	=	=	=
left lung, alveoli, lumen, pigmented macrophages	SHAM	DT2	0,356747		0,884714	0,416116	0,356747	DT2	=		=	=	=
left lung, alveoli, lumen, pigmented macrophages	SHAM	DT3	0,884714	0,884714		0,904741	0,884714	DT3	=	=		=	=
left lung, alveoli, lumen, pigmented macrophages	SHAM	DT6	1	0,416116	0,904741		1	DT6	=	=	=		=
left lung, alveoli, lumen, pigmented macrophages	SHAM	DT8	1	0,356747	0,884714	1		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 36 cont **Lung, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
left lung, alveoli, lumen, pigmented macrophage nests	3R4F	DT1		0,01819	0,000108	7,52E-11	2,69E-11	DT1		+	+++	+++	+++
left lung, alveoli, lumen, pigmented macrophage nests	3R4F	DT2	0,01819		0,522871	5,78E-06	6,2E-07	DT2	+		=	+++	+++
left lung, alveoli, lumen, pigmented macrophage nests	3R4F	DT3	0,000108	0,522871		0,000671	7,58E-05	DT3	+++	=		+++	+++
left lung, alveoli, lumen, pigmented macrophage nests	3R4F	DT6	7,52E-11	5,78E-06	0,000671		0,959687	DT6	+++	+++	+++		=
left lung, alveoli, lumen, pigmented macrophage nests	3R4F	DT8	2,69E-11	6,2E-07	7,58E-05	0,959687		DT8	+++	+++	+++	=	
left lung, alveoli, lumen, pigmented macrophage nests	THS 2.2	DT1		0	0	0	0	DT1					
left lung, alveoli, lumen, pigmented macrophage nests	THS 2.2	DT2	0		0	0	0	DT2					
left lung, alveoli, lumen, pigmented macrophage nests	THS 2.2	DT3	0	0		0	0	DT3					
left lung, alveoli, lumen, pigmented macrophage nests	THS 2.2	DT6	0	0	0		0	DT6					
left lung, alveoli, lumen, pigmented macrophage nests	THS 2.2	DT8	0	0	0	0		DT8					
left lung, alveoli, lumen, pigmented macrophage nests	SHAM	DT1		0	0	0	0	DT1					
left lung, alveoli, lumen, pigmented macrophage nests	SHAM	DT2	0		0	0	0	DT2					
left lung, alveoli, lumen, pigmented macrophage nests	SHAM	DT3	0	0		0	0	DT3					
left lung, alveoli, lumen, pigmented macrophage nests	SHAM	DT6	0	0	0		0	DT6					
left lung, alveoli, lumen, pigmented macrophage nests	SHAM	DT8	0	0	0	0		DT8					
left lung, alveoli, lumen, lymphocytes/plasmacells	3R4F	DT1		0,116666	0,222499	5,91E-08	6,8E-07	DT1		=	=	+++	+++
left lung, alveoli, lumen, lymphocytes/plasmacells	3R4F	DT2	0,116666		0,995083	0,000412	0,003573	DT2	=		=	+++	++
left lung, alveoli, lumen, lymphocytes/plasmacells	3R4F	DT3	0,222499	0,995083		7,67E-05	0,000781	DT3	=	=		+++	+++
left lung, alveoli, lumen, lymphocytes/plasmacells	3R4F	DT6	5,91E-08	0,000412	7,67E-05		0,949474	DT6	+++	+++	+++		=
left lung, alveoli, lumen, lymphocytes/plasmacells	3R4F	DT8	6,8E-07	0,003573	0,000781	0,949474		DT8	+++	++	+++	=	
left lung, alveoli, lumen, lymphocytes/plasmacells	THS 2.2	DT1		0,985617	0,969123	0,873379	0,838127	DT1		=	=	=	=
left lung, alveoli, lumen, lymphocytes/plasmacells	THS 2.2	DT2	0,985617		0,999954	0,991805	0,537976	DT2	=		=	=	=
left lung, alveoli, lumen, lymphocytes/plasmacells	THS 2.2	DT3	0,969123	0,999954		0,997536	0,464753	DT3	=	=		=	=
left lung, alveoli, lumen, lymphocytes/plasmacells	THS 2.2	DT6	0,873379	0,991805	0,997536		0,287533	DT6	=	=	=		=
left lung, alveoli, lumen, lymphocytes/plasmacells	THS 2.2	DT8	0,838127	0,537976	0,464753	0,287533		DT8	=	=	=	=	
left lung, alveoli, lumen, lymphocytes/plasmacells	SHAM	DT1		0,987073	0,999756	0,597992	0,989989	DT1		=	=	=	=
left lung, alveoli, lumen, lymphocytes/plasmacells	SHAM	DT2	0,987073		0,997675	0,321225	0,86946	DT2	=		=	=	=
left lung, alveoli, lumen, lymphocytes/plasmacells	SHAM	DT3	0,999756	0,997675		0,491903	0,96653	DT3	=	=		=	=
left lung, alveoli, lumen, lymphocytes/plasmacells	SHAM	DT6	0,597992	0,321225	0,491903		0,847842	DT6	=	=	=		=
left lung, alveoli, lumen, lymphocytes/plasmacells	SHAM	DT8	0,989989	0,86946	0,96653	0,847842		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 36 cont **Lung, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
	Group		p-value						levels of statistical significance				
left lung, alveoli, lumen, neutrophilic granulocytes	3R4F	DT1		0,131338	0,283549	3,19E-05	6,49E-06	DT1		=	=	+++	+++
left lung, alveoli, lumen, neutrophilic granulocytes	3R4F	DT2	0,131338		0,989991	0,060208	0,018856	DT2	=		=	=	+
left lung, alveoli, lumen, neutrophilic granulocytes	3R4F	DT3	0,283549	0,989991		0,014838	0,00387	DT3	=	=		+	++
left lung, alveoli, lumen, neutrophilic granulocytes	3R4F	DT6	3,19E-05	0,060208	0,014838		0,989023	DT6	+++	=	+		=
left lung, alveoli, lumen, neutrophilic granulocytes	3R4F	DT8	6,49E-06	0,018856	0,00387	0,989023		DT8	+++	+	++	=	
left lung, alveoli, lumen, neutrophilic granulocytes	THS 2.2	DT1		1	0,516904	1	1	DT1		=	=	=	=
left lung, alveoli, lumen, neutrophilic granulocytes	THS 2.2	DT2	1		0,516904	1	1	DT2	=		=	=	=
left lung, alveoli, lumen, neutrophilic granulocytes	THS 2.2	DT3	0,516904	0,516904		0,516904	0,516904	DT3	=	=		=	=
left lung, alveoli, lumen, neutrophilic granulocytes	THS 2.2	DT6	1	1	0,516904		1	DT6	=	=	=		=
left lung, alveoli, lumen, neutrophilic granulocytes	THS 2.2	DT8	1	1	0,516904	1		DT8	=	=	=	=	
left lung, alveoli, lumen, neutrophilic granulocytes	SHAM	DT1		1	0,80919	0,839893	0,80919	DT1		=	=	=	=
left lung, alveoli, lumen, neutrophilic granulocytes	SHAM	DT2	1		0,80919	0,839893	0,80919	DT2	=		=	=	=
left lung, alveoli, lumen, neutrophilic granulocytes	SHAM	DT3	0,80919	0,80919		1	1	DT3	=	=		=	=
left lung, alveoli, lumen, neutrophilic granulocytes	SHAM	DT6	0,839893	0,839893	1		1	DT6	=	=	=		=
left lung, alveoli, lumen, neutrophilic granulocytes	SHAM	DT8	0,80919	0,80919	1	1		DT8	=	=	=	=	
left lung, interstitium, lymphocytic cells	3R4F	DT1		0,53989	0,022157	2,92E-10	1E-08	DT1		=	+	+++	+++
left lung, interstitium, lymphocytic cells	3R4F	DT2	0,53989		0,54292	9,73E-08	3,61E-06	DT2	=		=	+++	+++
left lung, interstitium, lymphocytic cells	3R4F	DT3	0,022157	0,54292		1,05E-05	0,000385	DT3	+	=		+++	+++
left lung, interstitium, lymphocytic cells	3R4F	DT6	2,92E-10	9,73E-08	1,05E-05		0,805083	DT6	+++	+++	+++		=
left lung, interstitium, lymphocytic cells	3R4F	DT8	1E-08	3,61E-06	0,000385	0,805083		DT8	+++	+++	+++	=	
left lung, interstitium, lymphocytic cells	THS 2.2	DT1		0,141986	1	1	1	DT1		=	=	=	=
left lung, interstitium, lymphocytic cells	THS 2.2	DT2	0,141986		0,141986	0,141986	0,141986	DT2	=		=	=	=
left lung, interstitium, lymphocytic cells	THS 2.2	DT3	1	0,141986		1	1	DT3	=	=		=	=
left lung, interstitium, lymphocytic cells	THS 2.2	DT6	1	0,141986	1		1	DT6	=	=	=		=
left lung, interstitium, lymphocytic cells	THS 2.2	DT8	1	0,141986	1	1		DT8	=	=	=	=	
left lung, interstitium, lymphocytic cells	SHAM	DT1		0,925354	1	1	0,092382	DT1		=	=	=	=
left lung, interstitium, lymphocytic cells	SHAM	DT2	0,925354		0,925354	0,938917	0,405894	DT2	=		=	=	=
left lung, interstitium, lymphocytic cells	SHAM	DT3	1	0,925354		1	0,092382	DT3	=	=		=	=
left lung, interstitium, lymphocytic cells	SHAM	DT6	1	0,938917	1		0,12645	DT6	=	=	=		=
left lung, interstitium, lymphocytic cells	SHAM	DT8	0,092382	0,405894	0,092382	0,12645		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 36 cont **Lung, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)**

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
			p-value						levels of statistical significance				
left lung, blood vessels, perivascular lymphocytic cells	3R4F	DT1		0,96823	0,088541	4,05E-07	4,29E-09	DT1		=	=	+++	+++
left lung, blood vessels, perivascular lymphocytic cells	3R4F	DT2	0,96823		0,337469	6,27E-06	7,26E-08	DT2	=		=	+++	+++
left lung, blood vessels, perivascular lymphocytic cells	3R4F	DT3	0,088541	0,337469		0,00198	2,58E-05	DT3	=	=		++	+++
left lung, blood vessels, perivascular lymphocytic cells	3R4F	DT6	4,05E-07	6,27E-06	0,00198		0,656282	DT6	+++	+++	++		=
left lung, blood vessels, perivascular lymphocytic cells	3R4F	DT8	4,29E-09	7,26E-08	2,58E-05	0,656282		DT8	+++	+++	+++	=	
left lung, blood vessels, perivascular lymphocytic cells	THS 2.2	DT1		0,997733	0,999651	0,824776	0,100828	DT1		=	=	=	=
left lung, blood vessels, perivascular lymphocytic cells	THS 2.2	DT2	0,997733		0,999951	0,644095	0,048773	DT2	=		=	=	+
left lung, blood vessels, perivascular lymphocytic cells	THS 2.2	DT3	0,999651	0,999951		0,717162	0,064781	DT3	=	=		=	=
left lung, blood vessels, perivascular lymphocytic cells	THS 2.2	DT6	0,824776	0,644095	0,717162		0,584901	DT6	=	=	=		=
left lung, blood vessels, perivascular lymphocytic cells	THS 2.2	DT8	0,100828	0,048773	0,064781	0,584901		DT8	=	+	=	=	
left lung, blood vessels, perivascular lymphocytic cells	SHAM	DT1		0,999901	0,972981	1	0,148107	DT1		=	=	=	=
left lung, blood vessels, perivascular lymphocytic cells	SHAM	DT2	0,999901		0,990031	0,999801	0,110256	DT2	=		=	=	=
left lung, blood vessels, perivascular lymphocytic cells	SHAM	DT3	0,972981	0,990031		0,972811	0,037786	DT3	=	=		=	+
left lung, blood vessels, perivascular lymphocytic cells	SHAM	DT6	1	0,999801	0,972811		0,205514	DT6	=	=	=		=
left lung, blood vessels, perivascular lymphocytic cells	SHAM	DT8	0,148107	0,110256	0,037786	0,205514		DT8	=	=	+	=	
lung, XXL macrophages	3R4F	DT1		0,540809	0,229967	3,89E-05	6,9E-06	DT1		=	=	+++	+++
lung, XXL macrophages	3R4F	DT2	0,540809		0,98464	0,006068	0,001339	DT2	=		=	++	++
lung, XXL macrophages	3R4F	DT3	0,229967	0,98464		0,019445	0,004535	DT3	=	=		+	++
lung, XXL macrophages	3R4F	DT6	3,89E-05	0,006068	0,019445		0,985306	DT6	+++	++	+		=
lung, XXL macrophages	3R4F	DT8	6,9E-06	0,001339	0,004535	0,985306		DT8	+++	++	++	=	
lung, XXL macrophages	THS 2.2	DT1		0	0	0	0	DT1					
lung, XXL macrophages	THS 2.2	DT2	0		0	0	0	DT2					
lung, XXL macrophages	THS 2.2	DT3	0	0		0	0	DT3					
lung, XXL macrophages	THS 2.2	DT6	0	0	0		0	DT6					
lung, XXL macrophages	THS 2.2	DT8	0	0	0	0		DT8					
lung, XXL macrophages	SHAM	DT1		0	0	0	0	DT1					
lung, XXL macrophages	SHAM	DT2	0		0	0	0	DT2					
lung, XXL macrophages	SHAM	DT3	0	0		0	0	DT3					
lung, XXL macrophages	SHAM	DT6	0	0	0		0	DT6					
lung, XXL macrophages	SHAM	DT8	0	0	0	0		DT8					

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 37 Liver, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
					p-value				levels of statistical significance				
liver, parenchyma, micro-granuloma with micro-hemorrhage	3R4F	DT1		0,957914	0,993652	0,805444	0,981238	DT1		=	=	=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	3R4F	DT2	0,957914		0,998684	0,993652	0,999915	DT2	=		=	=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	3R4F	DT3	0,993652	0,998684		0,957914	0,999915	DT3	=	=		=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	3R4F	DT6	0,805444	0,993652	0,957914		0,981238	DT6	=	=	=		=
liver, parenchyma, micro-granuloma with micro-hemorrhage	3R4F	DT8	0,981238	0,999915	0,999915	0,981238		DT8	=	=	=	=	
liver, parenchyma, micro-granuloma with micro-hemorrhage	THS 2.2	DT1		0,993981	0,794128	0,498406	0,939135	DT1		=	=	=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	THS 2.2	DT2	0,993981		0,551696	0,746886	0,996341	DT2	=		=	=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	THS 2.2	DT3	0,794128	0,551696		0,068557	0,343589	DT3	=	=		=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	THS 2.2	DT6	0,498406	0,746886	0,068557		0,912711	DT6	=	=	=		=
liver, parenchyma, micro-granuloma with micro-hemorrhage	THS 2.2	DT8	0,939135	0,996341	0,343589	0,912711		DT8	=	=	=	=	
liver, parenchyma, micro-granuloma with micro-hemorrhage	SHAM	DT1		0,994224	0,501476	0,098945	0,411007	DT1		=	=	=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	SHAM	DT2	0,994224		0,281585	0,216883	0,656579	DT2	=		=	=	=
liver, parenchyma, micro-granuloma with micro-hemorrhage	SHAM	DT3	0,501476	0,281585		0,00165	0,014788	DT3	=	=		++	+
liver, parenchyma, micro-granuloma with micro-hemorrhage	SHAM	DT6	0,098945	0,216883	0,00165		0,927402	DT6	=	=	++		=
liver, parenchyma, micro-granuloma with micro-hemorrhage	SHAM	DT8	0,411007	0,656579	0,014788	0,927402		DT8	=	=	+	=	
liver, parenchyma, amount of fat	3R4F	DT1		0,939379	0,999782	0,999904	0,996667	DT1		=	=	=	=
liver, parenchyma, amount of fat	3R4F	DT2	0,939379		0,97588	0,893054	0,993539	DT2	=		=	=	=
liver, parenchyma, amount of fat	3R4F	DT3	0,999782	0,97588		0,997726	0,999782	DT3	=	=		=	=
liver, parenchyma, amount of fat	3R4F	DT6	0,999904	0,893054	0,997726		0,987732	DT6	=	=	=		=
liver, parenchyma, amount of fat	3R4F	DT8	0,996667	0,993539	0,999782	0,987732		DT8	=	=	=	=	
liver, parenchyma, amount of fat	THS 2.2	DT1		0,10902	0,031597	0,001579	0,007221	DT1		=	+	++	++
liver, parenchyma, amount of fat	THS 2.2	DT2	0,10902		0,981481	0,46413	0,793215	DT2	=		=	=	=
liver, parenchyma, amount of fat	THS 2.2	DT3	0,031597	0,981481		0,793215	0,977836	DT3	+	=		=	=
liver, parenchyma, amount of fat	THS 2.2	DT6	0,001579	0,46413	0,793215		0,981481	DT6	++	=	=		=
liver, parenchyma, amount of fat	THS 2.2	DT8	0,007221	0,793215	0,977836	0,981481		DT8	++	=	=	=	
liver, parenchyma, amount of fat	SHAM	DT1		0,361662	0,15996	0,611661	0,683403	DT1		=	=	=	=
liver, parenchyma, amount of fat	SHAM	DT2	0,361662		0,988932	0,993244	0,982977	DT2	=		=	=	=
liver, parenchyma, amount of fat	SHAM	DT3	0,15996	0,988932		0,896219	0,847633	DT3	=	=		=	=
liver, parenchyma, amount of fat	SHAM	DT6	0,611661	0,993244	0,896219		0,999956	DT6	=	=	=		=
liver, parenchyma, amount of fat	SHAM	DT8	0,683403	0,982977	0,847633	0,999956		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 37 cont Liver, findings with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)

FINDING_Text	Exposure Group		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
					p-value				levels of statistical significance				
liver, parenchyma, amount of glycogen	3R4F	DT1		0,990732	0,998675	0,999428	1	DT1		=	=	=	=
liver, parenchyma, amount of glycogen	3R4F	DT2	0,990732		0,999752	0,999313	0,990732	DT2	=		=	=	=
liver, parenchyma, amount of glycogen	3R4F	DT3	0,998675	0,999752		0,999998	0,998675	DT3	=	=		=	=
liver, parenchyma, amount of glycogen	3R4F	DT6	0,999428	0,999313	0,999998		0,999428	DT6	=	=	=		=
liver, parenchyma, amount of glycogen	3R4F	DT8	1	0,990732	0,998675	0,999428		DT8	=	=	=	=	
liver, parenchyma, amount of glycogen	THS 2.2	DT1		1	0,999969	0,414318	0,998562	DT1		=	=	=	=
liver, parenchyma, amount of glycogen	THS 2.2	DT2	1		0,999993	0,434574	0,999149	DT2	=		=	=	=
liver, parenchyma, amount of glycogen	THS 2.2	DT3	0,999969	0,999993		0,513237	0,999825	DT3	=	=		=	=
liver, parenchyma, amount of glycogen	THS 2.2	DT6	0,414318	0,434574	0,513237		0,58454	DT6	=	=	=		=
liver, parenchyma, amount of glycogen	THS 2.2	DT8	0,998562	0,999149	0,999825	0,58454		DT8	=	=	=	=	
liver, parenchyma, amount of glycogen	SHAM	DT1		0,983198	0,995802	0,962681	0,857464	DT1		=	=	=	=
liver, parenchyma, amount of glycogen	SHAM	DT2	0,983198		0,999832	0,999931	0,990577	DT2	=		=	=	=
liver, parenchyma, amount of glycogen	SHAM	DT3	0,995802	0,999832		0,998286	0,970746	DT3	=	=		=	=
liver, parenchyma, amount of glycogen	SHAM	DT6	0,962681	0,999931	0,998286		0,997415	DT6	=	=	=		=
liver, parenchyma, amount of glycogen	SHAM	DT8	0,857464	0,990577	0,970746	0,997415		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 38 Lung, morphometric endpoints with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)

FINDING_Text	Exposure		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
	Group		p-value						level of statistical significance				
lung, mean chord length	3R4F	DT1		0,010746	0,011529	2,29E-10	3,56E-11	DT1		+	+	+++	+++
lung, mean chord length	3R4F	DT2	0,010746		0,999956	3,51E-05	1,32E-07	DT2	+		=	+++	+++
lung, mean chord length	3R4F	DT3	0,011529	0,999956		1,46E-05	4,91E-08	DT3	+	=		+++	+++
lung, mean chord length	3R4F	DT6	2,29E-10	3,51E-05	1,46E-05		0,353188	DT6	+++	+++	+++		=
lung, mean chord length	3R4F	DT8	3,56E-11	1,32E-07	4,91E-08	0,353188		DT8	+++	+++	+++	=	
lung, mean chord length	THS 2.2	DT1		0,998131	0,041612	2,1E-05	0,000935	DT1		=	+	+++	+++
lung, mean chord length	THS 2.2	DT2	0,998131		0,083909	5,74E-05	0,002368	DT2	=		=	+++	++
lung, mean chord length	THS 2.2	DT3	0,041612	0,083909		0,114754	0,700911	DT3	+	=		=	=
lung, mean chord length	THS 2.2	DT6	2,1E-05	5,74E-05	0,114754		0,736308	DT6	+++	+++	=		=
lung, mean chord length	THS 2.2	DT8	0,000935	0,002368	0,700911	0,736308		DT8	+++	++	=	=	
lung, mean chord length	SHAM	DT1		0,771608	0,04664	3,08E-05	2,67E-05	DT1		=	+	+++	+++
lung, mean chord length	SHAM	DT2	0,771608		0,504333	0,001642	0,001819	DT2	=		=	++	++
lung, mean chord length	SHAM	DT3	0,04664	0,504333		0,065324	0,083085	DT3	+	=		=	=
lung, mean chord length	SHAM	DT6	3,08E-05	0,001642	0,065324		0,998986	DT6	+++	++	=		=
lung, mean chord length	SHAM	DT8	2,67E-05	0,001819	0,083085	0,998986		DT8	+++	++	=	=	
lung, destructive index	3R4F	DT1		0,011907	0,069134	3,9E-06	6,17E-08	DT1		+	=	+++	+++
lung, destructive index	3R4F	DT2	0,011907		0,937869	0,133341	0,005037	DT2	+		=	=	++
lung, destructive index	3R4F	DT3	0,069134	0,937869		0,017513	0,000366	DT3	=	=		+	+++
lung, destructive index	3R4F	DT6	3,9E-06	0,133341	0,017513		0,628492	DT6	+++	=	+		=
lung, destructive index	3R4F	DT8	6,17E-08	0,005037	0,000366	0,628492		DT8	+++	++	+++	=	
lung, destructive index	THS 2.2	DT1		0,97288	0,229411	0,000599	0,397181	DT1		=	=	+++	=
lung, destructive index	THS 2.2	DT2	0,97288		0,559085	0,003907	0,775114	DT2	=		=	++	=
lung, destructive index	THS 2.2	DT3	0,229411	0,559085		0,180353	0,994578	DT3	=	=		=	=
lung, destructive index	THS 2.2	DT6	0,000599	0,003907	0,180353		0,067181	DT6	+++	++	=		=
lung, destructive index	THS 2.2	DT8	0,397181	0,775114	0,994578	0,067181		DT8	=	=	=	=	
lung, destructive index	SHAM	DT1		0,316243	0,678415	0,054288	0,687906	DT1		=	=	=	=
lung, destructive index	SHAM	DT2	0,316243		0,95532	0,909187	0,951833	DT2	=		=	=	=
lung, destructive index	SHAM	DT3	0,678415	0,95532		0,501274	1	DT3	=	=		=	=
lung, destructive index	SHAM	DT6	0,054288	0,909187	0,501274		0,491976	DT6	=	=	=		=
lung, destructive index	SHAM	DT8	0,687906	0,951833	1	0,491976		DT8	=	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

Table 38 cont Lung, morphometric endpoints with statistically significant exposure effects for 3R4F or THS 2.2 (p-values and significance levels)

FINDING_Text	Exposure		DT1	DT2	DT3	DT6	DT8		DT1	DT2	DT3	DT6	DT8
	Group				p-value				level of statistical significance				
lung, bronchiolar attachements	3R4F	DT1		0,507103	0,290407	0,005723	0,000119	DT1		=	=	++	+++
lung, bronchiolar attachements	3R4F	DT2	0,507103		0,997189	0,296115	0,018144	DT2	=		=	=	+
lung, bronchiolar attachements	3R4F	DT3	0,290407	0,997189		0,454607	0,034508	DT3	=	=		=	+
lung, bronchiolar attachements	3R4F	DT6	0,005723	0,296115	0,454607		0,655702	DT6	++	=	=		=
lung, bronchiolar attachements	3R4F	DT8	0,000119	0,018144	0,034508	0,655702		DT8	+++	+	+	=	
lung, bronchiolar attachements	THS 2.2	DT1		0,386207	0,386207	0,0168	0,01022	DT1		=	=	+	+
lung, bronchiolar attachements	THS 2.2	DT2	0,386207		1	0,609603	0,494222	DT2	=		=	=	=
lung, bronchiolar attachements	THS 2.2	DT3	0,386207	1		0,609603	0,494222	DT3	=	=		=	=
lung, bronchiolar attachements	THS 2.2	DT6	0,0168	0,609603	0,609603		0,9997	DT6	+	=	=		=
lung, bronchiolar attachements	THS 2.2	DT8	0,01022	0,494222	0,494222	0,9997		DT8	+	=	=	=	
lung, bronchiolar attachements	SHAM	DT1		0,09456	0,569977	0,009331	8,01E-05	DT1		=	=	++	+++
lung, bronchiolar attachements	SHAM	DT2	0,09456		0,758686	0,891092	0,164253	DT2	=		=	=	=
lung, bronchiolar attachements	SHAM	DT3	0,569977	0,758686		0,22095	0,00547	DT3	=	=		=	++
lung, bronchiolar attachements	SHAM	DT6	0,009331	0,891092	0,22095		0,66483	DT6	++	=	=		=
lung, bronchiolar attachements	SHAM	DT8	8,01E-05	0,164253	0,00547	0,66483		DT8	+++	=	++	=	
lung, volume	3R4F	DT1		0,213278	0,000312	1,25E-05	0,003654	DT1		=	+++	+++	++
lung, volume	3R4F	DT2	0,213278		0,148305	0,012661	0,490422	DT2	=		=	+	=
lung, volume	3R4F	DT3	0,000312	0,148305		0,794112	0,958103	DT3	+++	=		=	=
lung, volume	3R4F	DT6	1,25E-05	0,012661	0,794112		0,407769	DT6	+++	+	=		=
lung, volume	3R4F	DT8	0,003654	0,490422	0,958103	0,407769		DT8	++	=	=	=	
lung, volume	THS 2.2	DT1		0,774734	0,028526	0,314077	0,003811	DT1		=	+	=	++
lung, volume	THS 2.2	DT2	0,774734		0,322785	0,943335	0,083198	DT2	=		=	=	=
lung, volume	THS 2.2	DT3	0,028526	0,322785		0,739505	0,96407	DT3	+	=		=	=
lung, volume	THS 2.2	DT6	0,314077	0,943335	0,739505		0,317525	DT6	=	=	=		=
lung, volume	THS 2.2	DT8	0,003811	0,083198	0,96407	0,317525		DT8	++	=	=	=	
lung, volume	SHAM	DT1		0,738691	0,119139	0,185608	0,003867	DT1		=	=	=	++
lung, volume	SHAM	DT2	0,738691		0,786319	0,857829	0,121839	DT2	=		=	=	=
lung, volume	SHAM	DT3	0,119139	0,786319		0,999983	0,632228	DT3	=	=		=	=
lung, volume	SHAM	DT6	0,185608	0,857829	0,999983		0,624754	DT6	=	=	=		=
lung, volume	SHAM	DT8	0,003867	0,121839	0,632228	0,624754		DT8	++	=	=	=	

DT: dissection time point =: p >0.05 (not statistically significant) +: p ≤0.05 ++: p ≤0.01 +++: p ≤0.001

DISCUSSION

Histotechnical processing:

The histological slide quality was sufficient to ensure a comparative histopathological and morphometric assessment of all study groups and dissection time points. Single slides were considered invalid if the imaging of target anatomical structures (nose) was inadequate or if the instillation of the lung parenchyma during fixation was inadequate. The number of invalid slides was within the normal range for this type of study and did not significantly influence the overall interpretation of the results.

Histopathological evaluation of the nose:

After continuous exposure to MSS from the 3R4F standard reference cigarette, typical epithelial adaptation was seen in the form of reserve cell hyperplasia and squamous epithelial metaplasia of the respiratory epithelium, and in the form of atrophy of the olfactory epithelium. The severity of effects based on mean scores was dependent on the exposure duration. Atrophy of the olfactory epithelium was statistically significant only after 8 months of 3R4F exposure. Effects were more prominent in the apical nose (levels 1 and 2) compared to the distal nose (levels 4). These observations are typically seen with 3R4F exposure.

After continuous exposure to aerosol from the THS 2.2, the typical epithelial adaptation seen for the 3R4F was generally not observed i.e., reserve cell hyperplasia of the respiratory epithelium was not statistically significant compared to SHAM and squamous epithelial metaplasia of the respiratory epithelium and atrophy of the olfactory epithelium were not present at all. The statistically significant mean severity score seen for reserve cell hyperplasia of the respiratory epithelium at nose level 1 for the THS 2.2 compared to SHAM at DT6 is considered to be a chance finding because a) the difference was slight (0.77) and b) there were no statistically significant differences seen at the other dissection time points.

Vacuolisation was seen in the respiratory epithelium and in the olfactory epithelium of the nose, and was generally more prominent at late dissection time points. Lower mean values were observed for the 3R4F_CONT group compared to the other study groups, especially in the respiratory epithelium of nose levels 1 and 2 (statistically significant for the 3R4F_CONT group at DT8, nose level 2). This may be due to a competitive effect of 3R4F exposure, whereby the tissue modification is present but in a different form, i.e., in this case epithelial hyperplasia and squamous epithelial metaplasia (respiratory epithelium) instead of vacuolisation. In the olfactory epithelium, the competitive effect, i.e., the appearance of epithelial atrophy instead of epithelial vacuolisation was not as prominent as in the respiratory epithelium because the atrophy of the olfactory epithelium was quantitatively minimal and limited to the dorsal meatus of the nose. For the THS 2.2 groups, epithelial vacuolisation was not statistically significantly different from SHAM (no competitive effect). In conclusion, this finding is considered a background finding in untreated ApoE-deficient mice, which may have appeared as epithelial adaptation in 3R4F-exposed animals, but not in animals exposed to aerosol from the THS 2.2.

3R4F exposure effects observed at DT2 recovered after cessation in a time-dependent manner (cessation periods of 1, 4, and 6 months or DT3, DT6, and DT8 respectively). Very similar recovery effects were seen after switching, with no statistically significant differences between the Cessation and THS 2.2_Switch groups.

In conclusion, there were no significant effects observed in the nose after exposure to aerosol from the THS 2.2 of up to 8 months. Furthermore, there were no new effects observed for the THS 2.2, i.e., effects that were also seen for the 3R4F. Cessation and switching resulted in very similar effects.

Histopathological evaluation of the lung related to inflammation and epithelial adaptation:

After continuous exposure to MSS from the 3R4F standard reference cigarette, typical inflammatory effects were seen in the lung parenchyma in the form of intra-alveolar accumulation of inflammatory cells in particular neutrophilic granulocytes, lymphocytes/plasma-cells, and macrophages (unpigmented, yellow pigmented, pigmented macrophage nests, and XXL-PAS-positive macrophages) as well as in form of interstitial accumulation of lymphocytic cells in the alveolar interstitium and peri-vascular area. The severity of effects based on mean scores was in general dependent on the exposure duration. In addition, a slight reserve cell hyperplasia of the bronchial epithelium was associated with 3R4F exposure but without any obvious time dependency on the exposure duration. All these observations are within the expected range for this type of experimental study after continuous exposure to the 3R4F.

After continuous exposure to aerosol from the THS 2.2, the typical inflammatory effects seen for the 3R4F were generally not observed i.e., intra-alveolar neutrophilic granulocytes, intra-alveolar lymphocytes/plasma-cells, intra-alveolar unpigmented macrophages, interstitial lymphocytic cells, perivascular lymphocytic cells and reserve cell hyperplasia of the bronchial epithelium were not statistically significant compared to SHAM and intra-alveolar pigmented macrophages and pigmented macrophage nests, intra-alveolar XXL-PAS-positive macrophages were not present at all. The statistically significant mean severity score for goblet cell hyperplasia of the main bronchus epithelium for the THS 2.2 compared to SHAM at DT2 is considered to be a chance finding because a) the difference was slight (0.5) and b) there were no statistically significant differences seen at the other dissection time points.

The effects of cessation after 2 months of 3R4F exposure can be grouped into three categories:
Category 1 includes the cell types that are removed (cleared) directly from the lung parenchyma after cessation. For these cell types, statistically significantly lower mean severity scores were seen at 1 month after cessation and the mean values decreased progressively with longer cessation periods. These endpoints, i.e., intra-alveolar neutrophilic granulocytes, intra-alveolar lymphocytes/plasma cells, intra-alveolar XXL-PAS-positive macrophages, intra-alveolar unpigmented macrophages, are considered to represent the acute component of the inflammatory response. The endpoint reserve cell hyperplasia of the bronchial epithelium also belongs in this category. A direct (1 month of

cessation) and complete recovery effect can be concluded for these endpoints within a time period of 6 months after cessation.

Category 2 includes the cell types that initially remain at the same level after cessation, but then begin to recover thereafter. For these cell types, similar mean severity scores (not statistically significant) were seen at 1 month after cessation. Thereafter, mean values were statistically significantly lower compared to the switching time point. At 6 months after cessation, mean values were statistically significantly higher compared to SHAM (incomplete recovery). This effect was seen for the endpoint pigmented macrophages in the alveolar lumen, which is considered to represent the sub-acute or chronic component of the inflammatory response. A delayed and incomplete recovery effect can be concluded for this endpoint within 6 months after cessation.

Category 3 includes the cell types that do not recover during the cessation period of 6 months. For these cell types, mean severity scores were not statistically significant between the switching time point and the end of the different cessation periods, though they were higher at 1 and 4 months after cessation than at 6 months. At 6 months after cessation, mean values were statistically significantly higher compared to SHAM (incomplete recovery). This effect was seen for the endpoints intra-alveolar pigmented macrophage nests and peri-vascular lymphocytic cells. Initial 3R4F exposure seems to trigger an inflammatory process that remains/progresses without further exposure after cessation. The endpoint pigmented macrophage nests is considered to represent the chronic component of the inflammatory response. For the time course of pigmented nest formation, a possible transition of pigmented macrophages to nest formation needs to be considered. The peri-vascular inflammatory response could be caused by hyperplasia of local lymphoid cell entities, or by an inflammatory cell migration. Lack of recovery within 6 months after cessation combined with initial progression after cessation can be concluded for these endpoints.

The endpoint lymphocytic cells in the alveolar interstitium do not fit in any of the categories because at the switching time point, no statistically significant effect of the 3R4F exposure was observed. However, mean values were statistically significantly higher (compared to the switching time point) at 1 month after cessation and declined thereafter (delayed recovery after initial progression).

The effects seen for the different inflammatory cell types after switching the exposure to the THS 2.2 were very similar to those seen after cessation and can be grouped in the same categories. Generally, no statistically significant differences were seen between the Cessation and THS 2.2_Switch groups at DT3, DT6, and DT8. However, the extent of recovery was slightly more pronounced/faster for the THS 2.2_Switch groups compared to the Cessation groups for the endpoints intra-alveolar lymphocytes/plasma cells, intra-alveolar unpigmented macrophages (statistical significant difference at DT8), and pigmented macrophages based on the numerical comparison of mean severity scores.

In conclusion, there were no significant effects observed in the lung after exposure to aerosol from the THS 2.2 of up to 8 months. Furthermore, there were no new effects observed for the THS 2.2, i.e., effects that were not also seen for the 3R4F. Cessation and switching resulted in very similar effects.

Lung emphysema evaluated histopathologically and by morphometric analysis:

Exposure effects on pulmonary emphysema were analysed using three morphometrical methods, i.e., mean chord length, destructive index and bronchiolar attachments. Each of these endpoints addresses different histomorphological changes that accompany the appearance of emphysema. The endpoint mean chord length reflects mainly the increase in alveolar space/diameter caused by a destruction of alveolar architecture in emphysematous tissue. However, mean chord length data can also increase when the alveolar parenchyma appears enlarged without tissue destruction (volume-dependent endpoint). The endpoint bronchiolar attachment reflects mainly the destruction of alveolar septa in emphysematous tissue in co-localisation with small to medium-sized bronchi. The endpoint destructive index is considered to be a histopathological evaluation of emphysema at randomly selected subunits of the parenchyma. For evaluation of emphysematous (destroyed) tissue, all histomorphological criteria for emphysema should be taken into consideration. In addition to the morphometrical endpoints, pulmonary emphysema was analysed by histopathological evaluation at 5 step serial lung sections according to a semi-quantitative severity grading. The interpretation of any emphysema effects should be based on the data from all endpoints and consider the individual characteristics of the different approaches.

After continuous exposure to MSS from the 3R4F standard reference cigarette, pulmonary emphysema was demonstrated for the histopathology score as well as for all morphometric endpoints, i.e., mean chord length, destructive index, and bronchiolar attachments. The severity of effects based on mean values generally dependent on the exposure duration. All endpoints indicated statistically significant emphysema at the switching time point with the exception of the bronchiolar attachments (statistically significant at DT3, DT6, and DT8).

After continuous exposure to aerosol from the THS 2.2, no statistically significant emphysema was seen for any endpoint (compared to SHAM).

No statistically significant changes in mean values were seen after cessation (compared to switching time point) with exception of the destructive index. This is indicative for an overall stable degree of emphysema. Mean values for the endpoint destructive index were statistically significantly lower after all cessation periods compared to the switching time point. The comparison between the Cessation groups at DT3, DT6, and DT8 did not reveal any significant differences (stable) for bronchiolar attachments. The discrepancy between cessation effects for the destructive index and the other endpoints cannot be clarified based on the available data. However, a relatively high mean value for destructive index at the switching time point combined with an inconsistent time dependency between DT1 and DT3 for the 3R4F groups (mean values: 18.9, 31.3 and 28.5 at DT1, DT2, and DT3, respectively) may be responsible for the observation.

The effects of switching were very similar to those seen after cessation for all emphysema endpoints. The comparisons between the Cessation and THS 2.2 Switch groups were not statistically significant at DT3, DT6, and DT8.

Hyperplasia of the alveolar epithelium was often co-localizes with emphysematous areas from histo-morphological perspective and was most probably based on a type II cell hyperplasia. In function of

reserve cells for injured type I pneumocytes, a pathophysiological correlation to the degeneration/destruction of the alveolar architecture during emphysema development can be speculated. Mean values of the endpoint corresponded with the histopathology score for emphysema in the 3R4F groups. The finding was not statistically significant after continuous exposure to aerosol from the THS 2.2. After cessation/switching, a recovery effect was seen for hyperplasia that was not seen for emphysema. There were no statistically significant differences between the Cessation and THS 2.2 groups.

In conclusion, there was no significant emphysema observed in the lung after exposure to aerosol from the THS 2.2 of up to 8 months. Overall, the severity of emphysema remained at a similar level after cessation, while the severity of pulmonary emphysema progressed under sustained 3R4F exposure. Cessation and switching resulted in very similar effects.

Lung volume:

The lung volume was determined at the histological step serial sections according to the Cavalierie method as described in the literature. Based on this technique, lung volume data are based on the anatomical architecture of the lung after instillation (outside the thorax), fixation (possible rejection of fixative due to the recoil of elastic lung fibers before cross linkage), and histotechnical processing (shrinkage due to ethanol incubation and paraffin embedding). The lung morphology in this state may differ significantly from the in-life situation. In consequence, lung volume data are considered to be an important reference parameter for the morphometrical assessment of lung emphysema on histological slides but lung volume data should not be considered as an endpoint of emphysema. Hyperinflation of the lung based on tissue destruction in emphysematous tissue (instillation with constant pressure) or other effects on lung elasticity, as well as artificial effects, as mentioned above may influence the lung volume data. In the present study, the time-dependent increase in lung volume seen in the SHAM groups between DT1 and DT8 is considered to be a natural age-related effect. Lung volume also increased in the 3R4F groups, but only between DT1 and DT6. Lung volume data were higher for the 3R4F groups compared to SHAM at DT2, DT3, DT6, and DT8 but the exposure effect was smaller and not statistically significant at DT2 and DT8. Data for the THS 2.2_CONT groups were not statistically significant compared to SHAM. After cessation/switching, data remained at a similar level compared to the switching time point (stable), and the data for the Cessation and THS 2.2_Switch groups were not statistically significantly different at DT3, D6, and DT8.

In conclusion, an increase in lung volume was associated with 3R4F exposure. The effect increased over time between DT2 and DT6 but was smaller and not statistically significant at DT8. The effect may be related to hyperinflation of the lung (instillation under constant pressure without volume limitation) which occurs in emphysematous tissue and is cause by tissue destruction, but may also be masked to some extent by artificial effects of the histotechnical processing. Continued exposure to aerosol from the THS 2.2 did not show any significant lung volume effects compared to SHAM and there were no statistically significant differences between the Cessation and THS 2.2_Switch groups.

Histopathological evaluation of the liver:

In the liver, histopathological alterations e.g. hepatocellular degeneration, increase of collagen fibres, fat deposits within hepatocytes, inflammation and bile duct proliferation were seen, all of which are considered typical histomorphological alterations in ApoE-deficient mice. The severity of these findings generally increased over time and is considered a typical age-related effect in ApoE-deficient mice. Overall, no statistically significant effects were observed in the 3R4F or THS 2.2 groups; however, a trend to a lower amount of fat (frozen section) and a lower amount of glycogen (AB-PAS-staining after digestion) in hepatocytes as well as to a lower amount of micro-granulomas (locally associated with micro-hemorrhage) was seen in association with 3R4F exposure (not-statistically significant). A similar trend was seen for the endpoint content of glycogen in hepatocytes, but not for the other endpoints in association with THS 2.2 exposure. Differences in hepatocellular fat and glycogen storage are considered to be related to differences in the metabolic status at the time of the dissection. Stress related to the exposure and caloric restriction may influence these observations; however, a detailed explanation of the effects cannot be given based on the histopathological evaluation.

There were generally no statistically significant differences between the Cessation and the THS 2.2 Switch groups at DT3, DT6 and DT8. For the endpoint content of glycogen, statistically significantly higher mean severity scores were observed for the THS 2.2_Switch group compared to the Cessation group at DT3. Because the difference in mean values was smaller at DT6 and DT8, and not statistically significant this is considered a chance finding.

In conclusion, typical histopathological findings were seen in the liver for ApoE-deficient mice. No statistically significant effects were observed after exposure to MSS from the 3R4F or aerosol from the THS 2.2. There were no significant differences between cessation and switching.

SUMMARY

ApoE-deficient mice were exposed to aerosol form the THS 2.2 or MSS from the 3R4F reference cigarette for up to 8 months.

The histological slide quality was adequate to ensure a comparative histopathological and morphometric assessment of all study groups and dissection time points.

No significant effects were observed in the nose and lung for the THS 2.2, while both statistically significant and time-dependent exposure effects were seen for the 3R4F. No new effects were observed for the THS 2.2, i.e., which were not already seen for the 3R4F.

No significant emphysema was observed in the lung for the THS 2.2, while both statistically significant and time-dependent exposure effects were seen for the 3R4F. Overall, the severity of emphysema remained stable after cessation, while the severity of pulmonary emphysema progressed under sustained 3R4F exposure.

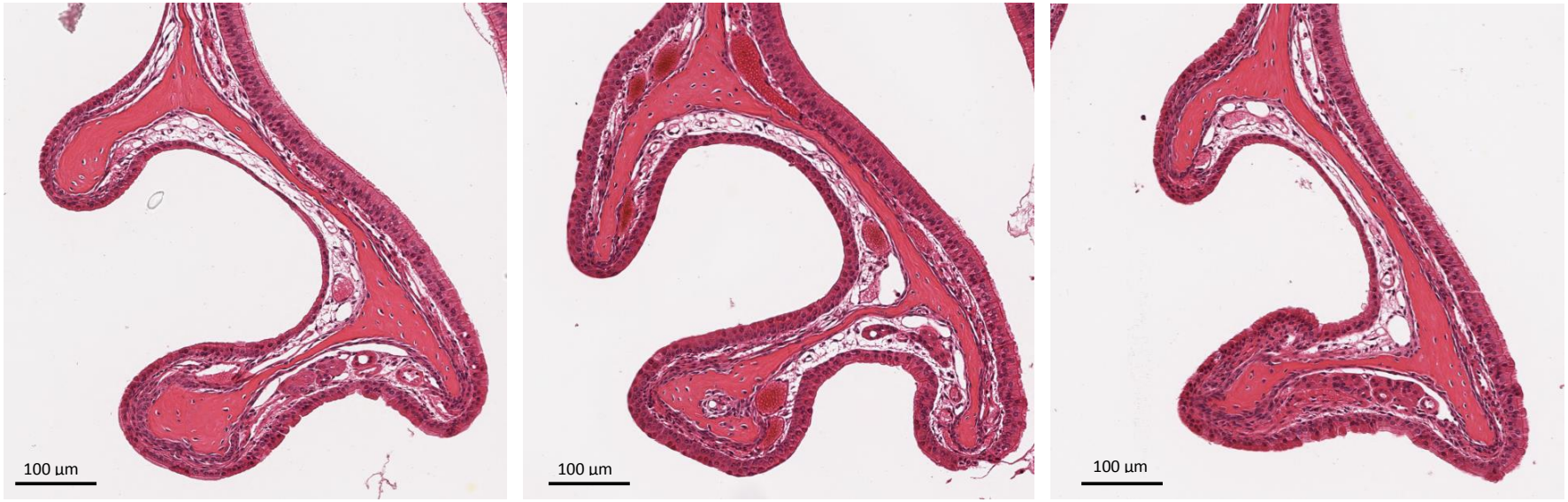
No effect on lung volume was observed for the THS 2.2, while a significant effect was seen for the 3R4F.

Typical histopathological findings were seen in the liver; no significant effects were seen for the THS 2.2 or for the 3R4F.

The effects of cessation were very similar to those of switching to the THS 2.2 for all end points.

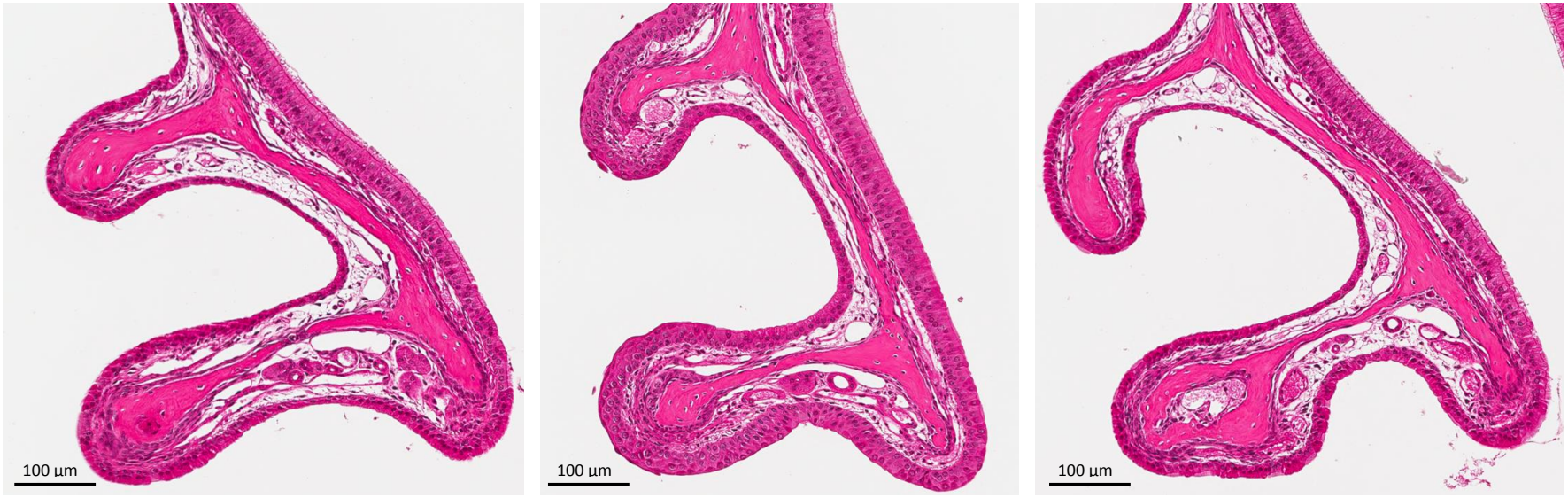
IMAGES

Image 1 **Nose level 1, respiratory epithelium, dissection time point 2, SHAM, 3R4F_CONT, THS 2.2_CONT (20x objective)**



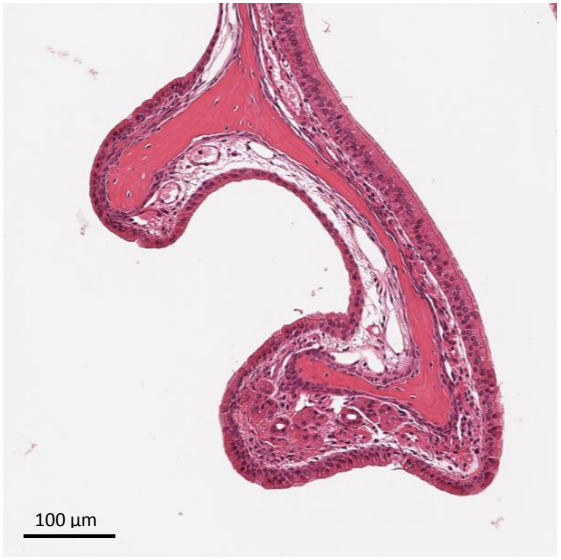
SHAM **3R4F_CONT** **THS 2.2_CONT**

Image 2 **Nose level 1, respiratory epithelium, dissection time point 3, SHAM, 3R4F_CONT, THS 2.2_CONT (20x objective)**

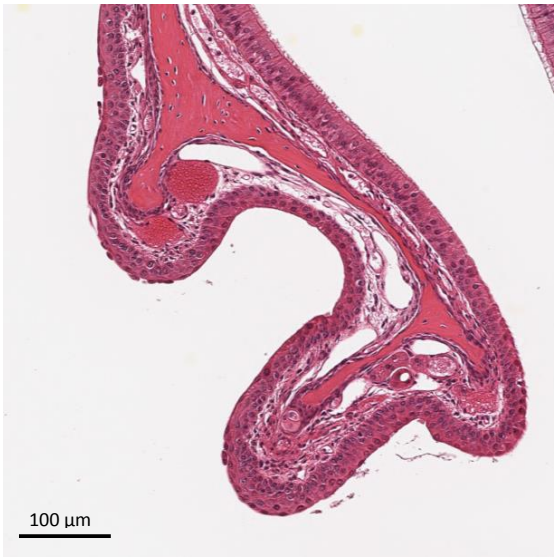


SHAM **3R4F_CONT** **THS 2.2_CONT**

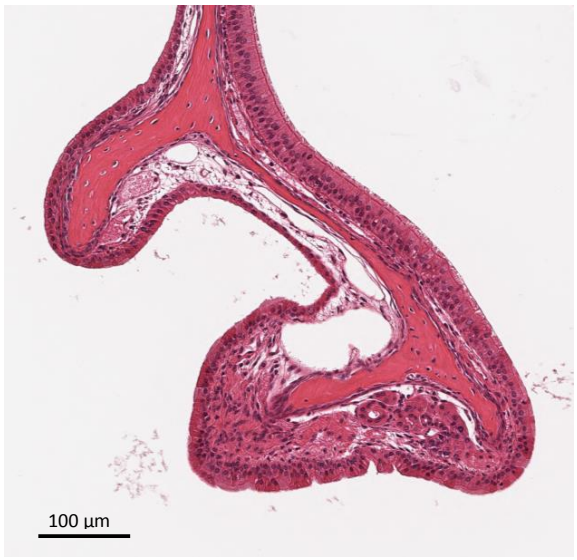
Image 3 **Nose level 1, respiratory epithelium, dissection time point 6, SHAM, 3R4F_CONT, THS 2.2_CONT (20x objective)**



SHAM

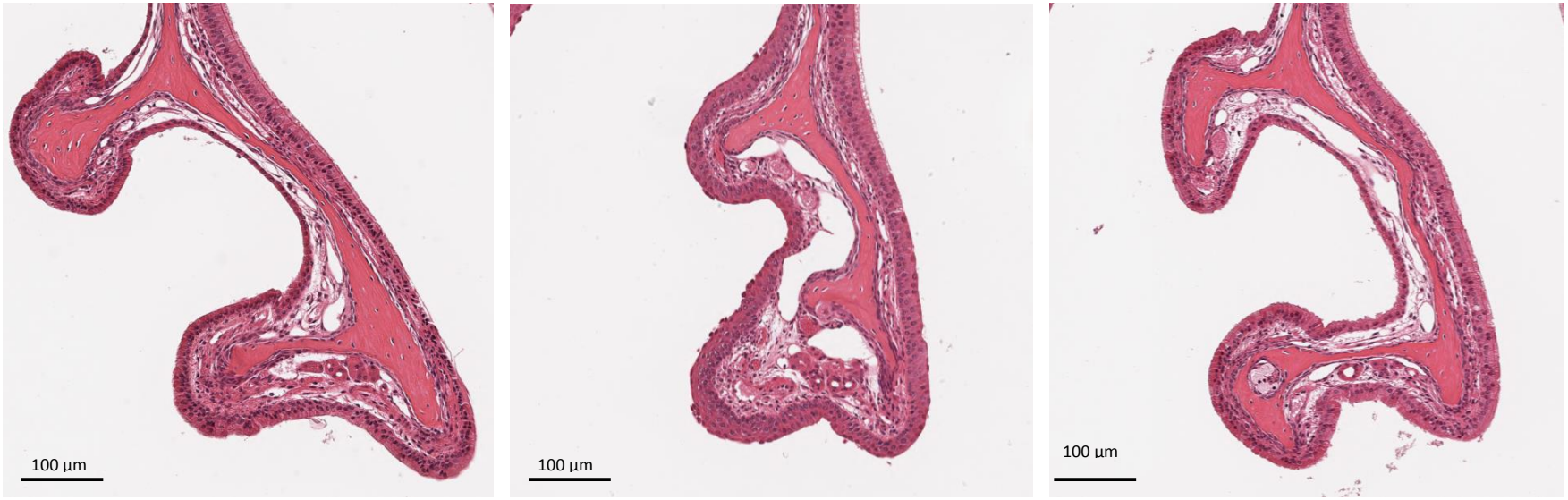


3R4F_CONT



THS 2.2_CONT

Image 4 **Nose level 1, respiratory epithelium, dissection time point 8, SHAM, 3R4F_CONT, THS 2.2_CONT (20x objective)**

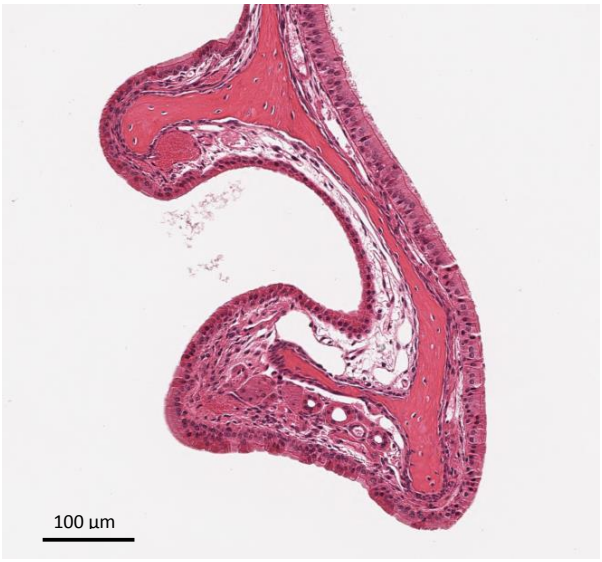


SHAM **3R4F_CONT** **THS 2.2_CONT**

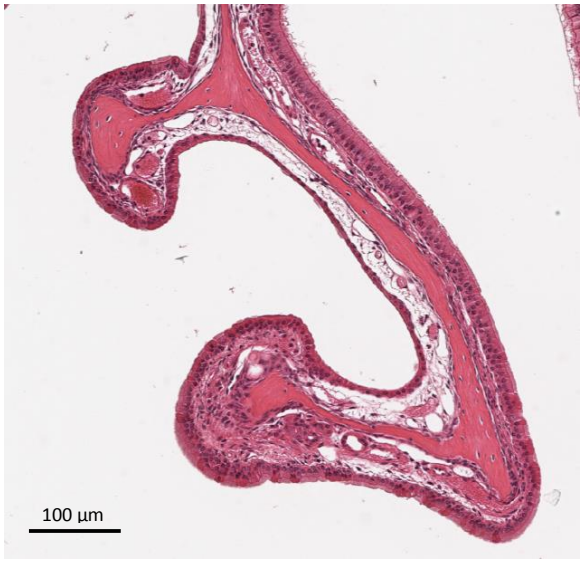
Image 5 Nose level 1,respiratory epithelium, Cessation (20x objective)



Cessation DT3

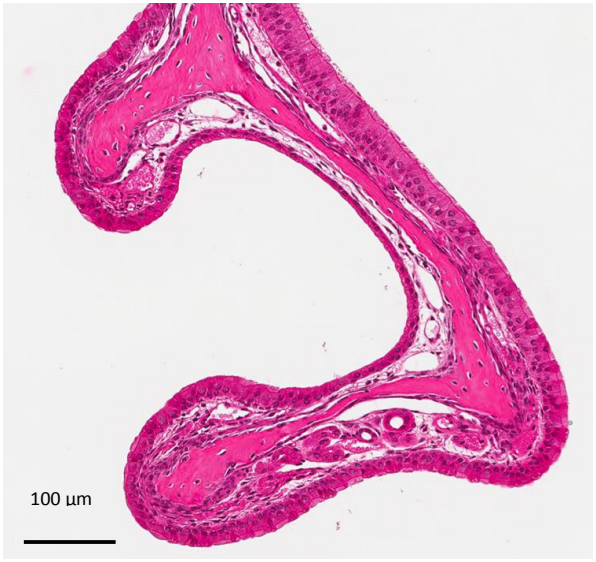


Cessation DT6

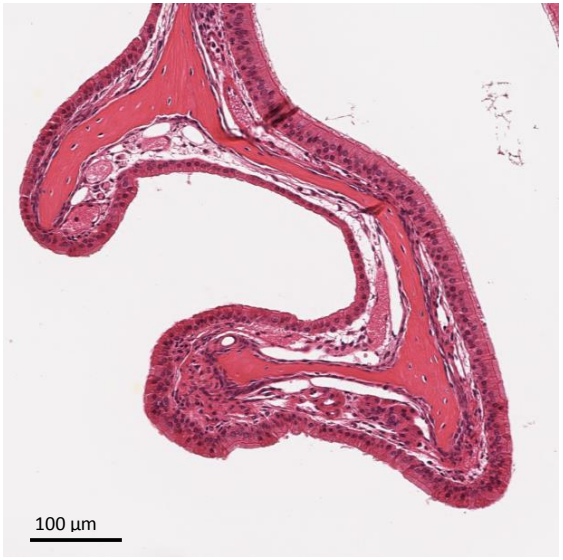


Cessation DT8

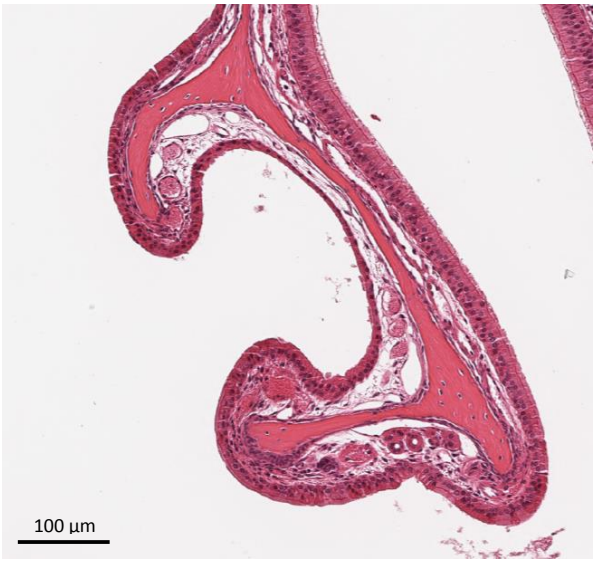
Image 6 Nose level 1,respiratory epithelium, THS 2.2_Switch (20x objective)



THS 2.2 Switch DT3

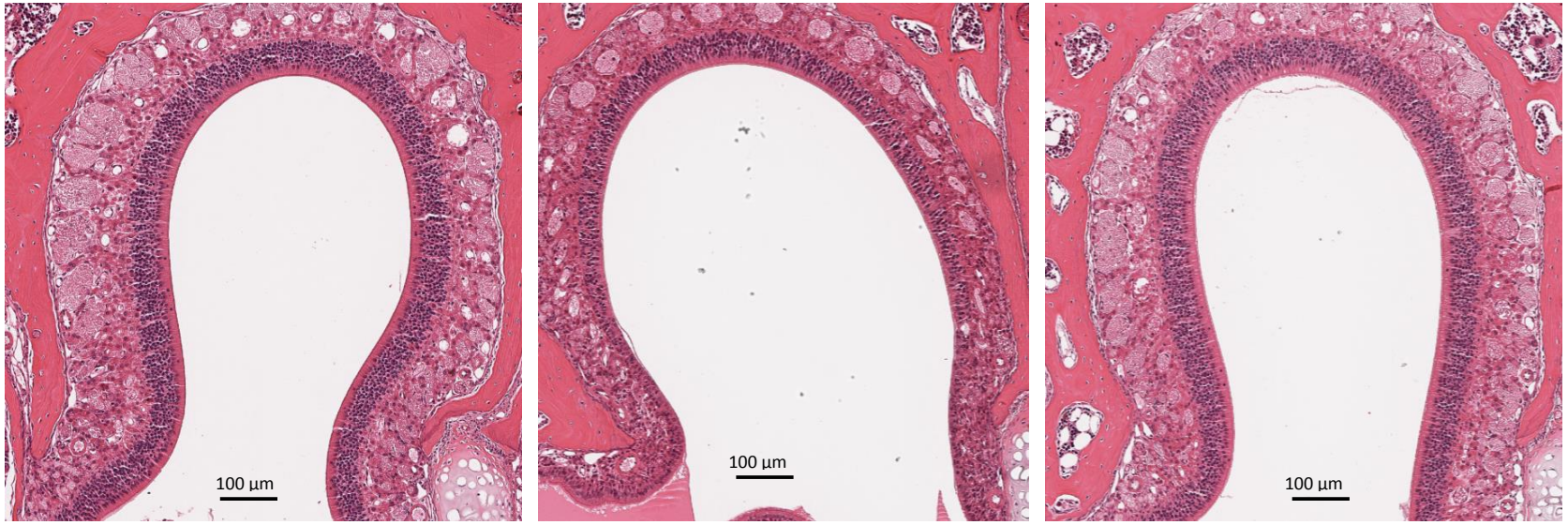


THS 2.2 Switch DT6



THS 2.2 Switch DT8

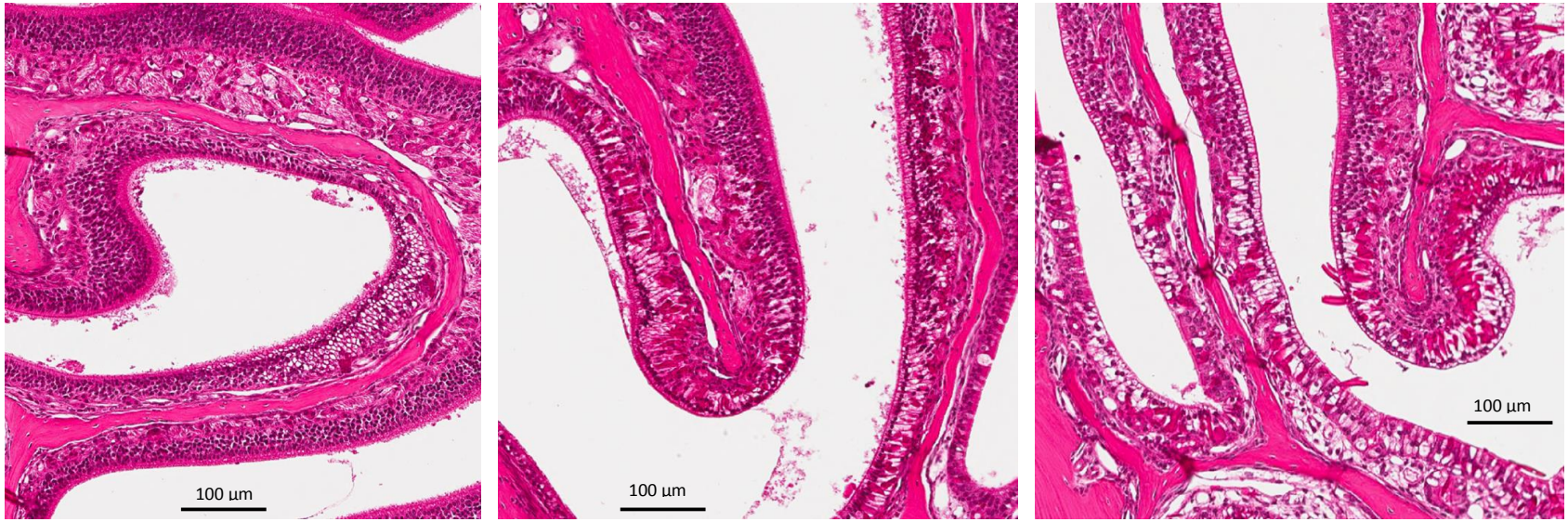
Image 7 **Nose level 2, olfactory epithelium, SHAM, dissection time point 8, 3R4F_CONT, THS 2.2_CONT (15x objective)**



SHAM **3R4F_CONT** **THS 2.2_CONT**

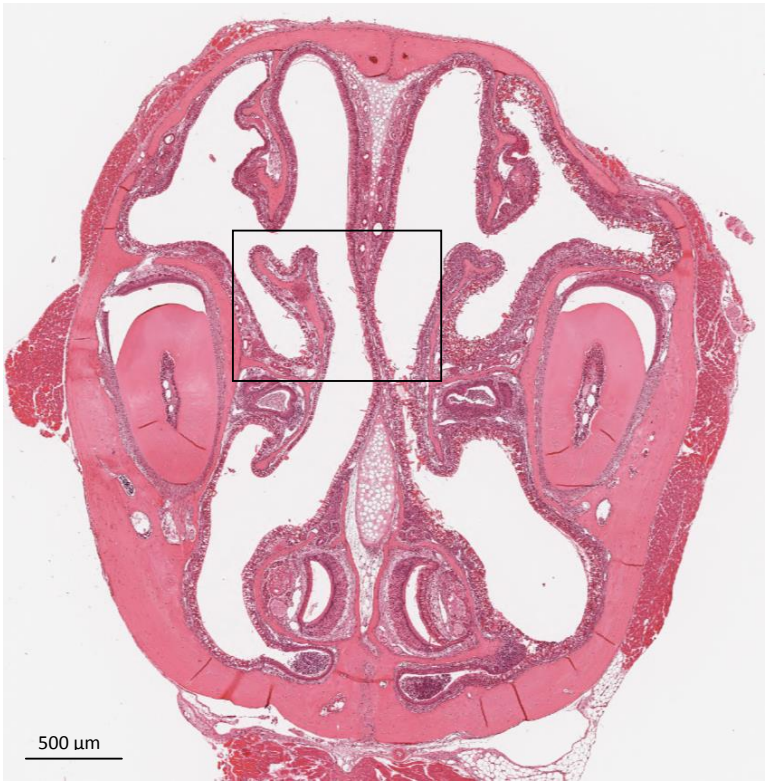
100 µm

Image 8 **Nose level 4, olfactory epithelium, vacuolisation, dissection time point 3, SHAM, 3R4F_CONT, THS 2.2_CONT (20x objective)**

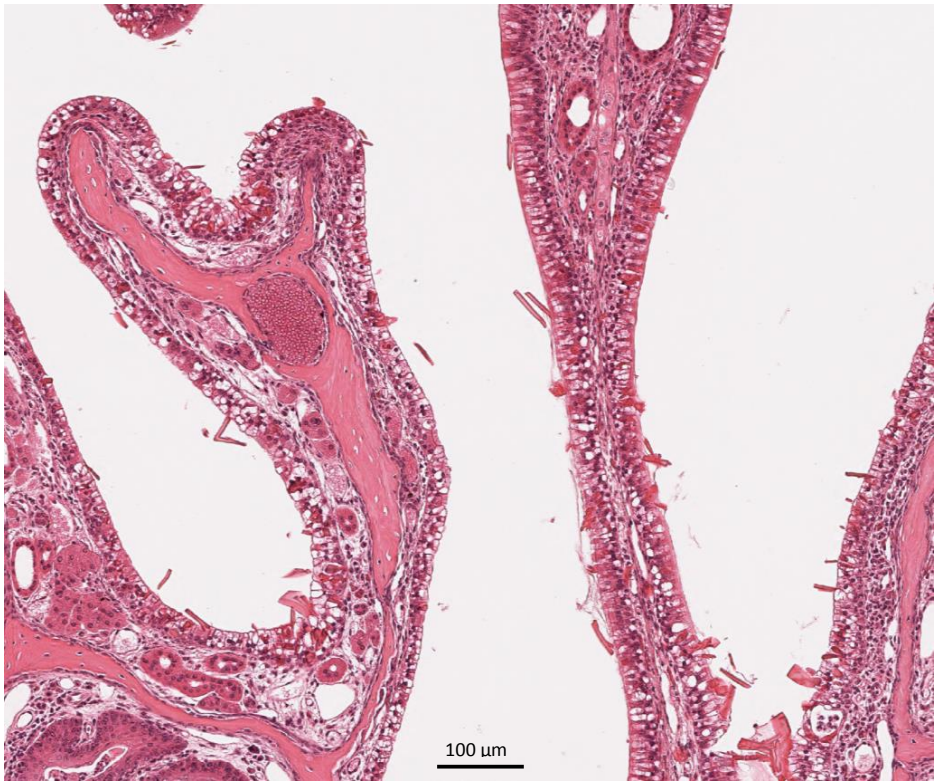


SHAM **3R4F_CONT** **THS 2.2_CONT**

Image 9 **Nose level 2, respiratory epithelium, vacuolisation, dissection time point 8, SHAM**



3 x objective



15 x objective, higher magnification (frame)

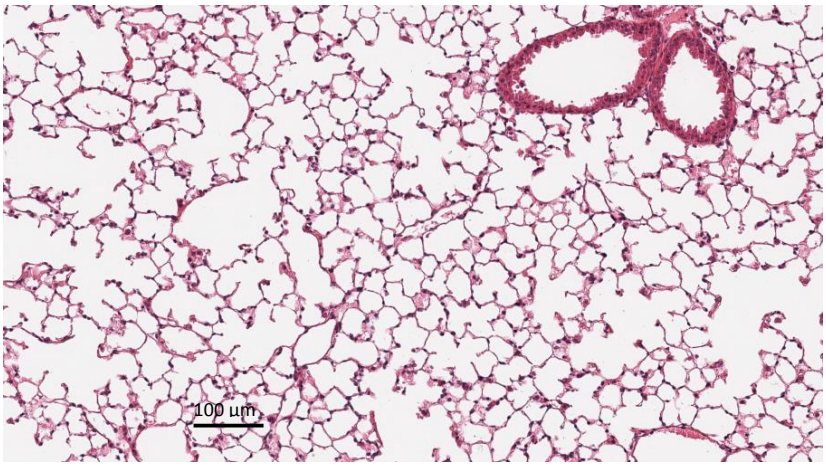


Image 10 **Left lung, dissection time point 2, SHAM, (20x objective)**

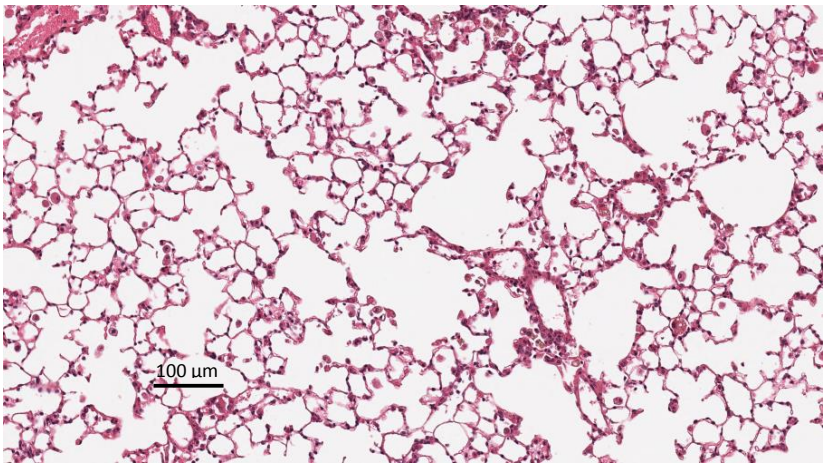


Image 11 **Left lung, dissection time point 2, 3R4F_CONT, (20x objective)**

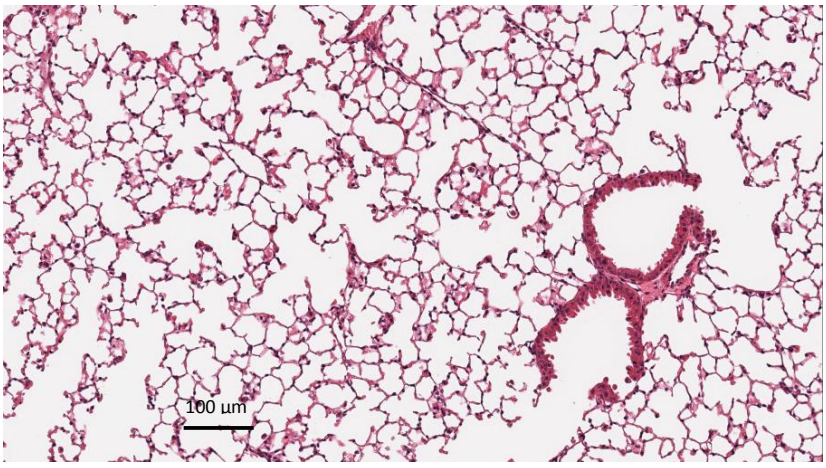


Image 12 **Left lung, dissection time point 2, THS 2.2_CONT, (20x objective)**

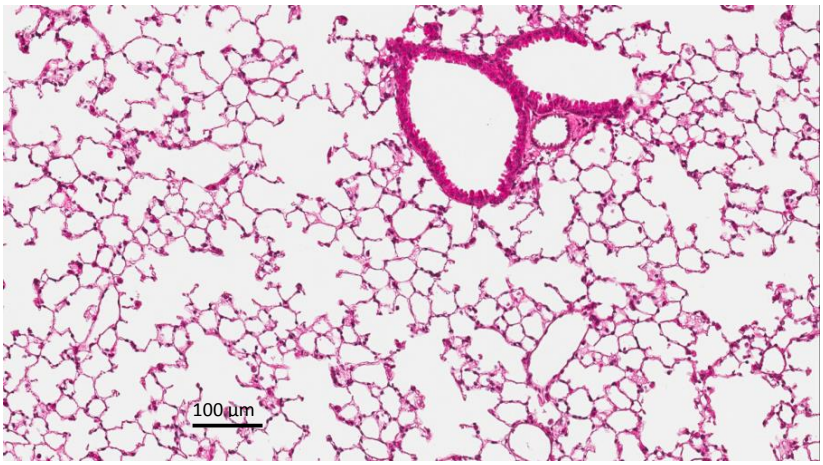


Image 13 **Left lung, dissection time point 3, SHAM, (20x objective)**

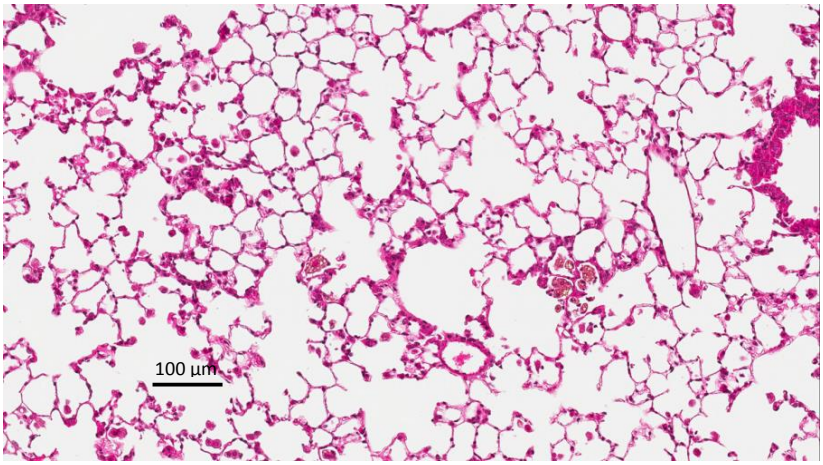


Image 14 **Left lung, dissection time point 3, 3R4F_CONT, (20x objective)**

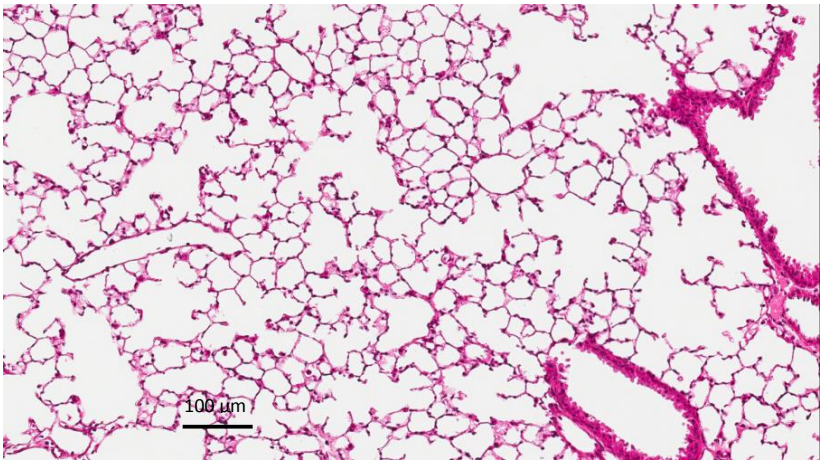


Image 15 **Left lung, dissection time point 3, THS 2.2_CONT, (20x objective)**

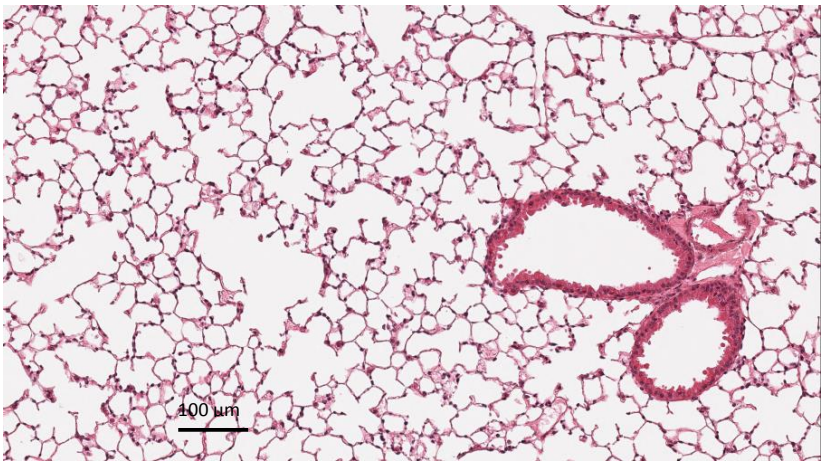


Image 16 **Left lung, dissection time point 6, SHAM, (20x objective)**

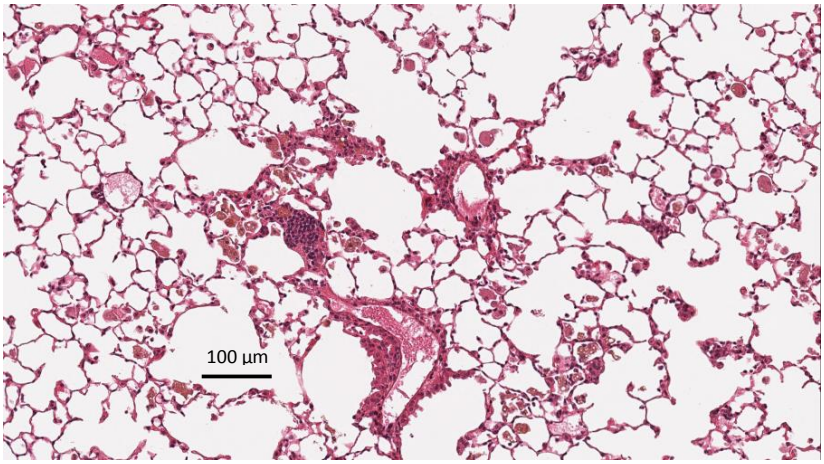


Image 17 **Left lung, dissection time point 6, 3R4F_CONT, (20x objective)**

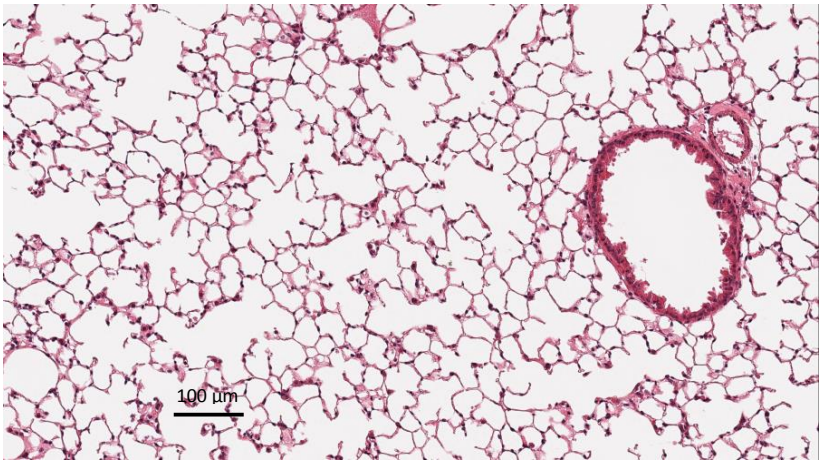


Image 18 **Left lung, dissection time point 6, THS 2.2_CONT, (20x objective)**

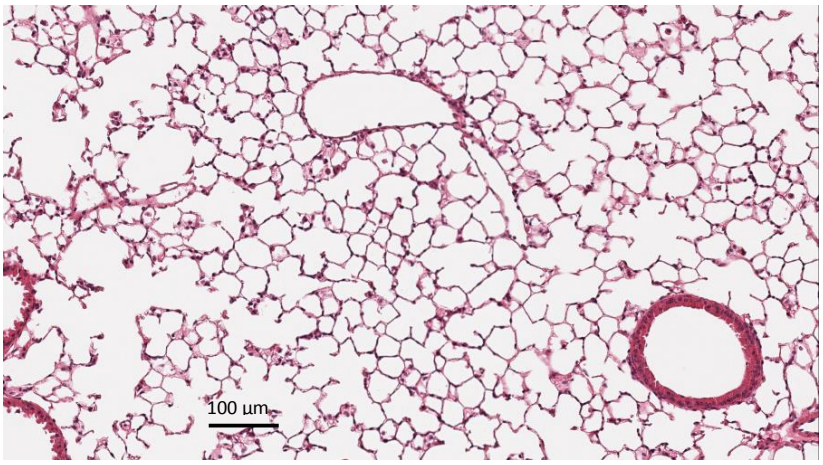


Image 19 **Left lung, dissection time point 8, SHAM, (20x objective)**

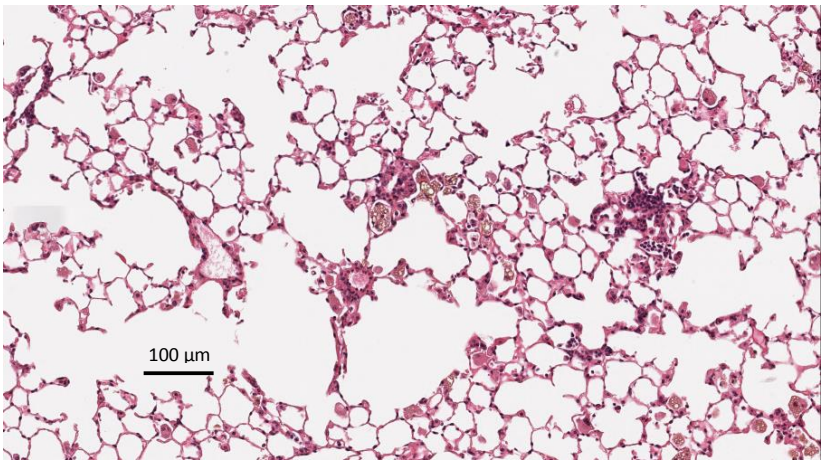


Image 20 **Left lung, dissection time point 8, 3R4F_CONT, (20x objective)**

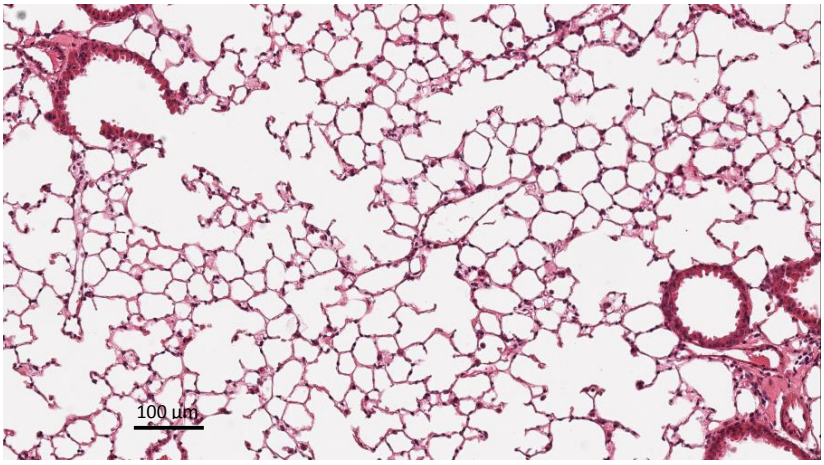


Image 21 **Left lung, dissection time point 8, THS 2.2_CONT, (20x objective)**

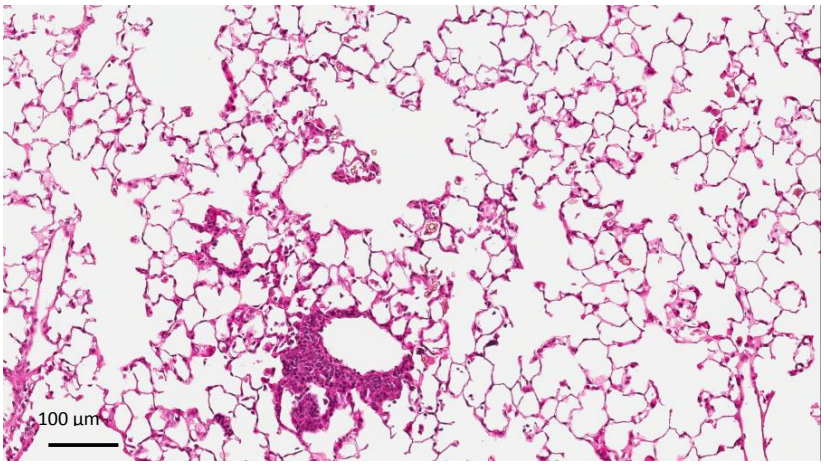


Image 22 **Left lung, dissection time point 3, Cessation, (20x objective)**

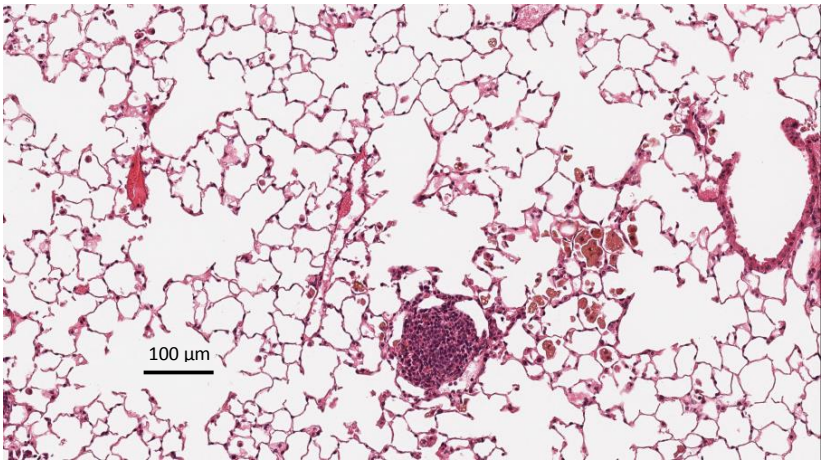


Image 23 **Left lung, dissection time point 6, Cessation, (20x objective)**

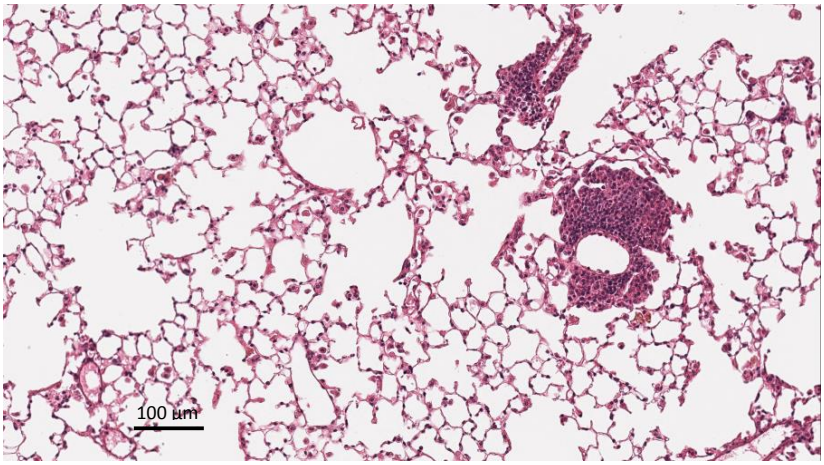


Image 24 **Left lung, dissection time point 8, Cessation, (20x objective)**

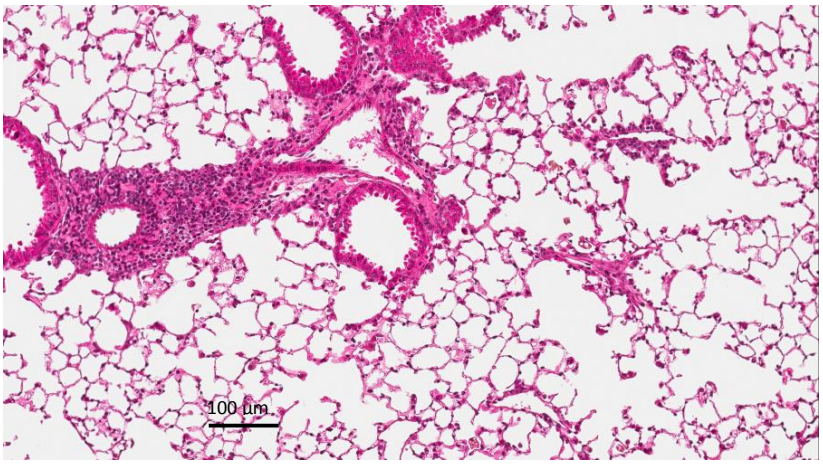


Image 25 **Left lung, dissection time point 3, THS 2.2_Twitch, (20x objective)**

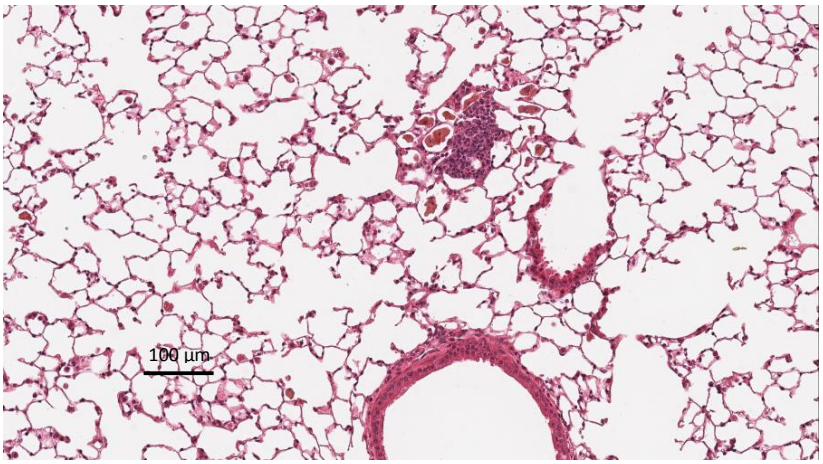


Image 26 **Left lung, dissection time point 6, THS 2.2_Twitch, (20x objective)**

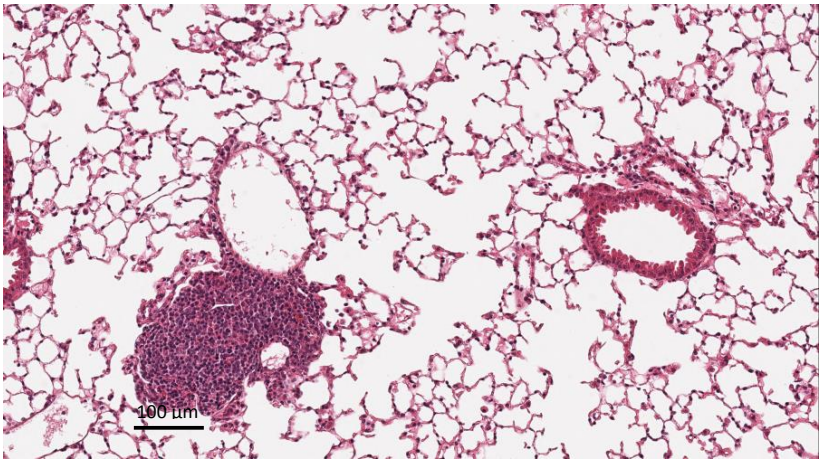


Image 27 **Left lung, dissection time point 8, THS 2.2_Twitch, (20x objective)**

STUDY PATHOLOGIST'S STATEMENT OF COMPLIANCE

The study pathologist acknowledges responsibility for the validity of all study data and confirms that the assessment is conducted in compliance with the project agreement.

16. Dec. 2014
Date

Dr. A. Büttner
(Board certified veterinary pathologist)

- end of document -

HISTOVIA
Toxicologic Pathology

P-15015

Conducted by Philip Morris Products S.A.

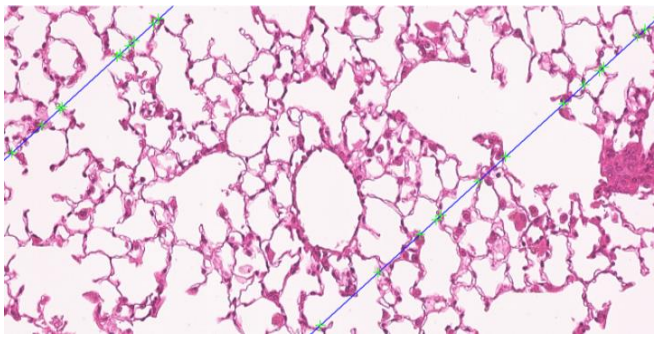
Histopathological and Morphometrical Assessment of Lung, Nose, and Liver of ApoE-Mice

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APPENDIX

16-Dec-2014

Consisting of 194 Pages



Determination of the Mean Chord Length

Contact: Dr. Ansgar Büttner
Phone: +49-2206-863774
E-Mail: a.buettner@histovia.com

Report Structure

The data for the entire project are reported in three parts:

- **in part I**, the data from the dissections performed 1, 2, and 3 months after the experimental start of the study are reported
- **in part II**, the data from the dissections performed 6 months after the experimental start of the study are reported
- **in part III**, the data from all dissection time points (1, 2, 3, 6, and 8 months after the start of exposure) are reported

Part I - II are **interim reports**, part III is the **final report**.

The individual animal data for the histopathological and morphometric al analysis are listed in the Appendix.

Contact: Dr. Ansgar Büttner
Phone: +49-2206-863774
E-Mail: a.buettner@histovia.com

Content:

Histopathology data 1

Dissection time point 1 1

Nose 1

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Liver 25

Morphometry data 28

Dissection time point 2 29

Nose 29

Lung 38

Liver 53

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Dissection time point 3 57

Nose 57

Lung 72

Liver 97

Morphometry data 101

Dissection time point 6 103

Nose 103

Lung 118

Liver 143

Morphometry data 147

Dissection time point 8 149

Nose 149

Lung 164

Liver 189

Morphometry data 193

HISTOPATHOLOGY DATA

DISSECTION TIME POINT 1

NOSE

Table 1 Individual histopathology data, nose level 1

Coded Animal Number			920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group			3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE								1		2
1100002	vacuolisation	HE					2					
1100003	reserve cell hyperplasia	HE	2				1	2		2	3	
1100004	squamous epithelial metaplasia	HE	2					2		2	3	
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE				2		1				
1100010	lymphocytis cells	HE					1					
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE					1	1		2	2	2
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 1 cont. Individual histopathology data, nose level 1

Coded Animal Number			920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group			3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE		1		1	1	1	2		1	
1100002	vacuolisation	HE						1				
1100003	reserve cell hyperplasia	HE	3	1	2	1		1	1			3
1100004	squamous epithelial metaplasia	HE	3		2							3
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE	1	1			1	1		1	1	1
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 1 cont. Individual histopathology data, nose level 1

Coded Animal Number			920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group			THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE	2			1	7*		1	1		
1100002	vacuolisation	HE					7*					1
1100003	reserve cell hyperplasia	HE	1			3	7*	1	3	1		3
1100004	squamous epithelial metaplasia	HE				3	7*		3			2
1100005	amount of cornification	HE					7*					
	lamina propria											
1100009	dilatation of blood vessels	HE					3					
1100010	lymphocytis cells	HE					7*					
	lumen											
1100011	red blood cells	HE					1					
1100012	eosinophilic material	HE		1		1	2	1	1	1		2
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: mechanical destruction of turbinates

Table 2 Individual histopathology data, nose level 2

Coded Animal Number			920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group			3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**										*	
1200001	degeneration	HE					1				7	
1200002	vacuolisation	HE					1			1	7	
1200003	reserve cell hyperplasia	HE									7	
1200004	squamous epithelial metaplasia	HE									7	
	lamina propria											
1200005	dilatation of blood vessels	HE				1					7	
	lumen											
1200006	eosinophilic material	HE									7	
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: inadequate orientation at lower part (late)

Table 2 cont. Individual histopathology data, nose level 2

Coded Animal Number			920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group			3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**									*	*	
1200001	degeneration	HE								7	7	
1200002	vacuolisation	HE								7	7	
1200003	reserve cell hyperplasia	HE								7	7	
1200004	squamous epithelial metaplasia	HE								7	7	
	lamina propria											
1200005	dilatation of blood vessels	HE								7	7	
	lumen											
1200006	eosinophilic material	HE								7	7	
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE				1f						1f
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

f: focal

*: inadequate orientation at lower part (late)

Table 2 cont. Individual histopathology data, nose level 2

Coded Animal Number			920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group			THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE									1	
1200002	vacuolisation	HE										
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE				2						
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 3 Individual histopathology data, nose level 4

Coded Animal Number			920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group			3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE				7						
1400002	vacuolisation	HE										
1400003	squamous epithelial metaplasia	HE				7						
	lamina propria											
1400004	loss of nerve bundles	HE				7						
	lumen											
1400006	red blood cells	HE				7						
1400007	amorphous eosinophilic material	HE				7						
1400008	necrotic cells	HE				7						
	pharyngeal duct											
1410001	vacuolisation	HE				7						
	molar teeth											
-	-	HE				7						
	olfactory bulb											
-	-	HE				7						

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 3 cont. Individual histopathology data, nose level 4

Coded Animal Number			920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group			3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE									3*	
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 3 cont. Individual histopathology data, nose level 4

Coded Animal Number			920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group			THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE		7								
1400002	vacuolisation	HE		7								
1400003	squamous epithelial metaplasia	HE		7								
	lamina propria											
1400004	loss of nerve bundles	HE		7								
	lumen											
1400006	red blood cells	HE		7								
1400007	amorphous eosinophilic material	HE		7								
1400008	necrotic cells	HE		7								
	pharyngeal duct											
1410001	vacuolisation	HE		7								
	molar teeth											
-	-	HE		7								
	olfactory bulb											
-	-	HE		7								

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

LUNG

Table 4 Individual histopathology data, lung section 1

Coded Animal Number		920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group		3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2					2		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1					1				
1002102	hypertrophy/hyperplasia						1				
	lumen										
1002201	macrophages without pigmentation	2	1	1		1	2		2	3	1
1002202	macrophages with pigmentation	2					2			2	
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates			1		1	1		1	1	
1002205	neutrophilic granulocytes						1			1	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						2			1	
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells						1			1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 4 cont. Individual histopathology data, lung section 1

Coded Animal Number		920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group		3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	1		1	1						2
	alveoli										
	epithelial findings				*	**					**
1002101	alveolar emphysema	1		1					1	1	2
1002102	hypertrophy/hyperplasia	1		1					1	1	2
	lumen										
1002201	macrophages without pigmentation	3	1	3	1			1	1		3
1002202	macrophages with pigmentation	2		2							2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	2	1	1	1			1	1		1
1002205	neutrophilic granulocytes	1		1							1
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate									2	1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1		1	2 f	2f					2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

f: focal
*: alveolar enlargement at hilus area
**: tip of the lung not enfold by instillation

Table 4 cont. Individual histopathology data, lung section 1

Coded Animal Number		920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group		THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1	1	2			7	3
	alveoli										
	epithelial findings										
1002101	alveolar emphysema				1	1					1
1002102	hypertrophy/hyperplasia				1	1					1
	lumen										
1002201	macrophages without pigmentation			1	2	2	1	2	1	1	3
1002202	macrophages with pigmentation				2			1			2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates			1	2	1	1	1	1	1	2
1002205	neutrophilic granulocytes				2	1		1			2
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate									1	1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells				2				1		1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 5 Individual histopathology data, lung section 2

Coded Animal Number		920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group		3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2		1		2	2			2	1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1			1				
1002102	hypertrophy/hyperplasia						1				
	lumen										
1002201	macrophages without pigmentation	2	1	1		1	3		1	3	1
1002202	macrophages with pigmentation	2					2			2	
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	1	1	1		1	1		1	1	1
1002205	neutrophilic granulocytes	1					1			1	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate	1					1				
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1		1			1			1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 5 cont. Individual histopathology data, lung section 2

Coded Animal Number		920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group		3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2		1	1	2			2		2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1		1			1		1
1002102	hypertrophy/hyperplasia			1					1		1
	lumen					*					*
1002201	macrophages without pigmentation	3	1	3	1			1	1		2
1002202	macrophages with pigmentation	2		2							2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	1	1	1	1			1	1		1
1002205	neutrophilic granulocytes	1		1							1
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate	1		1						2	1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1		1	1				1		2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Remarks:
*: tip of the lung not enfold by instillation

Table 5 cont. Individual histopathology data, lung section 2

Coded Animal Number		920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group		THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2	1	1				2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema				1			1	1		1
1002102	hypertrophy/hyperplasia				1			1			1
	lumen										
1002201	macrophages without pigmentation		1	1	3	2	1	2	1		3
1002202	macrophages with pigmentation				2			1			2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates			1	1	1	1	1	1		2
1002205	neutrophilic granulocytes				1	1		1			2
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				1	1			1		2
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells				1				1	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 6 Individual histopathology data, lung section 3

Coded Animal Number		920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group		3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2		1		1	1			2	
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema										
1002102	hypertrophy/hyperplasia			1							
	lumen										
1002201	macrophages without pigmentation	2	1	1		1	2		1	2	
1002202	macrophages with pigmentation	1					2			2	
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates			1		1	1		1	1	
1002205	neutrophilic granulocytes									1	
1002206	XXL, PAS-positive macrophages	3	0	0	0	0	4	0	0	2	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1					1				

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 6 cont. Individual histopathology data, lung section 3

Coded Animal Number		920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group		3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	1	1	1		2		1	2		2
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus			1	1	1				1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1							1
1002102	hypertrophy/hyperplasia			1							1
	lumen					*					*
1002201	macrophages without pigmentation	2		2		1		1			2
1002202	macrophages with pigmentation	2		2							2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	1		1				1			1
1002205	neutrophilic granulocytes	1		1							1
1002206	XXL, PAS-positive macrophages	12	0	11	0	0	0	0	0	0	8
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			1					2		2
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1				1					1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Remarks:
*: part of the lung not enfold by instillation

Table 6 cont. Individual histopathology data, lung section 3

Coded Animal Number		920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group		THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia			1	1	1	1	2			2
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus	7	1				1	7			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema				1					1	1
1002102	hypertrophy/hyperplasia				1					1	1
	lumen										
1002201	macrophages without pigmentation		1	1	2	1	1	2	1		3
1002202	macrophages with pigmentation				2			2			2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates		1	1	1	1	1	1	1		2
1002205	neutrophilic granulocytes				1			1			1
1002206	XXL, PAS-positive macrophages	0	0	0	28	0	0	14	0	0	59
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate								1		2 fe
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells				1	1		1		1	2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

fe: focally extensive

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 7 Individual histopathology data, lung section 4

Coded Animal Number		920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposue Group		3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2					2		1	1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema						1				
1002102	hypertrophy/hyperplasia						1				
	lumen										
1002201	macrophages without pigmentation	2	1	1	1	1	2		1	3	1
1002202	macrophages with pigmentation	2					1			2	
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	1		1		1	1		1	1	1
1002205	neutrophilic granulocytes	1					1			1	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	1			2	1				1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 7 cont. Individual histopathology data, lung section 4

Coded Animal Number		920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposue Group		3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2		1	1	2			2		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1					1		1
1002102	hypertrophy/hyperplasia			1					1		1
	lumen					*					*
1002201	macrophages without pigmentation	3		3	1				1		2
1002202	macrophages with pigmentation	2		2							2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	1		1					1		1
1002205	neutrophilic granulocytes	1		1							1
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate	1									
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1			1						2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Remarks:
*: part of the lung not enfold by instillation

Table 7 cont. Individual histopathology data, lung section 4

Coded Animal Number		920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposue Group		THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1	2	1	1		1	2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	1	1	1		1		1	1
1002102	hypertrophy/hyperplasia		1	1	1	1		2			1
	lumen										
1002201	macrophages without pigmentation			1	3	1	1	3			3
1002202	macrophages with pigmentation				2			2			2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates			1	1	1	1	2			2
1002205	neutrophilic granulocytes				1			1			1
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				1		1		2		1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells			1	1			1	1	1	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 8 Individual histopathology data, lung section 5

Coded Animal Number		920004	920036	920044	920076	920079	920113	920144	920145	920212	920214
Exposure Group		3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2					2			1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	1			2			1	
1002102	hypertrophy/hyperplasia						1				
	lumen										
1002201	marophages without pigmentation	3	1	1		1	3		1	3	
1002202	macrophages with pigmentation	2					2			2	
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates			1			1			1	
1002205	neurophilic granulocytes						1			1	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			1			1			1	
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells					1					

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 8 cont. Individual histopathology data, lung section 5

Coded Animal Number		920224	920304	920318	920368	920395	920458	920525	920568	920580	920649
Exposure Group		3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	7		7							7
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	2		2	1						1
1002102	hypertrophy/hyperplasia	1		1							2
	lumen					*					
1002201	marophages without pigmentation	3	1	3	1						3
1002202	macrophages with pigmentation	2		2							2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	2		2							1
1002205	neurophilic granulocytes	1		1							1
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1		1							

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Remarks:
*: part of the lung not enfold by instillation

Table 8 cont. Individual histopathology data, lung section 5

Coded Animal Number		920733	920840	920891	920909	920914	920934	920956	921009	921016	921105
Exposure Group		THS 2.2_CONT	THS 2.2_CONT	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT	SHAM	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1	1					7
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1			1	1		1			
1002102	hypertrophy/hyperplasia	1			1	1		2			
	lumen										
1002201	marophages without pigmentation				3	1	1	3			3
1002202	macrophages with pigmentation				2			2			2
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates				2	1	1	2			2
1002205	neurophilic granulocytes				1			2			1
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells				1					1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

LIVER

Table 9 Individual histopathology data, liver

Coded Animal Number			920017	920085	920136	920143	920166	920178	920249	920268	920278	920297
Exposure Group			SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
Code	Site / Finding	Staining										
	parenchyma											
4000001	micro-granuloma with micro-hemorrhage	HE	1	1			2	2		1	1	
4000002	cytoplasmatic vacuolisation, hepatocytes	HE		2		3	2	1		3	2	
4000003	hyperchromasia, hepatocytes	HE			3	2			2	2	3	3
4000004	mono-nuclear inflammatory cells	HE	1	1		1	1	2	1	1	1	1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	3	1	2	3	2	2	3	4	2
4000007	amount of glycogen	PAS	3	4	2	2	4	4	2	1	2	1
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE					1	1			1	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE			2	1	1	2	1	1	1	2
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE			2			1				1
4000013	increase of collagen fibers	HE	1		2			2				1

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 9 cont. Individual histopathology data, liver

Coded Animal Number			920321	920358	920383	920413	920635	920692	920701	920753	920822	920838
Exposure Group			SHAM	3R4F_CONT	SHAM	3R4F_CONT	SHAM	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	3R4F_CONT
Code	Site / Finding	Staining										
	parenchyma											
4000001	micro-granuloma with micro-hemorrhage	HE	1	1	1		2		1		1	
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	2	4	2		2	4	1	1	2	3
4000003	hyperchromasia, hepatocytes	HE		1	3	2		3				
4000004	mono-nuclear inflammatory cells	HE	1				1		1		1	
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	4	2	2	4	3	3	3	3	4
4000007	amount of glycogen	PAS	3	5	4	2	4	1	4	3	2	3
4000008	hemorrhage	HE										3
4000009	degeneration/necrosis, hepatocytes	HE		1	2	1	1			1	1	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	1	1	1	1	1			2	1	
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE		1			1			1		
4000013	increase of collagen fibers	HE		1		2	2		1	2		

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 9 cont. Individual histopathology data, liver

Coded Animal Number			920925	920994	921033	921103						
Exposure Group			THS 2.2_CONT	3R4F_CONT	SHAM	SHAM						
	Site / Finding	Staining										
Code	**parenchyma**											
4000001	micro-granuloma with micro-hemorrhage	HE	1	1		1						
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	3	1	3	3						
4000003	hyperchromasia, hepatocytes	HE										
4000004	mono-nuclear inflammatory cells	HE	1	1	1	1						
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	3	2	3						
4000007	amount of glycogen	PAS	3	4	4	5						
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE	1	2	1							
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	1	2	2	1						
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE	1	2	2							
4000013	increase of collagen fibers	HE	1	2	3							

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

MORPHOMETRY DATA

Table 10 Individual morphometrical data and histopathology data of alveolar emphysema

Animal ID	Exposure Group	LM	DI	BA	Lung Volume	Emphysema
920076	SHAM	39,9	11,5	17,6	81,1	0
920144	SHAM	40,1	5,2	15,9	164,7	0
920368	SHAM	39,8	10,1	14,8	132,7	0,2
920458	SHAM	39,9	7,1	14,8	142,5	0
920525	SHAM	42,6	17,9	16,2	164,7	0
920891	SHAM	42,4	7	15,2	156,8	0,2
920914	SHAM	invalid	invalid	invalid	invalid	0,6
920934	SHAM	44,4	11	16,5	115,0	0
921009	SHAM	44,2	14,5	16,7	126,8	0,2
921016	SHAM	48,4	14,8	14,6	109,1	0,4
920004	3R4F_CONT	37,6	12,2	16,5	114,5	0,4
920113	3R4F_CONT	43,4	20,9	16,9	124,4	1
920145	3R4F_CONT	37,9	3,9	16,2	155,3	0
920212	3R4F_CONT	47,1	11,8	12,3	133,7	0,2
920224	3R4F_CONT	43,3	21,7	14,2	121,9	0,8
920318	3R4F_CONT	47	18,9	10,4	132,2	1,2
920649	3R4F_CONT	48,7	27,5	12,3	177,9	1,2
920909	3R4F_CONT	46,6	23,3	13	142,5	1
920956	3R4F_CONT	45,6	26	16,1	134,7	0,6
921105	3R4F_CONT	51,5	22,8	13,6	130,3	0,8
920036	THS 2.2_CONT	46	5,2	17,8	149,4	0,2
920044	THS 2.2_CONT	42,5	6	14,6	116,0	0,4
920079	THS 2.2_CONT	37,5	6,3	16,2	173,0	0
920214	THS 2.2_CONT	43,3	6,8	12,7	174,5	0
920304	THS 2.2_CONT	43,8	3,2	14,9	105,7	0
920395	THS 2.2_CONT	invalid	invalid	invalid	invalid	0,2
920568	THS 2.2_CONT	43	12,7	16,6	89,0	0,6
920580	THS 2.2_CONT	41,2	17,8	15,8	117,5	0,2
920733	THS 2.2_CONT	44	7,5	15,8	125,8	0,2
920840	THS 2.2_CONT	42,4	10,7	16,8	146,5	0,2

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

DISSECTION TIME POINT 2

NOSE

Table 11 Individual histopathology data, nose level 1

Coded Animal Number			920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group			THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE				2		7*	1		1	
1100002	vacuolisation	HE						7*				
1100003	reserve cell hyperplasia	HE		3	3	1	1	7*	3		3	
1100004	squamous epithelial metaplasia	HE		3	3			7*	3		3	
1100005	amount of cornification	HE						7*				
	lamina propria											
1100009	dilatation of blood vessels	HE						7*				
1100010	lymphocytis cells	HE						7*				
	lumen											
1100011	red blood cells	HE						7*				
1100012	eosinophilic material	HE	1		1	1		7*		1		
1100013	necrotic cells	HE						7*				

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: mechanical destruction

Table 11 cont. Individual histopathology data, nose level 1

Coded Animal Number			920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group			SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE			1	2				1		
1100002	vacuolisation	HE										
1100003	reserve cell hyperplasia	HE		3		1	1	1	3	1		
1100004	squamous epithelial metaplasia	HE		2					2			
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE			1	1				1		
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 11 cont. Individual histopathology data, nose level 1

Coded Animal Number			920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group			THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding	Staining	#									
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE		2	1						2	
1100002	vacuolisation	HE		2								
1100003	reserve cell hyperplasia	HE		1		3		3	3	3		
1100004	squamous epithelial metaplasia	HE				3		3	3	2		
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										1
	lumen											
1100011	red blood cells	HE		2								
1100012	eosinophilic material	HE	2	2	1	4			2		1	
1100013	necrotic cells	HE	1*			3						

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

#: severe purulent and necrotizing inflammation at peripheral muscle tissue

*: with plant material (ventral lumen)

Table 12 Individual histopathology data, nose level 2

Coded Animal Number			920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group			THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE			1							2**
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE						3				
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium						*					
1210001	hyperplasia, epithelial layers	HE					7					
1210002	vacuolisation	HE								1		
1210003	atrophy	HE					7					
1210004	squamous epithelial metaplasia	HE					7					
	lamina propria											
1210005	loss of nerve bundles	HE					7					
	lumen											
1210006	red blood cells	HE					7					
1210007	amorphous eosinophilic material	HE					7					
1210008	necrotic cells	HE					7					

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: tissue missing
**: eosinophilic crystals

Table 12 cont. Individual histopathology data, nose level 2

Coded Animal Number			920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group			SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE	2*									
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 12 cont. Individual histopathology data, nose level 2

Coded Animal Number			920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group			THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**		**									
1200001	degeneration	HE	7									
1200002	vacuolisation	HE	7					1				
1200003	reserve cell hyperplasia	HE	7									
1200004	squamous epithelial metaplasia	HE	7									
	lamina propria											
1200005	dilatation of blood vessels	HE	7									
	lumen											
1200006	eosinophilic material	HE	7									
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE							1f	1f		
1210002	vacuolisation	HE	1*									
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

**: inadequate orientation at lower part (late)

f: focal

#: purulent inflammation
at peripheral muscle tissue
(consider also findings at level 1)

Table 13 Individual histopathology data, nose level 4

Coded Animal Number			920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group			THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE								1*	1	
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 13 cont. Individual histopathology data, nose level 4

Coded Animal Number			920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group			SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**							*				
1400001	atrophy	HE						7				
1400002	vacuolisation	HE				1	1	7			1	
1400003	squamous epithelial metaplasia	HE						7				
	lamina propria											
1400004	loss of nerve bundles	HE						7				
	lumen											
1400006	red blood cells	HE						7		1		
1400007	amorphous eosinophilic material	HE						7				
1400008	necrotic cells	HE						7				
	pharyngeal duct											
1410001	vacuolisation	HE						7				
	molar teeth											
-	-	HE						7				
	olfactory bulb											
-	-	HE						7				

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: mechanical destruction

Table 13 cont. Individual histopathology data, nose level 4

Coded Animal Number			920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group			THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE	4*					1		1		
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE	2*									
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals
mf: multifocal

LUNG

Table 14 Individual histopathology data, lung section 1

Coded Animal Number		920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group		THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding										
Code	**bronchi**		*								
1001001	reserve cell hyperplasia		2	7	1			2			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		2	7		1		2		1	1
1002102	hypertrophy/hyperplasia		2	7		1		2		1	
	lumen										
1002201	macrophages without pigmentation		3	7		2	1	4	1	3	2
1002202	macrophages with pigmentation		3	7		1		3		2	1
1002203	pigmented macrophage nests			7				1			
1002204	lymphocytic infiltrates		2	7		1		2	1	2	
1002205	neutrophilic granulocytes		2	7		1		2		2	
1002207	amorphous eosinophilic material			7							
1002210	brownisch deposits			7							
1002209	transudate / exudate			7				2			
1002208	erytrocytes			7							
	interstitium										
1002301	lymphocytic cells			7							
1002302	thickened and cell-rich			7							
	blood vessels										
1002401	perivascular lymphocytic cells		1	7				1		1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

*: no tissue available

Table 14 cont. Individual histopathology data, lung section 1

Coded Animal Number		920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group		SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia			1				1			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1		1		1	1			
1002102	hypertrophy/hyperplasia		1		1			1			
	lumen										
1002201	macrophages without pigmentation		3	2	1	1	2	3	1		
1002202	macrophages with pigmentation		3					2			
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates		2	1	1	1	1	1	1		
1002205	neutrophilic granulocytes		2					1			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate								1		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells						1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells				1		1	1			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 14 cont. Individual histopathology data, lung section 1

Coded Animal Number		920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group		THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1			1			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1	1		2	1		2	
1002102	hypertrophy/hyperplasia			1	1		2	1		1	
	lumen										
1002201	macrophages without pigmentation			1	3	1	4	3	2	2	
1002202	macrophages with pigmentation				3		2	3	1		
1002203	pigmented macrophage nests							1			
1002204	lymphocytic infiltrates			1	2	1	2	2	1	1	
1002205	neutrophilic granulocytes				2		2	2			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate					1				1	
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells				1		1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2			1		1	1			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 15 Individual histopathology data, lung section 2

Coded Animal Number		920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group		THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding										
Code	**bronchi**			*							
1001001	reserve cell hyperplasia		2	7	1	1		3		2	1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	7	1	1		2		1	
1002102	hypertrophy/hyperplasia			7		1		2		1	1
	lumen										
1002201	macrophages without pigmentation		3	7	1	2		3	1	2	1
1002202	macrophages with pigmentation		3	7				3		2	
1002203	pigmented macrophage nests			7				1			
1002204	lymphocytic infiltrates		2	7	1	1		2	1	2	1
1002205	neutrophilic granulocytes		2	7		1		2		1	
1002207	amorphous eosinophilic material			7							
1002210	brownisch deposits			7							
1002209	transudate / exudate			7				2			
1002208	erytrocytes			7							
	interstitium										
1002301	lymphocytic cells			7							
1002302	thickened and cell-rich			7							
	blood vessels										
1002401	perivascular lymphocytic cells		2	7				2			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

*: no tissue available

Table 15 cont. Individual histopathology data, lung section 2

Coded Animal Number		920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group		SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2				1	1			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	1			2	1	1		
1002102	hypertrophy/hyperplasia		1	1			1	1			
	lumen										
1002201	macrophages without pigmentation		3	1	1	1	2	3	1		
1002202	macrophages with pigmentation		2					2			
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates		2	1	1	1	1	1	1		
1002205	neutrophilic granulocytes		1					1			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells					1	2	1	1	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 15 cont. Individual histopathology data, lung section 2

Coded Animal Number		920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group		THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1		1	1	1	1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1		1	1	2	2	1	1	
1002102	hypertrophy/hyperplasia				1		2	2	1		
	lumen										
1002201	macrophages without pigmentation		1	1	3		4	3	2	1	
1002202	macrophages with pigmentation				3		3	3	2		
1002203	pigmented macrophage nests				1		1	1	1		
1002204	lymphocytic infiltrates		1	1	2		2	2	2	1	
1002205	neutrophilic granulocytes				2		2	2	1		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		1			1				1	
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells						1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1			1		1	1	1	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 16 Individual histopathology data, lung section 3

Coded Animal Number		920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group		THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2	7	1	1		2	7		
1001002	BALT hyperplasia, main bronchus			7							
1001003	goblet cell hyperplasia, main bronchus		1	7		1					
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	7	1			2		1	
1002102	hypertrophy/hyperplasia		1	7				1		1	
	lumen										
1002201	macrophages without pigmentation	1	3	7		2		4	1	3	
1002202	macrophages with pigmentation		3	7				3		2	
1002203	pigmented macrophage nests		1	7							
1002204	lymphocytic infiltrates	1	2	7		1		2	1	2	
1002205	neutrophilic granulocytes		2	7				2		1	
1002206	XXL, PAS-positive macrophages	0	27	.	0	0	0	34	0	22	0
1002207	amorphous eosinophilic material			7							
1002210	brownisch deposits			7							
1002209	transudate / exudate	1		7		1		2			
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells			7							
1002302	thickened and cell-rich			7							
	blood vessels										
1002401	perivascular lymphocytic cells		2	7		1		1		1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

*: no tissue available

Table 16 cont. Individual histopathology data, lung section 3

Coded Animal Number		920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group		SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1					1			
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus	1	1					1	1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1				1	1			
1002102	hypertrophy/hyperplasia						1	1			
	lumen										
1002201	macrophages without pigmentation	1	3	1		1	1	3	1		
1002202	macrophages with pigmentation		3					2			
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates	1	2	1		1	1	1	1		
1002205	neutrophilic granulocytes		2					1			
1002206	XXL, PAS-positive macrophages	0	58	0	0	0	0	18	0	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells							1			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 16 cont. Individual histopathology data, lung section 3

Coded Animal Number		920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group		THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1	1	2	1			
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus					1				1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema					1	2	1	1	1	
1002102	hypertrophy/hyperplasia						2	1	1	1	
	lumen										
1002201	macrophages without pigmentation		1		2		4	3	3	1	
1002202	macrophages with pigmentation				2		3	3	2		
1002203	pigmented macrophage nests						2	1	2		
1002204	lymphocytic infiltrates		1		1		2	2	2	1	
1002205	neutrophilic granulocytes						2	2	1		
1002206	XXL, PAS-positive macrophages	0	0	0	32	0	97	63	53	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		1								
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1					1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2					1	1			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 17 Individual histopathology data, lung section 4

Coded Animal Number		920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposue Group		THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding										
Code	**bronchi**			*							
1001001	reserve cell hyperplasia		2	7	1			2	1	1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	7		1		1		1	1
1002102	hypertrophy/hyperplasia		1	7				1		1	1
	lumen										
1002201	macrophages without pigmentation	1	3	7		2		3		2	1
1002202	macrophages with pigmentation		3	7				3		2	
1002203	pigmented macrophage nests			7							
1002204	lymphocytic infiltrates	1	2	7		1		2		1	1
1002205	neutrophilic granulocytes		2	7				2		1	
1002207	amorphous eosinophilic material			7							
1002210	brownisch deposits			7							
1002209	transudate / exudate			7				1			
1002208	erytrocytes			7							
	interstitium										
1002301	lymphocytic cells			7							
1002302	thickened and cell-rich			7							
	blood vessels										
1002401	perivascular lymphocytic cells		1	7				1			

*: no tissue available

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 17 cont. Individual histopathology data, lung section 4

Coded Animal Number		920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposue Group		SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2					1			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	1			2	1			
1002102	hypertrophy/hyperplasia		1				1	1			
	lumen										
1002201	macrophages without pigmentation		3	1			2	2			
1002202	macrophages with pigmentation		2					2			
1002203	pigmented macrophage nests							1			
1002204	lymphocytic infiltrates		2	1			1	1			
1002205	neutrophilic granulocytes		2					1			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						1				
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells							1	1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1						2		1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 17 cont. Individual histopathology data, lung section 4

Coded Animal Number		920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposue Group		THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1		1	1	1	1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1		1		2	2	2	1	
1002102	hypertrophy/hyperplasia				1		2	1	2	1	
	lumen										
1002201	macrophages without pigmentation		1		3	1	4	3	3	1	
1002202	macrophages with pigmentation				3		3	3	2		
1002203	pigmented macrophage nests				1		2	1			
1002204	lymphocytic infiltrates		1		2		2	2	2	1	
1002205	neutrophilic granulocytes				1		2	2	1		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells				1		1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	1		1		2		1		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 18 Individual histopathology data, lung section 5

Coded Animal Number		920013	920018	920086	920124	920151	920265	920311	920324	920401	920427
Exposure Group		THS 2.2_CONT	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	SHAM
	Site / Finding										
Code	**bronchi**			*							
1001001	reserve cell hyperplasia		7	7				7		1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			7	1	1		1		1	1
1002102	hypertrophy/hyperplasia			7				1		1	
	lumen										
1002201	marophages without pigmentation		3	7	1	2		3		3	
1002202	macrophages with pigmentation		3	7				3		2	
1002203	pigmented macrophage nests			7							
1002204	lymphocytic infiltrates		2	7	1	1		2		2	
1002205	neurophilic granulocytes		2	7				1		1	
1002207	amorphous eosinophilic material			7							
1002210	brownisch deposits			7							
1002209	transudate / exudate			7							
1002208	erytrocytes			7							
	interstitium										
1002301	lymphocytis cells			7							
1002302	thickened and cell-rich			7							
	blood vessels										
1002401	perivascular lymphocytic cells			7				1		1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

*: no tissue available

Table 18 cont. Individual histopathology data, lung section 5

Coded Animal Number		920442	920467	920474	920493	920516	920528	920531	920536	920572	920639
Exposure Group		SHAM	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia			7		7	1				
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1		1		2	2	1		
1002102	hypertrophy/hyperplasia		1				1	2	1		
	lumen										
1002201	marophages without pigmentation		3	1	1		2	3			
1002202	macrophages with pigmentation		3					3			
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates		2	1	1		1	2			
1002205	neurophilic granulocytes		2					1			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells							1			
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells							1			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 18 cont. Individual histopathology data, lung section 5

Coded Animal Number		920694	920714	920757	920833	920867	920876	920952	920959	920973	921087
Exposure Group		THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	3R4F_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1			7	7		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1		1	1	2	2	2	1	
1002102	hypertrophy/hyperplasia				1		2	2	2	1	
	lumen										
1002201	marophages without pigmentation		1	1	3	1	3	3	3	1	
1002202	macrophages with pigmentation				2		3	3	3		
1002203	pigmented macrophage nests				1		2		2		
1002204	lymphocytic infiltrates		1	1	2	1	2	2	2	1	
1002205	neurophilic granulocytes				1		2	1	1		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		2								
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1			1		1	1	1	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

LIVER

Table 19 Individual histopathology data, liver

Coded Animal Number			920027	920104	920141	920240	920262	920271	920325	920332	920486	920513
Exposure Group			3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	SHAM	3R4F_CONT	3R4F_CONT	THS 2.2_CONT	SHAM	SHAM
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	1	1	1		1	1		1	1	1
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	1	2	2		1	1	1	3	2	1
4000003	hyperchromasia, hepatocytes	HE	1	2		1	1	3	3			3
4000004	mono-nuclear inflammatory cells	HE	1	1	1		1	1		1	1	1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	4	2	2	3	3	3	3	4	4
4000007	amount of glycogen	PAS	2	3	4	2	4	1	5	2	2	4
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE	1	1					1	2	2	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	2	2	1	1	1	2	1	1	
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE	1	1	1		1	1				
4000013	increase of collagen fibers	HE	1	2	1	1		2	2	2	1	

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 19 cont. Individual histopathology data, liver

Coded Animal Number			920578	920631	920690	920764	920788	920807	920819	920872	920890	920975
Exposure Group			3R4F_CONT	SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	2	1	1	1	1	1	1	1	2	
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	7*		1	2	3	1	2		3	3
4000003	hyperchromasia, hepatocytes	HE	7*	2			1		3	1	3	
4000004	mono-nuclear inflammatory cells	HE	1	1	1	1	1	1	1	1	1	1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	3	3	3	4	4	3	3	4	4
4000007	amount of glycogen	PAS	3	5	1	2	2	3	3	3	4	4
4000008	hemorrhage	HE									1	
4000009	degeneration/necrosis, hepatocytes	HE		1	1			2	1	1	1	1
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	2	2	1	2	2	2	2	2	1
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE			1	1	1	2	2	1		1
4000013	increase of collagen fibers	HE			2	1	1	2	1	1	2	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: thick slide

Table 19 cont. Individual histopathology data, liver

Coded Animal Number			921020	921044	921046	921055						
Exposure Group			THS 2.2_CONT	SHAM	3R4F_CONT	THS 2.2_CONT						
Code	Site / Finding	Staining										
	parenchyma											
4000001	micro-granuloma with micro-hemorrhage	HE		1	1	1						
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	1	4		1						
4000003	hyperchromasia, hepatocytes	HE			3							
4000004	mono-nuclear inflammatory cells	HE			1	1						
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	4	2	4						
4000007	amount of glycogen	PAS	4	4	2	3						
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE	1	1	1	1						
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	2	2	1						
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE			1	1						
4000013	increase of collagen fibers	HE	1	1	2	2						

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

MORPHOMETRY DATA

Table 20 **Individual morphometrical data and histopathology data of alveolar emphysema**

Animal ID	Exposure Group	LM	DI	BA	Lung Volume	Emphysema
920151	SHAM	45,3	10,7	14,2	153,4	0,8
920427	SHAM	invalid	invalid	invalid	invalid	0,6
920442	SHAM	46,7	22,7	14,1	145,5	0
920474	SHAM	40,4	13,7	14,4	141,1	0,4
920536	SHAM	42,6	15,9	15,9	147,5	0,4
920572	SHAM	44,7	16,7	11,9	140,1	0
920714	SHAM	44,3	19,4	13,5	145,5	0,6
920867	SHAM	invalid	invalid	invalid	invalid	0,6
920973	SHAM	44,5	26,3	13,9	138,1	1,2
921087	SHAM	43	4,6	16,5	163,7	0
920018	3R4F_CONT	49,4	25	13,4	225,1	1
920086	3R4F_CONT	invalid	invalid	invalid	invalid	invalid
920311	3R4F_CONT	53,5	31,5	13,5	150,9	1,6
920401	3R4F_CONT	50,1	23,8	13,3	140,6	1
920467	3R4F_CONT	47,7	29,8	11,7	165,6	1
920531	3R4F_CONT	49	31,5	14,6	138,6	1,2
920833	3R4F_CONT	53,1	33,1	13,1	147,9	0,8
920876	3R4F_CONT	53,2	45	12,8	151,4	2
920952	3R4F_CONT	53,9	38,6	11,7	189,7	1,6
920959	3R4F_CONT	46,1	23,2	13,8	185,3	1,2
920013	THS 2.2_CONT	42,6	1,6	17,8	130,7	0
920124	THS 2.2_CONT	45,9	12,8	14,8	151,9	0,6
920265	THS 2.2_CONT	38,6	8,5	13,3	148,9	0
920324	THS 2.2_CONT	45,1	10	15,6	156,8	0
920493	THS 2.2_CONT	44,6	21,4	12,2	151,4	0,4
920516	THS 2.2_CONT	42,4	3,6	14,3	123,4	0
920528	THS 2.2_CONT	invalid	invalid	invalid	invalid	1,6
920639	THS 2.2_CONT	42	15,2	12,9	174,0	0
920694	THS 2.2_CONT	39,8	0,8	15,1	143,5	0
920757	THS 2.2_CONT	46,5	17,3	13,2	147,9	0,2

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

DISSECTION TIME POINT 3

NOSE

Table 21 Individual histopathology data, nose level 1

Coded Animal Number			920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group			THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**			*						##		
1100001	degeneration/atrophy	HE		7	1	2	1		1	7	1	
1100002	vacuolisation	HE		7						7		
1100003	reserve cell hyperplasia	HE		7	1		1	1	1	7		3
1100004	squamous epithelial metaplasia	HE		7						7		3
1100005	amount of cornification	HE		7						7		
	lamina propria											
1100009	dilatation of blood vessels	HE		7						7		
1100010	lymphocytis cells	HE		7						7		
	lumen											
1100011	red blood cells	HE		7						7		
1100012	eosinophilic material	HE	1	7	1	1	1		1	7		1
1100013	necrotic cells	HE		7			1#			7		

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: target level not imaged

#: with plant material (ventral lumen)

##: lateral compression of the tissue

Table 21 cont. Individual histopathology data, nose level 1

Coded Animal Number			920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group			THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE	2			1			2	1		
1100002	vacuolisation	HE	1	2					1			1
1100003	reserve cell hyperplasia	HE	1	1	1		2	1	1	1	4	2
1100004	squamous epithelial metaplasia	HE									4	
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE				1						
1100012	eosinophilic material	HE				1	2	1	1	1		
1100013	necrotic cells	HE		2#								

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

#: with plant material (ventral lumen)

Table 21 cont. Individual histopathology data, nose level 1

Coded Animal Number			920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group			3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**							##		**		
1100001	degeneration/atrophy	HE		1			1	7	1	7		
1100002	vacuolisation	HE	2		4*	4*		7		7		2
1100003	reserve cell hyperplasia	HE	3	2	1	1		7	2	7		1
1100004	squamous epithelial metaplasia	HE	3				2	7		7		
1100005	amount of cornification	HE						7		7		
	lamina propria											
1100009	dilatation of blood vessels	HE						7		7		
1100010	lymphocytis cells	HE						7		7		
	lumen											
1100011	red blood cells	HE						7		7		
1100012	eosinophilic material	HE			1	1	1	7		7	1	
1100013	necrotic cells	HE	1#					7		7		2#

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals
#: with plant material (ventral lumen)
**: target level not imaged
##: lateral compression of the tissue

Table 21 cont. Individual histopathology data, nose level 1

Coded Animal Number			920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group			THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE	1						2		1	
1100002	vacuolisation	HE			3	2			1		1	1
1100003	reserve cell hyperplasia	HE	1	2	2	1	1	4	1	4	2	2
1100004	squamous epithelial metaplasia	HE			1			3		3	1	
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE						2				
1100012	eosinophilic material	HE		2	2	1	2	2			1	
1100013	necrotic cells	HE							2#			

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 21 cont. Individual histopathology data, nose level 1

Coded Animal Number			920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group			Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding	Staining										
Code	respiratory epithelium											
1100001	degeneration/atrophy	HE	1			1		1				
1100002	vacuolisation	HE		1			1	1	1			
1100003	reserve cell hyperplasia	HE	1	4	2	1	2	2	1		4	1
1100004	squamous epithelial metaplasia	HE		3							3	
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE					1					
1100012	eosinophilic material	HE					1			2		
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 22 Individual histopathology data, nose level 2

Coded Animal Number			920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group			THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**			*			**			**		
1200001	degeneration	HE		7			7			7		
1200002	vacuolisation	HE	1	7	1		7			7		
1200003	reserve cell hyperplasia	HE		7			7			7		1
1200004	squamous epithelial metaplasia	HE		7			7			7		
	lamina propria											
1200005	dilatation of blood vessels	HE		7			7			7		
	lumen											
1200006	eosinophilic material	HE		7			7			7		
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE		7								
1210002	vacuolisation	HE		7						1		
1210003	atrophy	HE		7								
1210004	squamous epithelial metaplasia	HE		7								
	lamina propria											
1210005	loss of nerve bundles	HE		7								
	lumen											
1210006	red blood cells	HE		7								
1210007	amorphous eosinophilic material	HE		7								
1210008	necrotic cells	HE		7								

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: lateral compression of the tissue
**: inadequate orientation at lower part (late)

Table 22 cont. Individual histopathology data, nose level 2

Coded Animal Number			920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group			THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**			*								
1200001	degeneration	HE		7								
1200002	vacuolisation	HE		7						1		
1200003	reserve cell hyperplasia	HE		7								
1200004	squamous epithelial metaplasia	HE		7								
	lamina propria											
1200005	dilatation of blood vessels	HE		7								
	lumen											
1200006	eosinophilic material	HE		7								
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE		1f		1f						
1210002	vacuolisation	HE				1						
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

f: focal
*: inadequate orientation at lower part (late)

Table 22 cont. Individual histopathology data, nose level 2

Coded Animal Number			920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group			3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**		#			#	#	**				#
1200001	degeneration	HE	7			7	7	7				7
1200002	vacuolisation	HE	7			7	7	7	1			7
1200003	reserve cell hyperplasia	HE	7			7	7	7				7
1200004	squamous epithelial metaplasia	HE	7			7	7	7				7
	lamina propria											
1200005	dilatation of blood vessels	HE	7			7	7	7				7
	lumen											
1200006	eosinophilic material	HE	7			7	7	7				7
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE	1f					7				
1210002	vacuolisation	HE						7		1		1
1210003	atrophy	HE						7				
1210004	squamous epithelial metaplasia	HE						7				
	lamina propria											
1210005	loss of nerve bundles	HE						7				
	lumen											
1210006	red blood cells	HE						7				
1210007	amorphous eosinophilic material	HE						7				
1210008	necrotic cells	HE						7				

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: plant material
**: lateral compression
#: inadequate orientation at lower part (late)

Table 22 cont. Individual histopathology data, nose level 2

Coded Animal Number			920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group			THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
Code	Site / Finding	Staining										
	respiratory epithelium					*			*			
1200001	degeneration	HE				7			7			
1200002	vacuolisation	HE			1	7			7			
1200003	reserve cell hyperplasia	HE				7			7	1		
1200004	squamous epithelial metaplasia	HE				7			7			
	lamina propria											
1200005	dilatation of blood vessels	HE				7			7			
	lumen											
1200006	eosinophilic material	HE				7			7			
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										2f
1210002	vacuolisation	HE							2			
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: inadequate orientation at lower part (late)

Table 22 cont. Individual histopathology data, nose level 2

Coded Animal Number			920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group			Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE		2								3
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 23 Individual histopathology data, nose level 4

Coded Animal Number			920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group			THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE		2								1
1400002	vacuolisation	HE	1				2*			2		1
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE					2					
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct						**					
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals
**: red blood cells, lumen

Table 23 cont. Individual histopathology data, nose level 4

Coded Animal Number			920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group			THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE	1	2							1	
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct		**									
1410001	vacuolisation	HE		1								
	molar teeth											
-	-	HE										
	olfactory bulb								*			
-	-	HE									7	

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: peripheral cyst-like formation with compression of brain tissue

**: red blood cells, lumen

Table 23 cont. Individual histopathology data, nose level 4

Coded Animal Number			920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group			3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**				*							
1400001	atrophy	HE			7							
1400002	vacuolisation	HE	2	1	7	3**	3**	1				4**
1400003	squamous epithelial metaplasia	HE			7							
	lamina propria											
1400004	loss of nerve bundles	HE			7							
	lumen											
1400006	red blood cells	HE			7							
1400007	amorphous eosinophilic material	HE			7							
1400008	necrotic cells	HE			7							
	pharyngeal duct											
1410001	vacuolisation	HE	4			2	2					3**
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: inadequate orientation
**: eosinophilic crystals

Table 23 cont. Individual histopathology data, nose level 4

Coded Animal Number			920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group			THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE	1			2		1	4*	1		
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct									**		
1410001	vacuolisation	HE							1			
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals
**: red blood cells, lumen

Table 23 cont. Individual histopathology data, nose level 4

Coded Animal Number			920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group			Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**								*			
1400001	atrophy	HE										
1400002	vacuolisation	HE		2						1		
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*. intra-epithelial cyst formation

LUNG

Table 24 Individual histopathology data, lung section 1

Coded Animal Number		920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2		2						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		3	1	1	1	1		1	1	2
1002102	hypertrophy/hyperplasia		2						1		1
	lumen										
1002201	macrophages without pigmentation	1	4		1	1	2		2		3
1002202	macrophages with pigmentation	1	4				3		3		4
1002203	pigmented macrophage nests	1	1				2		1		1
1002204	lymphocytic infiltrates		2		1	1	1		1		2
1002205	neutrophilic granulocytes		2						1		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		2			1					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1				1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		3				1		1		2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 24 cont. Individual histopathology data, lung section 1

Coded Animal Number		920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group		THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	1	1	2	2		2	1	
1002102	hypertrophy/hyperplasia						1		1		
	lumen										
1002201	macrophages without pigmentation	1	2	1	1	1	1		2	1	
1002202	macrophages with pigmentation		3			2	2		2	2	
1002203	pigmented macrophage nests		2			1	2		1		
1002204	lymphocytic infiltrates	1	2		1	1	2		1		
1002205	neutrophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			1							
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					1			1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		2			1	1			1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 24 cont. Individual histopathology data, lung section 1

Coded Animal Number		920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group		3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1	2	2	2	1	2		
1002102	hypertrophy/hyperplasia				1	1	1		1		
	lumen										
1002201	macrophages without pigmentation	2	1	2	2	3	2	1	2		1
1002202	macrophages with pigmentation	1	1	3	2	3	4	2	1		
1002203	pigmented macrophage nests			1		1	3	1			
1002204	lymphocytic infiltrates	1		1	1	2	2		1		1
1002205	neutrophilic granulocytes					2	1				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				2						
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1	1		1	1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	2	1		4	3	1	1		1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 24 cont. Individual histopathology data, lung section 1

Coded Animal Number		920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group		THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia			7		7	2		2	1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1		1		3	1	3	2	
1002102	hypertrophy/hyperplasia						3		3	1	
	lumen										
1002201	macrophages without pigmentation	1	2	1	1	1	4	1	4	2	1
1002202	macrophages with pigmentation		1	2			4		4	3	
1002203	pigmented macrophage nests			1						2	
1002204	lymphocytic infiltrates	1	1		1	1	2	1	2	1	1
1002205	neutrophilic granulocytes						2		2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate					1	2	2	2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells								1	1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1			1	2		2	2	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 24 cont. Individual histopathology data, lung section 1

Coded Animal Number		920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group		Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2				1				
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	2	2		1	2	1	1	3	1
1002102	hypertrophy/hyperplasia	1	2	1			1			2	
	lumen										
1002201	macrophages without pigmentation	2	4	1		1	3	1	1	3	2
1002202	macrophages with pigmentation	3	3	1		3	3				2
1002203	pigmented macrophage nests	1	1			2					
1002204	lymphocytic infiltrates	1	2	1		2	2	1	1	1	1
1002205	neutrophilic granulocytes		1				2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						2	1			
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1		1		1	1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2	1	1		3	2				2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 25 Individual histopathology data, lung section 2

Coded Animal Number		920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**						*				
1001001	reserve cell hyperplasia		2		1		1		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		3		1	1	2		2	1	2
1002102	hypertrophy/hyperplasia		2				1		1		2
	lumen										
1002201	macrophages without pigmentation	1	4		1	1	2		2		4
1002202	macrophages with pigmentation	2	4				3		3		3
1002203	pigmented macrophage nests	2	2				3				1
1002204	lymphocytic infiltrates		3		1	1	2		1		2
1002205	neutrophilic granulocytes		2						1		2
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		2			2					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1	1				1		1		1
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	3		1		1		2		2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

*: bronchiolo-alveolar adenoma

Table25 cont. Individual histopathology data, lung section 2

Coded Animal Number		920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group		THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	1	1	2	2		2	1	
1002102	hypertrophy/hyperplasia						1		1		
	lumen										
1002201	macrophages without pigmentation	1	2	1	1	1	1		2	1	
1002202	macrophages with pigmentation		3			2	2		2	2	
1002203	pigmented macrophage nests		2			1	2		1		
1002204	lymphocytic infiltrates	1	2		1	1	2		1		
1002205	neutrophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			1							
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					1			1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		2			1	1			1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 25 cont. Individual histopathology data, lung section 2

Coded Animal Number		920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group		3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						2				1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1	3	2	3	2	2	1	1
1002102	hypertrophy/hyperplasia				2	2	2	1	1		
	lumen										
1002201	macrophages without pigmentation	2	1	1	2	4	3	2	1	1	1
1002202	macrophages with pigmentation		1	1	3	3	4	3	2		
1002203	pigmented macrophage nests		1	1	1	1	4	3	2		
1002204	lymphocytic infiltrates	1	1	1	2	2	2	2		1	1
1002205	neutrophilic granulocytes					2	2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				3	1					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		2			1	1	1			
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	3	1	2	2	3	3	3	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 25 cont. Individual histopathology data, lung section 2

Coded Animal Number		920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group		THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						2		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1			3	1	2	2	
1002102	hypertrophy/hyperplasia						2		2	1	
	lumen										
1002201	macrophages without pigmentation		2	1		1	4	1	4	2	
1002202	macrophages with pigmentation		1	3			4		4	3	
1002203	pigmented macrophage nests			3			1			2	
1002204	lymphocytic infiltrates		1	1			2	1	3	2	
1002205	neutrophilic granulocytes						2		3	1	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						2		2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells			1					1	1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1	2		2	2		3	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 25 cont. Individual histopathology data, lung section 2

Coded Animal Number		920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group		Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	2	1	1	2	1	2	1	3	1
1002102	hypertrophy/hyperplasia		1					1		2	
	lumen										
1002201	macrophages without pigmentation	2	4	2	1	2	3	2	1	3	2
1002202	macrophages with pigmentation	3	3	1		3	3			2	2
1002203	pigmented macrophage nests	1	1			2				2	1
1002204	lymphocytic infiltrates	1	2	1	1	2	1	2	1	1	1
1002205	neutrophilic granulocytes		2			1	1				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		1					1			
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					2					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3			1	4	3			1	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 26 Individual histopathology data, lung section 3

Coded Animal Number		920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2		2						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		3	1	1	1	1		1	1	2
1002102	hypertrophy/hyperplasia		2						1		1
	lumen										
1002201	macrophages without pigmentation	1	4		1	1	2		2		3
1002202	macrophages with pigmentation	1	4				3		3		4
1002203	pigmented macrophage nests	1	1				2		1		1
1002204	lymphocytic infiltrates		2		1	1	1		1		2
1002205	neutrophilic granulocytes		2						1		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		2			1					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1				1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		3				1		1		2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 26 cont. Individual histopathology data, lung section 3

Coded Animal Number		920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group		THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										1
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus	1	7			2		7			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1			1		1	1	
1002102	hypertrophy/hyperplasia								1		
	lumen										
1002201	macrophages without pigmentation		1		1	1	1		2	1	
1002202	macrophages with pigmentation		2			1	1		2	2	
1002203	pigmented macrophage nests		1				1				
1002204	lymphocytic infiltrates		1		1				1		
1002205	neutrophilic granulocytes										
1002206	XXL, PAS-positive macrophages	0	0	0	0	0	0	0	0	11	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			3					2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1								
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	2		1	2			1		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 26 cont. Individual histopathology data, lung section 3

Coded Animal Number		920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group		3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			1	2	2	2	1	2		
1002102	hypertrophy/hyperplasia				1	1	1		1		
	lumen										
1002201	macrophages without pigmentation	2	1	2	2	3	2	1	2		1
1002202	macrophages with pigmentation	1	1	3	2	3	4	2	1		
1002203	pigmented macrophage nests			1		1	3	1			
1002204	lymphocytic infiltrates	1		1	1	2	2		1		1
1002205	neutrophilic granulocytes					2	1				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				2						
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1	1		1	1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	2	1		4	3	1	1		1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 26 cont. Individual histopathology data, lung section 3

Coded Animal Number		920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group		THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						2		2		
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus									1	7
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1				2	1	3	1	
1002102	hypertrophy/hyperplasia						2		2		
	lumen										
1002201	macrophages without pigmentation		1	1		1	4	1	4	2	
1002202	macrophages with pigmentation		1	2			4		4	3	
1002203	pigmented macrophage nests						1			2	
1002204	lymphocytic infiltrates						2	1	2	2	
1002205	neutrophilic granulocytes						2		2		
1002206	XXL, PAS-positive macrophages	0	0	0	0	0	123	0	97	25	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						2		2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells						1			1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells					1	1		3	2	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 26 cont. Individual histopathology data, lung section 3

Coded Animal Number		920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group		Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2								
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus						1	7			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	1	2	1	1	1	2	
1002102	hypertrophy/hyperplasia		2		1	1		1	1	2	
	lumen										
1002201	macrophages without pigmentation	2	4	1	1	3	3	1	1	3	2
1002202	macrophages with pigmentation	3	4			3	2			2	
1002203	pigmented macrophage nests	1	2			3				2	
1002204	lymphocytic infiltrates	1	2		1	2	1	1	1	1	1
1002205	neutrophilic granulocytes		2			1					
1002206	XXL, PAS-positive macrophages	5	28	0	0	27	5	0	0	5	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits						2				
1002209	transudate / exudate		1		1						
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					1	1			1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	1			3	1	1			1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 27 Individual histopathology data, lung section 4

Coded Animal Number		920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposue Group		THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1		1						1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3				2		1	1	2
1002102	hypertrophy/hyperplasia		3				1				2
	lumen										
1002201	macrophages without pigmentation	2	4				2		2		4
1002202	macrophages with pigmentation	2	4				3		2		4
1002203	pigmented macrophage nests	2	1				1		2		2
1002204	lymphocytic infiltrates	1	2				2		1		2
1002205	neutrophilic granulocytes		2								2
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		2			1					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1				1				1
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	1				2				1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 27 cont. Individual histopathology data, lung section 4

Coded Animal Number		920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposue Group		THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia							1			1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1				1	1		2	1	
1002102	hypertrophy/hyperplasia	1									
	lumen										
1002201	macrophages without pigmentation		1	1		1	1		1	1	
1002202	macrophages with pigmentation		2			1	1		2	1	
1002203	pigmented macrophage nests						2				
1002204	lymphocytic infiltrates		1	1					1		
1002205	neutrophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			3							
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		2		1		1		1		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 27 cont. Individual histopathology data, lung section 4

Coded Animal Number		920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposue Group		3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema			2	2	2	1	2	2		
1002102	hypertrophy/hyperplasia			1	1	1	1	1	1		
	lumen										
1002201	macrophages without pigmentation	2	2	2	2	4	3	2	1	1	1
1002202	macrophages with pigmentation		2	2	3	3	4	3	2		
1002203	pigmented macrophage nests					1	3	2	2		
1002204	lymphocytic infiltrates	1	1	1	1	2	1	1		3*	
1002205	neutrophilic granulocytes	1				1	1			2*	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				2						
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells			1			1	1	1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	2	1	2	1	2	2	2	3*	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: in one area

Table 27 cont. Individual histopathology data, lung section 4

Coded Animal Number		920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposue Group		THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						1		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1			1	3	1	2	1	
1002102	hypertrophy/hyperplasia						3		1		
	lumen										
1002201	macrophages without pigmentation		1	1		1	4		4	2	1
1002202	macrophages with pigmentation		2	2			4		3	3	
1002203	pigmented macrophage nests		1	2						3	
1002204	lymphocytic infiltrates						2		2	1	1
1002205	neutrophilic granulocytes						2		2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						2		2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells									1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1				1		2	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 27 cont. Individual histopathology data, lung section 4

Coded Animal Number		920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposue Group		Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	2	1	2	1	1	1	2	1
1002102	hypertrophy/hyperplasia		2	1		1			1	2	
	lumen										
1002201	macrophages without pigmentation	2	4	2	1	2	3	1	1	2	2
1002202	macrophages with pigmentation	3	3	2		3	2			1	2
1002203	pigmented macrophage nests		1			2				1	1
1002204	lymphocytic infiltrates	2	2	1	1	2	2	1	1	1	1
1002205	neutrophilic granulocytes		2				1				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		1						1		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					2					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2		1	1	3	3				1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 28 Individual histopathology data, lung section 5

Coded Animal Number		920003	920046	920049	920064	920127	920133	920150	920173	920179	920204
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_Switch	SHAM	3R4F_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7		1						
	alveoli	*									
	epithelial findings										
1002101	alveolar emphysema	1	3	1		1	2	1	1		2
1002102	hypertrophy/hyperplasia		2				1				2
	lumen										
1002201	marophages without pigmentation	2	4		1	1	2		1		3
1002202	macrophages with pigmentation	1	3				3		2		4
1002203	pigmented macrophage nests	1	1				3		1		2
1002204	lymphocytic infiltrates	1	2		1	1	1		1		2
1002205	neurophilic granulocytes		2								2
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		1								
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells										1
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1				1		1		1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

*: focal osseus metaplasia

Table 28 cont. Individual histopathology data, lung section 5

Coded Animal Number		920221	920238	920308	920313	920329	920335	920352	920359	920417	920422
Exposure Group		THS 2.2_CONT	Cessation	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia							1	7		2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	1	2	1	1	1	1	1	1
1002102	hypertrophy/hyperplasia										
	lumen										
1002201	marophages without pigmentation	1	2		1	1	1		2	2	
1002202	macrophages with pigmentation		3			2	2		3	1	
1002203	pigmented macrophage nests		1			1	1				
1002204	lymphocytic infiltrates	1	1		1		2		2		
1002205	neurophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate			3		1					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells		1						1		
1002302	thickened and cell-rich			2							
	blood vessels										
1002401	perivascular lymphocytic cells		3				3		1		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 28 cont. Individual histopathology data, lung section 5

Coded Animal Number		920429	920440	920465	920477	920479	920500	920512	920514	920521	920544
Exposure Group		3R4F_CONT	THS 2.2_Switch	Cessation	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				7	7					
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1	2	2	3	2	1	1	
1002102	hypertrophy/hyperplasia				1	1	1	1			
	lumen										
1002201	marophages without pigmentation	2	1	1	2	3	3	3	1		
1002202	macrophages with pigmentation		1	1	3	3	3	3	2		
1002203	pigmented macrophage nests						1	2	2		
1002204	lymphocytic infiltrates	1			1	2	2	2			
1002205	neurophilic granulocytes					1	2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate				2						
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells				1		1	1	1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1			1	2	2	4	1		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 28 cont. Individual histopathology data, lung section 5

Coded Animal Number		920552	920719	920738	920742	920801	920810	920812	920814	920821	920859
Exposure Group		THS 2.2_CONT	THS 2.2_Switch	THS 2.2_Switch	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						1		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		2	1	1		3	1	2	2	
1002102	hypertrophy/hyperplasia						3		2	1	
	lumen										
1002201	marophages without pigmentation		1	1			4		4	2	
1002202	macrophages with pigmentation		1	2			4		4	2	
1002203	pigmented macrophage nests			2			1		1		
1002204	lymphocytic infiltrates						2		2	1	
1002205	neurophilic granulocytes						2		2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						2		2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells						1		1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1	1			2		2	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 28 cont. Individual histopathology data, lung section 5

Coded Animal Number		920895	920916	920933	920969	920986	920992	920993	921004	921030	921054
Exposure Group		Cessation	3R4F_CONT	Cessation	SHAM	THS 2.2_Switch	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		2							7	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	4	2	1	3	2	1	1	2	1
1002102	hypertrophy/hyperplasia		2			1	1		1	1	
	lumen										
1002201	marophages without pigmentation	2	4	1	1	2	3		1	3	1
1002202	macrophages with pigmentation	3	3	1		3	1		1	2	1
1002203	pigmented macrophage nests	1	2	1		2				2	
1002204	lymphocytic infiltrates	1	2		1	2	1			1	1
1002205	neurophilic granulocytes		2								
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		2						1		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells	1				2					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	1			2	2				

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

LIVER

Table 29 Individual histopathology data, liver

Coded Animal Number			920009	920025	920096	920102	920108	920126	920153	920158	920167	920169
Exposure Group			SHAM	THS 2.2_CONT	SHAM	THS 2.2_Switch	Cessation	THS 2.2_Switch	3R4F_CONT	SHAM	Cessation	3R4F_CONT
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	1			1			1			
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	2		1	2	3	3	2	4		2
4000003	hyperchromasia, hepatocytes	HE					3	1	1		2	2
4000004	mono-nuclear inflammatory cells	HE				1	2	1	2	1		1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	4	4	2	4	3	4	4	4	4
4000007	amount of glycogen	PAS	4	4	3	3	2	4	2	3	1	1
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE				2	2		1	1		
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE		1	1	2	1				1	1
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE			1	2						
4000013	increase of collagen fibers	HE			1	1						1

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 29 cont. Individual histopathology data, liver

Coded Animal Number			920170	920185	920301	920316	920455	920489	920494	920495	920524	920573
Exposure Group			Cessation	THS 2.2_Switch	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	3R4F_CONT	Cessation	3R4F_CONT
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	2							1	1	1
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	1	2	4	1		3	2	4		3
4000003	hyperchromasia, hepatocytes	HE			2	1	1	1		2	2	1
4000004	mono-nuclear inflammatory cells	HE			1	1	1	1	1	1	2	2
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	4	4	3	3	2	5	4	2	4	4
4000007	amount of glycogen	PAS	3	2	2	3	4	3	3	5	2	2
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE					1		3	1	1	1
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE		1	1		1		1		1	1
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE										2
4000013	increase of collagen fibers	HE	1						1		1	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 29 cont. Individual histopathology data, liver

Coded Animal Number			920587	920600	920604	920633	920642	920660	920677	920796	920803	920808
Exposure Group			THS 2.2_CONT	SHAM	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	Cessation	Cessation	SHAM
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE			1	1	1	1	1		1	
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	3	3	2	2	3	1		3	4	1
4000003	hyperchromasia, hepatocytes	HE	3	1				3	3	1		3
4000004	mono-nuclear inflammatory cells	HE	2	1	1	2	2	2	1	1	1	
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	5	5	2	3	3	4	5	4	3
4000007	amount of glycogen	PAS	2	4	7	3	3	1	1	2	2	3
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE	2		2	1	2			1		1
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	1	1	1	2		2	2	1	1	2
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE			1	2		2	1	2	1	2
4000013	increase of collagen fibers	HE			1	1		2	2	2	1	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 29 cont. Individual histopathology data, liver

Coded Animal Number			920837	920908	920927	920961	920987	920995	920999	921002	921052	921079
Exposure Group			THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_CONT	THS 2.2_CONT
Code	Site / Finding	Staining										
	parenchyma											
4000001	micro-granuloma with micro-hemorrhage	HE	1	1			1	1		2	1	2
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	2	2		3	2	2	2	4	2	2
4000003	hyperchromasia, hepatocytes	HE		2	3	2	3		3	2		
4000004	mono-nuclear inflammatory cells	HE	1	1	1	1	1	1	1	2	1	1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	4	3	4	3	3	4	3	2	5	4
4000007	amount of glycogen	PAS	4	4	3	4	3	4	2	5	2	3
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE					1		1		2	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	2	1	1	2	2	2	3	2	2
4000014	brownish pigment	HE										
4000012	bile duct hyperplasia	HE	1	2			2	2	2	2	2	2
4000013	increase of collagen fibers	HE	1	1			1	2		1		1

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

MORPHOMETRY DATA

Table 30 Individual morphometrical data and histopathology data of alveolar emphysema

Animal ID	Exposure Group	LM	DI	BA	Lung Volume	Emphysema
920049	SHAM	45,2	12,6	14	158,8	0,4
920064	SHAM	47,8	26	14,8	132,7	0,4
920127	SHAM	49,8	23,5	15	194,6	0,8
920179	SHAM	48,6	20,1	14,1	145,5	0,6
920352	SHAM	47,3	17,5	13,7	111,1	0,4
920742	SHAM	46,7	9	16,6	180,4	0,4
920801	SHAM	45,8	9,1	14	147,0	0,2
920969	SHAM	43,9	4,4	15,1	223,2	0,8
920993	SHAM	42,6	9,5	15,7	157,3	1,2
921004	SHAM	42,2	12,3	16,8	147,5	1
920046	3R4F_CONT	54,2	45,6	12,6	225,6	2,8
920204	3R4F_CONT	49,2	35,4	12,2	188,3	2
920417	3R4F_CONT	47	18,7	14,3	179,4	0,8
920429	3R4F_CONT	47,5	17,8	13,3	165,2	0,6
920479	3R4F_CONT	52	25,3	11,8	204,0	2
920514	3R4F_CONT	50,9	21	14,1	229,0	1,6
920810	3R4F_CONT	50,5	23,4	11,7	152,4	2,8
920814	3R4F_CONT	50	31	14,4	270,3	2,4
920916	3R4F_CONT	55,9	42,2	11,3	179,9	2,8
921030	3R4F_CONT	47,5	24,4	13,1	186,8	2,4
920150	THS 2.2_CONT	45,7	9,3	13,1	invalid	0,2
920221	THS 2.2_CONT	43	12,7	14,6	169,6	0,8
920308	THS 2.2_CONT	47	17,4	13,9	211,8	0,8
920313	THS 2.2_CONT	45,8	11,6	14,9	196,1	0,8
920422	THS 2.2_CONT	invalid	invalid	invalid	106,2	0,2
920521	THS 2.2_CONT	53,8	23,4	14,6	189,7	0,6
920544	THS 2.2_CONT	51,7	9,1	14,5	150,9	0,2
920552	THS 2.2_CONT	46,2	16,1	15,9	194,2	0,4
920812	THS 2.2_CONT	43,2	18,6	14,1	127,8	1
920859	THS 2.2_CONT	44,2	10,3	13,6	199,6	0

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

Table 30 cont. **Individual morphometrical data and histopathology data of alveolar emphysema**

Animal ID	Exposure Group	LM	DI	BA	Lung Volume	Emphysema
920238	Cessation	43,7	8,8	13,5	186,3	0,6
920335	Cessation	50,1	13,5	14,1	171,5	1,2
920359	Cessation	47,9	21,7	15	152,9	1,4
920465	Cessation	46,8	24,5	15,9	149,4	1,2
920477	Cessation	45	19,4	14,5	186,8	2,4
920500	Cessation	47,4	12,2	15,1	220,2	2,2
920512	Cessation	50,2	13,6	15	203,5	1,8
920895	Cessation	46,7	22,6	14,7	213,8	1
920933	Cessation	53,1	12	13,6	151,9	1,6
920992	Cessation	46,3	19,5	16,7	162,2	1,4
920003	THS 2.2_Switch	47,1	11,8	17,9	invalid	0,4
920133	THS 2.2_Switch	44,2	21,3	13,4	169,6	1,6
920173	THS 2.2_Switch	47,1	23,9	13,9	137,6	1,2
920329	THS 2.2_Switch	48,4	4,8	13,5	216,8	1
920440	THS 2.2_Switch	42,7	16,7	18	102,2	0
920719	THS 2.2_Switch	46,1	10,4	14,8	169,6	1
920738	THS 2.2_Switch	45,1	6,4	17,3	164,2	0,4
920821	THS 2.2_Switch	51,2	22	17,6	172,5	1,6
920986	THS 2.2_Switch	47,9	30,5	15,2	137,6	2
921054	THS 2.2_Switch	44,8	15,8	15,9	169,6	0,8

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

DISSECTION TIME POINT 6

NOSE

Table 31 Individual histopathology data, nose level 1

Coded Animal Number			920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group			THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE			1			1				1
1100002	vacuolisation	HE			1			1		4*		2
1100003	reserve cell hyperplasia	HE		3			1	1		1	4	
1100004	squamous epithelial metaplasia	HE		3							3	
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE			1	1						
1100013	necrotic cells	HE										2**

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

**: with plant material (ventral lumen)
locally associated epithelial degeneration

Table 31 cont. Individual histopathology data, nose level 1

Coded Animal Number			920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group			THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding	Staining	#									
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE							2			
1100002	vacuolisation	HE	1	2			4		2		4	
1100003	reserve cell hyperplasia	HE	1	1	1	2	1	3	1	1		1
1100004	squamous epithelial metaplasia	HE						3				
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE										
1100010	lymphocytis cells	HE				2						
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE		2	1	1		1	1	1	1	2
1100013	necrotic cells	HE				2	1					

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

#: dilatatio of naso-lacrimal duct

Table 31 cont. Individual histopathology data, nose level 1

Coded Animal Number			920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group			3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE			1				1	1	1	
1100002	vacuolisation	HE	1	3*			1		1			
1100003	reserve cell hyperplasia	HE	4	1	2	4	4	1	1			1
1100004	squamous epithelial metaplasia	HE	4			3	3					
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE			2							
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE						1	2		1	2
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 31 cont. Individual histopathology data, nose level 1

Coded Animal Number			920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group			SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding	Staining	#									
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE						1		1		1
1100002	vacuolisation	HE				2*		4*				
1100003	reserve cell hyperplasia	HE		4		1	4	2	4	1	1	1
1100004	squamous epithelial metaplasia	HE		4			4		4			
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE						2				
1100010	lymphocytis cells	HE									1	
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE		1			1	1		1	1	1
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals
#: red blood cells in the noso-lacrimal duct lumen

Table 31 cont. Individual histopathology data, nose level 1

Coded Animal Number			921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group			THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE					1		1			
1100002	vacuolisation	HE	1	1			1	1		1	2	
1100003	reserve cell hyperplasia	HE	1		1	4	1	1	2		1	
1100004	squamous epithelial metaplasia	HE				4						
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE								3		
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE	1	1	1		2		1			
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 32 Individual histopathology data, nose level 2

Coded Animal Number			920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group			THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE				1	1			4*	1	4*
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE								1f		
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

f: focal

Table 32 cont. Individual histopathology data, nose level 2

Coded Animal Number			920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group			THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE		1		3			2	1	5*	
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE		2f								
1210002	vacuolisation	HE									2*	
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 32 cont. Individual histopathology data, nose level 2

Coded Animal Number			920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group			3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
Code	Site / Finding respiratory epithelium	Staining										
1200001	degeneration	HE										
1200002	vacuolisation	HE	2	4*		2		1				1
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 32 cont. Individual histopathology data, nose level 2

Coded Animal Number			920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group			SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE		1			1	2		1		
1200003	reserve cell hyperplasia	HE										
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE							2			
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE				2f		1f	2f			
1210002	vacuolisation	HE						1				
1210003	atrophy	HE		2								
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

f: focal

Table 32 cont. Individual histopathology data, nose level 2

Coded Animal Number			921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group			THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE	7									
1200002	vacuolisation	HE	7							2		
1200003	reserve cell hyperplasia	HE	7									
1200004	squamous epithelial metaplasia	HE	7									
	lamina propria											
1200005	dilatation of blood vessels	HE	7							3		
	lumen											
1200006	eosinophilic material	HE	7				1					
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE	7		1f							
1210002	vacuolisation	HE	7									
1210003	atrophy	HE	7									
1210004	squamous epithelial metaplasia	HE	7									
	lamina propria											
1210005	loss of nerve bundles	HE	7									
	lumen											
1210006	red blood cells	HE	7									
1210007	amorphous eosinophilic material	HE	7									
1210008	necrotic cells	HE	7									

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

f: focal

Table 33 Individual histopathology data, nose level 4

Coded Animal Number			920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group			THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE						1*	1*			1*
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE	1									
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 33 cont. Individual histopathology data, nose level 4

Coded Animal Number			920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group			THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE			1	3*			1	1	4*	1
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE								1	1	
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE									2	
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE									5*	
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 33 cont. Individual histopathology data, nose level 4

Coded Animal Number			920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group			3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE	2*	2*	1*		1	2*				1
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE						1	1	1		
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE		1								
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 33 cont. Individual histopathology data, nose level 4

Coded Animal Number			920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group			SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE					1					
1400002	vacuolisation	HE	1	1	1	1	1	2*	1*	1*		3*
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE			1	1	1		1			
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 33 cont. Individual histopathology data, nose level 4

Coded Animal Number			921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group			THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE	4*			1			2*			
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE							1	1		
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

LUNG

Table 34 Individual histopathology data, lung section 1

Coded Animal Number		920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group		THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	2	2	1		1	2	
1002102	hypertrophy/hyperplasia		2							1	
	lumen										
1002201	macrophages without pigmentation	1	3	1	1	1	2		1	3	1
1002202	macrophages with pigmentation		3			2			3	3	
1002203	pigmented macrophage nests		2			1			1	3	
1002204	lymphocytic infiltrates	1	2	1	1	1	1		1	2	1
1002205	neutrophilic granulocytes		2							1	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1							2	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		2	1	1		2		4	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 34 cont. Individual histopathology data, lung section 1

Coded Animal Number		920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group		THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	1		1	2		1	1	2
1002102	hypertrophy/hyperplasia						2				
	lumen										
1002201	macrophages without pigmentation	1	1	1		1	3			1	1
1002202	macrophages with pigmentation						3			3	2
1002203	pigmented macrophage nests									1	2
1002204	lymphocytic infiltrates	1	1	1		1	2			1	1
1002205	neutrophilic granulocytes						2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells									1	
1002302	thickened and cell-rich										3
	blood vessels										
1002401	perivascular lymphocytic cells	4		3						2	3

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 34 cont. Individual histopathology data, lung section 1

Coded Animal Number		920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group		3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	7				3					
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	1	1	3	3	1	2	2		1
1002102	hypertrophy/hyperplasia	2			3	4					
	lumen										
1002201	macrophages without pigmentation	3		1	5	4	2	1	1		1
1002202	macrophages with pigmentation	4			4	4	1	1	2		
1002203	pigmented macrophage nests	1			2	3	1		1		
1002204	lymphocytic infiltrates	2		1	3	2	1	1	1		1
1002205	neutrophilic granulocytes	2			2	2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1	1		1	2			2		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2	2		3	1	2	2	2		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 34 cont. Individual histopathology data, lung section 1

Coded Animal Number		920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group		SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	2	3	1	2	1	1	1
1002102	hypertrophy/hyperplasia		2		1	2		2			
	lumen										
1002201	macrophages without pigmentation		4		3	4	1	3	2	1	2
1002202	macrophages with pigmentation		4		4	4		3		1	1
1002203	pigmented macrophage nests		1		4	2		1			2
1002204	lymphocytic infiltrates		3		2	3	1	2	1	1	1
1002205	neutrophilic granulocytes		2		2	2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		2		1	2		1			
1002302	thickened and cell-rich										2
	blood vessels										
1002401	perivascular lymphocytic cells		3	1	3	4		2	2		1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 34 cont. Individual histopathology data, lung section 1

Coded Animal Number		921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group		THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		7		2		2	1		1	
1002102	hypertrophy/hyperplasia		7		2						
	lumen										
1002201	macrophages without pigmentation	1	7		4	1	2	1		1	
1002202	macrophages with pigmentation		7		4		1				
1002203	pigmented macrophage nests		7		1		1				
1002204	lymphocytic infiltrates	1	7		3	1	1	1		1	
1002205	neutrophilic granulocytes		7		2						
1002207	amorphous eosinophilic material		7								
1002210	brownisch deposits		7								
1002209	transudate / exudate		7								
1002208	erytrocytes		7								
	interstitium										
1002301	lymphocytic cells		7		1						
1002302	thickened and cell-rich		7								
	blood vessels										
1002401	perivascular lymphocytic cells		7		2		1				

*: pronounced intra-alveolar hemorrhage and edema

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 35 Individual histopathology data, lung section 2

Coded Animal Number		920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group		THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	1	1	2	1	1	2	1
1002102	hypertrophy/hyperplasia		2				1			1	
	lumen										
1002201	macrophages without pigmentation	1	4		1	1	2		1	4	1
1002202	macrophages with pigmentation		4						3	4	
1002203	pigmented macrophage nests		1						1	2	
1002204	lymphocytic infiltrates	1	2		1	1	1		1	3	1
1002205	neutrophilic granulocytes		2						1	2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate									2	
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1							2	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	2		1	1	2		2	3	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 35 cont. Individual histopathology data, lung section 2

Coded Animal Number		920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group		THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		1	1	1	1	3			1	2
1002102	hypertrophy/hyperplasia						2				
	lumen										
1002201	macrophages without pigmentation			1			3			2	1
1002202	macrophages with pigmentation						3		1	3	2
1002203	pigmented macrophage nests						1			2	3
1002204	lymphocytic infiltrates			1			2			2	1
1002205	neutrophilic granulocytes						2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells									1	1
1002302	thickened and cell-rich										3
	blood vessels										
1002401	perivascular lymphocytic cells	4		1		2	3			3	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 35 cont. Individual histopathology data, lung section 2

Coded Animal Number		920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group		3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2		1		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	2	1	1	3	4	1	1	1		1
1002102	hypertrophy/hyperplasia	1			3	3					
	lumen										
1002201	macrophages without pigmentation	3		1	4	4	1	1	1		1
1002202	macrophages with pigmentation	4			4	4	2	1	2		
1002203	pigmented macrophage nests	1			3	3	2		1		
1002204	lymphocytic infiltrates	2		1	2	3	1	1	1		1
1002205	neutrophilic granulocytes	2			2	2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate					1					
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells				1	2	2	1	2		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2	2	1	3	2	3	2	4		2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 35 cont. Individual histopathology data, lung section 2

Coded Animal Number		920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group		SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia					1		1			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	2	1	2	3	1	2	1	1	2
1002102	hypertrophy/hyperplasia		2			2		2			
	lumen										
1002201	macrophages without pigmentation		4	1	2	4	1	4	1	1	2
1002202	macrophages with pigmentation		4		2	4		4		1	1
1002203	pigmented macrophage nests		2		2	2		1			
1002204	lymphocytic infiltrates		3	1	1	2	1	2	1	1	1
1002205	neutrophilic granulocytes		2		1	2		2			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		2	1	1	2		1			
1002302	thickened and cell-rich										2
	blood vessels										
1002401	perivascular lymphocytic cells	2	2	2	2	4	1	1	2	2	4

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 35 cont. Individual histopathology data, lung section 2

Coded Animal Number		921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group		THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7	7	2						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		7	7	2		1	1			
1002102	hypertrophy/hyperplasia		7	7	2						
	lumen										
1002201	macrophages without pigmentation	1	7	7	4		2				
1002202	macrophages with pigmentation		7	7	4		2				
1002203	pigmented macrophage nests		7	7	2		1				
1002204	lymphocytic infiltrates	1	7	7	3		1				
1002205	neutrophilic granulocytes		7	7	2						
1002207	amorphous eosinophilic material		7	7							
1002210	brownisch deposits		7	7							
1002209	transudate / exudate		7	7	2	1					
1002208	erytrocytes		7	7							
	interstitium										
1002301	lymphocytic cells		7	7	2						
1002302	thickened and cell-rich		7	7							
	blood vessels										
1002401	perivascular lymphocytic cells	1	7	7	4				1		

*: pronounced intra-alveolar hemorrhage and edema

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 36 Individual histopathology data, lung section 3

Coded Animal Number		920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group		THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1							7	
1001002	BALT hyperplasia, main bronchus									7	
1001003	goblet cell hyperplasia, main bronchus									7	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		2		1	2	1			7	
1002102	hypertrophy/hyperplasia		1							7	
	lumen										
1002201	macrophages without pigmentation		3			1	1		1	7	
1002202	macrophages with pigmentation		3			2			3	7	
1002203	pigmented macrophage nests		1			1			3	7	
1002204	lymphocytic infiltrates		2			1	1		1	7	
1002205	neutrophilic granulocytes		2							7	
1002206	XXL, PAS-positive macrophages	0	73	0	0	0	0	0	0	.	0
1002207	amorphous eosinophilic material									7	
1002210	brownisch deposits									7	
1002209	transudate / exudate									7	
1002208	erytrocytes									7	
	interstitium										
1002301	lymphocytic cells		1			1			1	7	
1002302	thickened and cell-rich									7	
	blood vessels										
1002401	perivascular lymphocytic cells	1	2			2	2			7	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 36 cont. Individual histopathology data, lung section 3

Coded Animal Number		920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group		THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1			2	1		1	2
1002102	hypertrophy/hyperplasia						1				
	lumen										
1002201	macrophages without pigmentation		1				3	1	1	1	1
1002202	macrophages with pigmentation		1				3		1	3	2
1002203	pigmented macrophage nests		1				1			1	2
1002204	lymphocytic infiltrates		1				2		1	1	1
1002205	neutrophilic granulocytes						2				
1002206	XXL, PAS-positive macrophages	0	0	0	0	0	67	0	0	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells						1			1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	1				1		1	4	2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 36 cont. Individual histopathology data, lung section 3

Coded Animal Number		920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group		3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2	1	1		1		
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus	7	1	2	1						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	1	1	3	3	2		2	1	1
1002102	hypertrophy/hyperplasia	2			3	3					
	lumen										
1002201	macrophages without pigmentation	4	1		4	4	1		1		
1002202	macrophages with pigmentation	4			4	4	2		1		
1002203	pigmented macrophage nests	2			3	2	1		1		
1002204	lymphocytic infiltrates	2	2		2	2	1		1		
1002205	neutrophilic granulocytes	2			2	2					
1002206	XXL, PAS-positive macrophages	53	0	0	98	183	0	0	0	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										1
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1			2	1					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	3		3	3	1	2	4		1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 36 cont. Individual histopathology data, lung section 3

Coded Animal Number		920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group		SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1								
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus			7		1		1			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		2	1	1	2	1	2	2	1	1
1002102	hypertrophy/hyperplasia		3			2		1			
	lumen										
1002201	macrophages without pigmentation		4		2	4	1	3	2	1	2
1002202	macrophages with pigmentation		4		2	4		3		2	1
1002203	pigmented macrophage nests		3		3	2		1		1	
1002204	lymphocytic infiltrates		3		1	2	1	2	1	1	1
1002205	neutrophilic granulocytes		2			2		2			
1002206	XXL, PAS-positive macrophages	0	173	0	0	165	0	102	0	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		2		1	2		1		1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		4	4	4	3		2	1	4	2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 36 cont. Individual histopathology data, lung section 3

Coded Animal Number		921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group		THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7		2						
1001002	BALT hyperplasia, main bronchus		7								
1001003	goblet cell hyperplasia, main bronchus		7								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	7		3		1	1		1	
1002102	hypertrophy/hyperplasia		7		2						
	lumen										
1002201	macrophages without pigmentation		7		5		1	1			
1002202	macrophages with pigmentation		7		4		2				
1002203	pigmented macrophage nests		7		3						
1002204	lymphocytic infiltrates		7		3		1	1			
1002205	neutrophilic granulocytes		7		3						
1002206	XXL, PAS-positive macrophages	0	.	0	163	0	0	0	0	0	
1002207	amorphous eosinophilic material		7								
1002210	brownisch deposits		7								
1002209	transudate / exudate		7							1	
1002208	erytrocytes		7								
	interstitium										
1002301	lymphocytic cells		7		2						
1002302	thickened and cell-rich		7								
	blood vessels										
1002401	perivascular lymphocytic cells	2	7		4		1				

*: pronounced intra-alveolar hemorrhage and edema

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 37 Individual histopathology data, lung section 4

Coded Animal Number		920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposue Group		THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	2	1	2	1	1		1	3	
1002102	hypertrophy/hyperplasia		1							2	
	lumen										
1002201	macrophages without pigmentation		4			1			2	4	1
1002202	macrophages with pigmentation		4			1			3	4	
1002203	pigmented macrophage nests		2						3	2	
1002204	lymphocytic infiltrates		2			1			3f	3	1
1002205	neutrophilic granulocytes		2						4f	2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate		1				1		2		
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		1							2	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		2				1		4	3	1

f: focal

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 37 cont. Individual histopathology data, lung section 4

Coded Animal Number		920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposue Group		THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	2		1	2		1	1	2
1002102	hypertrophy/hyperplasia						2				
	lumen										
1002201	macrophages without pigmentation	1		1			4		1	1	1
1002202	macrophages with pigmentation						4		1	3	1
1002203	pigmented macrophage nests						2			2	3
1002204	lymphocytic infiltrates	1		1			2		1	1	1
1002205	neutrophilic granulocytes						2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells						1			1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	1				2			4	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 37 cont. Individual histopathology data, lung section 4

Coded Animal Number		920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposue Group		3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2	2	1				
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	4	2	1	4	3	2	1	2	1	2
1002102	hypertrophy/hyperplasia	2			3	3					
	lumen										
1002201	macrophages without pigmentation	4	1	1	4	4	1		1		1
1002202	macrophages with pigmentation	4			4	4	2		2		
1002203	pigmented macrophage nests	2			3	3	3		2		
1002204	lymphocytic infiltrates	3	1	1	3	3	1		1		1
1002205	neutrophilic granulocytes	3			2	2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate	2									
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1			2	2	1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	4	2	1	3	1	2	1	1		

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 37 cont. Individual histopathology data, lung section 4

Coded Animal Number		920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposue Group		SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	2	1	3	1	2	1	2	1
1002102	hypertrophy/hyperplasia		2			3		1			1
	lumen										
1002201	macrophages without pigmentation		4	1	2	4	1	4	1	1	2
1002202	macrophages with pigmentation		4	1	2	4		4		2	1
1002203	pigmented macrophage nests		3		3	4		2		2	
1002204	lymphocytic infiltrates		3	1		3	1	3	1	1	1
1002205	neutrophilic granulocytes		2			2		2			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells		2		1	2		1		1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		3		3	4	1	3		3	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 37 cont. Individual histopathology data, lung section 4

Coded Animal Number		921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposue Group		THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7								
	alveoli	2									
	epithelial findings										
1002101	alveolar emphysema	1	7		2		1	1	1	1	
1002102	hypertrophy/hyperplasia		7		2						
	lumen										
1002201	macrophages without pigmentation	1	7		5		2				
1002202	macrophages with pigmentation	1	7		5		2				
1002203	pigmented macrophage nests		7		2		3				
1002204	lymphocytic infiltrates	1	7		3		2				
1002205	neutrophilic granulocytes		7		3						
1002207	amorphous eosinophilic material		7								
1002210	brownisch deposits		7								
1002209	transudate / exudate		7		3						
1002208	erytrocytes		7								
	interstitium										
1002301	lymphocytic cells		7		3						
1002302	thickened and cell-rich		7								
	blood vessels										
1002401	perivascular lymphocytic cells	1	7		4		2				

*: pronounced intra-alveolar hemorrhage and edema

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 38 Individual histopathology data, lung section 5

Coded Animal Number		920029	920070	920125	920134	920182	920252	920259	920281	920294	920296
Exposure Group		THS 2.2_CONT	3R4F_CONT	SHAM	SHAM	Cessation	SHAM	SHAM	Cessation	3R4F_CONT	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7								
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	1	2	1		1	2	
1002102	hypertrophy/hyperplasia		2							1	
	lumen										
1002201	marophages without pigmentation		3		1	1			1	4	
1002202	macrophages with pigmentation		3			1			2	4	
1002203	pigmented macrophage nests								3	2	
1002204	lymphocytic infiltrates		2		1	1			1	2	
1002205	neurophilic granulocytes		1							2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate						1				
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells								1	2	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1						1	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 38 cont. Individual histopathology data, lung section 5

Coded Animal Number		920298	920309	920340	920372	920375	920405	920424	920470	920529	920546
Exposure Group		THS 2.2_Switch	Cessation	Cessation	THS 2.2_CONT	THS 2.2_CONT	3R4F_CONT	SHAM	Cessation	Cessation	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	2	2	1		3	1	1	1	1
1002102	hypertrophy/hyperplasia						2				
	lumen										
1002201	marophages without pigmentation	1					4			1	1
1002202	macrophages with pigmentation						4			2	1
1002203	pigmented macrophage nests						3			2	
1002204	lymphocytic infiltrates	1					2			1	1
1002205	neurophilic granulocytes						2				
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells						1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells						1			3	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 38 cont. Individual histopathology data, lung section 5

Coded Animal Number		920550	920606	920651	920703	920743	920749	920806	920839	920873	920894
Exposure Group		3R4F_CONT	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	Cessation	SHAM	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	7			7	1		7	7		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	1		3	3	2	2	1		2
1002102	hypertrophy/hyperplasia	2			3	2					
	lumen										
1002201	marophages without pigmentation	4			4	4		1	1		1
1002202	macrophages with pigmentation	4			4	4	1		1		
1002203	pigmented macrophage nests	3			1	2					
1002204	lymphocytic infiltrates	2			2	2		1	1		1
1002205	neurophilic granulocytes	2			2	2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells	1			1	1	1				
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3			3	1					1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 38 cont. Individual histopathology data, lung section 5

Coded Animal Number		920898	920912	920919	920920	920935	920937	920947	920953	920960	920978
Exposure Group		SHAM	3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7			1					
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	2	2	2	3	1	3	2	2	1
1002102	hypertrophy/hyperplasia		2		1	3		2			
	lumen										
1002201	marophages without pigmentation		3	1	2	4	1	3	1		1
1002202	macrophages with pigmentation		3		2	4		3			
1002203	pigmented macrophage nests				2	2					
1002204	lymphocytic infiltrates		2	1	1	2	1	2	1		1
1002205	neurophilic granulocytes		2			2		2			
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells		1			2		1			
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		2	1	1	3		1		1	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 38 cont. Individual histopathology data, lung section 5

Coded Animal Number		921007	921011	921017	921018	921028	921038	921069	921090	921091	
Exposure Group		THS 2.2_Switch	SHAM	THS 2.2_CONT	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		7		7						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	2	7	1	2		2	1		1	
1002102	hypertrophy/hyperplasia		7		2						
	lumen										
1002201	marophages without pigmentation		7		4		1	1		1	
1002202	macrophages with pigmentation		7		4		1				
1002203	pigmented macrophage nests		7								
1002204	lymphocytic infiltrates		7		3		1	1		1	
1002205	neurophilic granulocytes		7		2						
1002207	amorphous eosinophilic material		7								
1002210	brownisch deposits		7								
1002209	transudate / exudate		7								
1002208	erytrocytes		7								
	interstitium										
1002301	lymphocytis cells		7		2						
1002302	thickened and cell-rich		7								
	blood vessels										
1002401	perivascular lymphocytic cells		7		3		2				

*: pronounced intra-alveolar hemorrhage and edema

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

LIVER

Table 39 Individual histopathology data, liver

Coded Animal Number			920006	920033	920039	920080	920091	920120	920122	920229	920244	920327
Exposure Group			3R4F_CONT	Cessation	3R4F_CONT	Cessation	THS 2.2_CONT	Cessation	3R4F_CONT	SHAM	THS 2.2_Switch	THS 2.2_CONT
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	1	1	1		1	2	2	1	1	1
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	4	3	3	4	3	2	2	3	4	5
4000003	hyperchromasia, hepatocytes	HE			2						2	
4000004	mono-nuclear inflammatory cells	HE		1	2		1				1	1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	5	3	4	5	3	4	4	5	5
4000007	amount of glycogen	PAS	4	1	2	2	3	3	2	2		2
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE		2	2	2	1		1	1	2	2
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	1	3	2	2	3	2	2	2	3	3
4000014	brownish pigment	HE		1	1							1
4000012	bile duct hyperplasia	HE	1	2	2	2	2	1	2	1	2	3
4000013	increase of collagen fibers	HE	1	2	2	2	2	2	2	1	2	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 39 cont. Individual histopathology data, liver

Coded Animal Number			920333	920353	920356	920399	920404	920423	920432	920485	920523	920543
Exposure Group			SHAM	THS 2.2_Switch	Cessation	Cessation	SHAM	SHAM	3R4F_CONT	THS 2.2_CONT	THS 2.2_Switch	3R4F_CONT
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	1			3	3	2	1	3	2	
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	3	3	3	3	2	1	2		3	1
4000003	hyperchromasia, hepatocytes	HE	1					2	1	1		1
4000004	mono-nuclear inflammatory cells	HE	1		1	1	1	1	1		1	
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	5	4	4	5	2	3	3	3	4	4
4000007	amount of glycogen	PAS	2	3	2	3	4	3	3	3	2	
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE	2			2	2				1	
	periportal/interstitial area		*									
4000011	mono-nuclear inflammatory cells	HE	2	2	2	2	1	2	2	2	2	2
4000014	brownish pigment	HE		1								
4000012	bile duct hyperplasia	HE	2	2	1	1	1	1	2	2	1	2
4000013	increase of collagen fibers	HE	2	2	1	2	1	1	2	2	1	3

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

* focal hemorrhage

Table 39 cont. Individual histopathology data, liver

Coded Animal Number			920679	920684	920698	920710	920760	920784	920789	920790	920795	920860
Exposure Group			THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	SHAM	SHAM	THS 2.2_Switch	THS 2.2_CONT	Cessation
Code	Site / Finding parenchyma	Staining										
4000001	micro-granuloma with micro-hemorrhage	HE	1		2	1	2	1	2		1	1
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	2	3	2	2	3	3	2	2	4	2
4000003	hyperchromasia, hepatocytes	HE				1						
4000004	mono-nuclear inflammatory cells	HE			1	1	1		1	1		
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	5	3*	3	4	5	3	4	5	4	4
4000007	amount of glycogen	PAS	1	3	2	1	2	4	4		2	1
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE					2		2		1	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2		2	2	2	1	1	2	1	1
4000014	brownish pigment	HE		1	2							1
4000012	bile duct hyperplasia	HE	1	1	2	3	2	1		3		
4000013	increase of collagen fibers	HE	2	2	2	3	2	2	1	3	1	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: black pigmentation

Table 39 cont. Individual histopathology data, liver

Coded Animal Number			920877	920966	920997	921021	921043	921045	921058	921095	921096	921098
Exposure Group			THS 2.2_Switch	Cessation	SHAM	SHAM	THS 2.2_Switch	THS 2.2_Switch	3R4F_CONT	THS 2.2_CONT	Cessation	3R4F_CONT
Code	Site / Finding	Staining										
	parenchyma											
4000001	micro-granuloma with micro-hemorrhage	HE	1		2	2	1	1	1	1	1	1
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	2		4	2	3	3	1	4	3	1
4000003	hyperchromasia, hepatocytes	HE		1					2			
4000004	mono-nuclear inflammatory cells	HE		1	2	1	1	1		1	1	1
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	4	3	3	2	3	3	4	3	2
4000007	amount of glycogen	PAS	3	2	4	3	4	3	3	2	3	3
4000008	hemorrhage	HE			3							
4000009	degeneration/necrosis, hepatocytes	HE			2	1	1	2	2	2	2	2
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	2	2	1	1	2	2	2	2	2
4000014	brownish pigment	HE			2							
4000012	bile duct hyperplasia	HE	1	2	2			1	2	1	1	1
4000013	increase of collagen fibers	HE	1	2	2	1	1	1	2	2	2	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

MORPHOMETRY DATA

Table 40 Individual morphometrical data and histopathology data of alveolar emphysema

Animal ID	Exposure group	LM	DI	BA	Lung Volume	Emphysema
920125	SHAM	46,8	15	14,87	174,0	0,8
920134	SHAM	43,8	25	15,28	135,7	1,4
920252	SHAM	49,8	14,8	13,66	150,9	1,2
920259	SHAM	51,4	20,2	12,32	152,4	0,2
920424	SHAM	51,8	23,5	12,54	201,0	0,4
920873	SHAM	51,6	11,5	14,27	120,4	0,4
920898	SHAM	51,7	23,7	13,24	161,2	0,8
921011	SHAM	invalid	invalid	invalid	invalid	invalid
921028	SHAM	49,1	15,5	13,82	174,5	0
920070	3R4F_CONT	53	35,1	11,88	157,3	2,6
920294	3R4F_CONT	56,7	54,6	12,28	invalid	2,25
920405	3R4F_CONT	57,1	30,8	12,35	211,4	2,4
920550	3R4F_CONT	58,7	43,3	11,48	235,9	3
920703	3R4F_CONT	65	43,8	11,69	228,1	3,2
920743	3R4F_CONT	59,4	41,7	11,44	214,8	3,2
920912	3R4F_CONT	67,9	37,8	12,28	239,4	2,4
920935	3R4F_CONT	64,8	45,1	10,35	252,1	2,8
920947	3R4F_CONT	55,5	22	9,4	225,6	2,2
921018	3R4F_CONT	57,9	46	14,88	155,3	2,2
920029	THS 2.2_CONT	45,5	7,1	17,61	157,8	0,8
920296	THS 2.2_CONT	47,4	25,6	10,62	182,8	0,2
920372	THS 2.2_CONT	49,8	20,1	15,5	170,1	0,4
920375	THS 2.2_CONT	52,2	20,8	12,65	155,8	0,6
920651	THS 2.2_CONT	47,6	23,2	14,41	123,4	0,8
920894	THS 2.2_CONT	53,7	25,9	12,1	140,1	1,4
920937	THS 2.2_CONT	55,5	19,4	13,66	195,1	1
920953	THS 2.2_CONT	48,9	29,5	12,99	156,3	1,4
921017	THS 2.2_CONT	48,3	11,6	13,01	116,5	0,25
921091	THS 2.2_CONT	52,3	19,7	10,66	170,1	0,8

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

Table 40 cont. **Individual morphometrical data and histopathology data of alveolar emphysema**

Animal ID	Exposure group	LM	DI	BA	Lung Volume	Emphysema
920182	Cessation	52,3	21,5	11,77	160,2	1,6
920281	Cessation	52,5	21,3	12,43	206,4	0,8
920309	Cessation	47,3	4,6	13,93	197,6	1
920340	Cessation	52,9	26,8	13,2	155,8	1,4
920470	Cessation	53,4	25,3	11,32	166,1	0,6
920529	Cessation	52,1	24	13,15	171,0	1
920749	Cessation	54,9	29,7	13,69	206,9	1,6
920839	Cessation	54,9	26,9	11,63	144,5	1,6
920919	Cessation	49,4	13,4	14,21	177,4	1,4
920978	Cessation	49,5	23	11,97	144,5	1,2
920298	THS 2.2_Switch	48,7	4	11,57	204,0	0,8
920546	THS 2.2_Switch	50,1	29,6	16,15	134,7	1,8
920606	THS 2.2_Switch	54,3	17,3	12,82	145,0	1,2
920806	THS 2.2_Switch	53,5	31,4	13,1	159,7	1,2
920920	THS 2.2_Switch	49,1	27	12,6	132,2	1,6
920960	THS 2.2_Switch	49,2	18,7	14,21	200,5	1,4
921007	THS 2.2_Switch	47,7	9,5	14,98	185,3	0,8
921038	THS 2.2_Switch	48,8	24,3	15,47	131,2	1,4
921069	THS 2.2_Switch	45,6	8,2	15,06	179,4	1
921090	THS 2.2_Switch	50,3	10,6	13,06	147,5	0,2

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

DISSECTION TIME POINT 8

NOSE

Table 41 Individual histopathology data, nose level 1

Coded Animal Number			920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group			SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
Code	Site / Finding	Staining										
	respiratory epithelium											
1100001	degeneration/atrophy	HE		1				2	1			
1100002	vacuolisation	HE			2			3			1	
1100003	reserve cell hyperplasia	HE		1	2	3	4	1	1	5	1	2
1100004	squamous epithelial metaplasia	HE				4	4			3		1
1100005	amount of cornification	HE				1						
	lamina propria											
1100009	dilatation of blood vessels	HE							2			
1100010	lymphocytis cells	HE			1							
	lumen								*			
1100011	red blood cells	HE										
1100012	eosinophilic material	HE	1			4	1				1	1
1100013	necrotic cells	HE				1*						

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

*: plant material

Table 41 cont. **Individual histopathology data, nose level 1**

Coded Animal Number			920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group			THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**				**							
1100001	degeneration/atrophy	HE		3	7	1			1		2	1
1100002	vacuolisation	HE			7		4#					
1100003	reserve cell hyperplasia	HE	1	4	7	1	1	1		4		1
1100004	squamous epithelial metaplasia	HE		4	7					4		
1100005	amount of cornification	HE			7					1		
	lamina propria											
1100009	dilatation of blood vessels	HE			7	2						
1100010	lymphocytis cells	HE			7							
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE					1	1	1			1
1100013	necrotic cells	HE			4*							

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

*: plant material and bacterial colonies locally associated (neutrophilic granulocytes)

**: section taken too early

#: eosinophilic crystals

Table 41 cont. **Individual histopathology data, nose level 1**

Coded Animal Number			920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group			3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE			2					4*		
1100002	vacuolisation	HE					2		3			1
1100003	reserve cell hyperplasia	HE	4	1		5	1	4		7	4	2
1100004	squamous epithelial metaplasia	HE	4			4		4		7	4	
1100005	amount of cornification	HE	1							7		
	lamina propria											
1100009	dilatation of blood vessels	HE						2				
1100010	lymphocytis cells	HE								4**		
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE	1	1	1					1		
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

*: focal ulceration
**: mixed inflammatory cells

Table 41 cont. **Individual histopathology data, nose level 1**

Coded Animal Number			920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group			SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE		7								1
1100002	vacuolisation	HE		5*	4#							1
1100003	reserve cell hyperplasia	HE	2	7				1	1			1
1100004	squamous epithelial metaplasia	HE		7								
1100005	amount of cornification	HE		7								
	lamina propria											
1100009	dilatation of blood vessels	HE				3						
1100010	lymphocytis cells	HE										
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE	1					1		1		
1100013	necrotic cells	HE		2**		2**						

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

*: eosinophilic crystals (very severe alteration)
**: plant material
#: eosinophilic crystals

Table 41 cont. **Individual histopathology data, nose level 1**

Coded Animal Number			920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group			SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1100001	degeneration/atrophy	HE								1		
1100002	vacuolisation	HE		1	4	2						2
1100003	reserve cell hyperplasia	HE	1	1	1	2	4	1	1	1	1	
1100004	squamous epithelial metaplasia	HE					4					
1100005	amount of cornification	HE										
	lamina propria											
1100009	dilatation of blood vessels	HE							2			
1100010	lymphocytis cells	HE		2								
	lumen											
1100011	red blood cells	HE										
1100012	eosinophilic material	HE	1	1				2				1
1100013	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

Table 42 **Individual histopathology data, nose level 2**

Coded Animal Number			920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group			SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE				7						
1200002	vacuolisation	HE	1		1	7			1		1	
1200003	reserve cell hyperplasia	HE				7				1		
1200004	squamous epithelial metaplasia	HE				7						
	lamina propria											
1200005	dilatation of blood vessels	HE				7						
	lumen											
1200006	eosinophilic material	HE				7						
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE									1	
1210002	vacuolisation	HE										
1210003	atrophy	HE				2				1		
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 42 cont. Individual histopathology data, nose level 2

Coded Animal Number			920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group			THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE	1		4*		1	4*	2		2	1
1200003	reserve cell hyperplasia	HE		1						1		
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE	1									
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE										
1210002	vacuolisation	HE			4*							
1210003	atrophy	HE		1						1		
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 42 cont. Individual histopathology data, nose level 2

Coded Animal Number			920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group			3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding	Staining										
Code	**respiratory epithelium**											
1200001	degeneration	HE										
1200002	vacuolisation	HE	1		1		2			1		1
1200003	reserve cell hyperplasia	HE				1		1			1	
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE									2	2
1210002	vacuolisation	HE										
1210003	atrophy	HE	1			2		1			1	
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation
Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 42 cont. Individual histopathology data, nose level 2

Coded Animal Number			920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group			SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding	Staining										
Code	**respiratory epithelium**		#									
1200001	degeneration	HE		7								
1200002	vacuolisation	HE	1	5*	3			2	1	1	2	2
1200003	reserve cell hyperplasia	HE		7								
1200004	squamous epithelial metaplasia	HE		7								
	lamina propria											
1200005	dilatation of blood vessels	HE				3						
	lumen											
1200006	eosinophilic material	HE		1**								
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE					1					2+
1210002	vacuolisation	HE										
1210003	atrophy	HE										
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals (very severe alteration)
**: plant material
#: septum: cyst formation filled with ceratine
+: intra-epithelial cyst formation

Table 42 cont. Individual histopathology data, nose level 2

Coded Animal Number			920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group			SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding	Staining										
Code	**respiratory epithelium**					#						
1200001	degeneration	HE										
1200002	vacuolisation	HE			3	3			1	1	1	
1200003	reserve cell hyperplasia	HE					1					
1200004	squamous epithelial metaplasia	HE										
	lamina propria											
1200005	dilatation of blood vessels	HE										
	lumen											
1200006	eosinophilic material	HE										
	olfactory epithelium											
1210001	hyperplasia, epithelial layers	HE	1	1								
1210002	vacuolisation	HE										
1210003	atrophy	HE					1					
1210004	squamous epithelial metaplasia	HE										
	lamina propria											
1210005	loss of nerve bundles	HE										
	lumen											
1210006	red blood cells	HE										
1210007	amorphous eosinophilic material	HE										
1210008	necrotic cells	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

#: septum: cyst formation filled with ceratine

Table 43 Individual histopathology data, nose level 4

Coded Animal Number			920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group			SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**										#	
1400001	atrophy	HE				1	1					
1400002	vacuolisation	HE				3*		2*	1			
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE				3						
1400008	necrotic cells	HE										
	pharyngeal duct					**						
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals
**: red blood cells in the lumen
#: focal respiratory metaplasia

Table 43 cont. Individual histopathology data, nose level 4

Coded Animal Number			920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group			THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE		1								
1400002	vacuolisation	HE			4*		2*	2*	1	1		1
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 43 cont. **Individual histopathology data, nose level 4**

Coded Animal Number			920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group			3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE				1					1	
1400002	vacuolisation	HE				2*	1	1				1
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 43 cont. Individual histopathology data, nose level 4

Coded Animal Number			920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group			SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE										
1400002	vacuolisation	HE	2*	5*	4*	2*		1			3*	
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE		4*	2							
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

Table 43 cont. Individual histopathology data, nose level 4

Coded Animal Number			920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group			SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding											
Code	**Nose level 4 olfactory epithelium**											
1400001	atrophy	HE					1					
1400002	vacuolisation	HE	1		1	2*	1		2*		1	
1400003	squamous epithelial metaplasia	HE										
	lamina propria											
1400004	loss of nerve bundles	HE										
1400009	fatty changes	HE										
	lumen											
1400006	red blood cells	HE										
1400007	amorphous eosinophilic material	HE										
1400008	necrotic cells	HE										
	pharyngeal duct											
1410001	vacuolisation	HE										
	molar teeth											
-	-	HE										
	olfactory bulb											
-	-	HE										

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

*: eosinophilic crystals

LUNG

Table 44 Individual histopathology data, lung section 1

Coded Animal Number		920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group		SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2	2					
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1		3	2		1	3	1	2
1002102	hypertrophy/hyperplasia				2	2			2		
	lumen										
1002201	macrophages without pigmentation	1	1	1	4	4			4	1	1
1002202	macrophages with pigmentation				4	4			5		1
1002203	pigmented macrophage nests				2	3			1		1
1002204	lymphocytic infiltrates			2	3	2			3	2f	
1002205	neutrophilic granulocytes				2	2			2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells			1	2	1			2		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	1	1	3	3	1		4	2	2

f: focal

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 44 cont. Individual histopathology data, lung section 1

Coded Animal Number		920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia					7		7			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema		4	1	2		1	7	3	1	2
1002102	hypertrophy/hyperplasia		3					7	2		
	lumen										
1002201	macrophages without pigmentation		4		1	1		7	4	1	1
1002202	macrophages with pigmentation		4					7	4		
1002203	pigmented macrophage nests		2					7			
1002204	lymphocytic infiltrates		2		1	1		7	2	1	
1002205	neutrophilic granulocytes		2					7	2		
1002207	amorphous eosinophilic material							7			
1002210	brownisch deposits							7			
1002209	transudate / exudate							7			
1002208	erytrocytes							7			
	interstitium										
1002301	lymphocytic cells		1					7	1		
1002302	thickened and cell-rich							7			
	blood vessels										
1002401	perivascular lymphocytic cells		2		1		1	7	2	1	4

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 44 cont. Individual histopathology data, lung section 1

Coded Animal Number		920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group		3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2		7				
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	2		4	1	2	7	1	2	2
1002102	hypertrophy/hyperplasia	2			7		2	7		2	
	lumen										
1002201	macrophages without pigmentation	4	2		4		4		2	4	
1002202	macrophages with pigmentation	4	1		4	1	4		1	4	
1002203	pigmented macrophage nests	1			1		1			3	
1002204	lymphocytic infiltrates	2	1		2		2		1	3	
1002205	neutrophilic granulocytes	2			2		2			2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1									
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	4	1	3		1		1	4	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 44 cont. Individual histopathology data, lung section 1

Coded Animal Number		920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group		SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1			1		1	2		1	1
1002102	hypertrophy/hyperplasia										
	lumen										
1002201	macrophages without pigmentation				1		1	2		1	1
1002202	macrophages with pigmentation							1	2		
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates				1		1	1			1
1002205	neutrophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1									
1002302	thickened and cell-rich	2									
	blood vessels										
1002401	perivascular lymphocytic cells	1		1			1		4	3	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 44 cont. Individual histopathology data, lung section 1

Coded Animal Number		920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group		SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia					1				7	
	alveoli										
	epithelial findings		*								
1002101	alveolar emphysema	1		2		2	2	1	1	1	1
1002102	hypertrophy/hyperplasia					2					
	lumen										
1002201	macrophages without pigmentation	1		1		4		1		1	
1002202	macrophages with pigmentation			1		4		1			
1002203	pigmented macrophage nests					1					
1002204	lymphocytic infiltrates	1		1		3		1		1	
1002205	neutrophilic granulocytes					2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells			2	1	2		2			

*: hyper-inflated area

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 45 Individual histopathology data, lung section 2

Coded Animal Number		920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group		SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				2	1			2		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1	3	3	1	1	3		1
1002102	hypertrophy/hyperplasia				2	2			2		
	lumen										
1002201	macrophages without pigmentation	1		2	4	4	1	1	4	1	1
1002202	macrophages with pigmentation				4	4			4		2
1002203	pigmented macrophage nests				3	2			2		
1002204	lymphocytic infiltrates	1		1	3	3	1	1	3	1	1
1002205	neutrophilic granulocytes				2	2			2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1		1	2	1			1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2		4	3	3	2	4	4	2	3

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 45 cont. Individual histopathology data, lung section 2

Coded Animal Number		920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1	1				7	2		1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	1	1	1	7	3	1	
1002102	hypertrophy/hyperplasia		2					7	2		
	lumen										
1002201	macrophages without pigmentation		4			1		7	4	1	
1002202	macrophages with pigmentation		5					7	5	2	
1002203	pigmented macrophage nests		1					7	2	2	
1002204	lymphocytic infiltrates		2			1		7	2	1	
1002205	neutrophilic granulocytes		2					7	2		
1002207	amorphous eosinophilic material							7			
1002210	brownisch deposits							7			
1002209	transudate / exudate							7			
1002208	erytrocytes							7			
	interstitium										
1002301	lymphocytic cells		1					7	1		
1002302	thickened and cell-rich							7			
	blood vessels										
1002401	perivascular lymphocytic cells	4	2		3	1	1	7	4	4	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 45 cont. Individual histopathology data, lung section 2

Coded Animal Number		920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group		3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	2					1			1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	4	2	1	4	1	3	2	2	3	2
1002102	hypertrophy/hyperplasia	2			7		2			2	
	lumen										
1002201	macrophages without pigmentation	4	2		4		4	2	2	4	
1002202	macrophages with pigmentation	5	1		4		4	1	1	4	
1002203	pigmented macrophage nests	2	2				3			3	
1002204	lymphocytic infiltrates	2	2	1	2		3	1	1	2	
1002205	neutrophilic granulocytes	2			2		2			2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate							2			
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1	2				1			1	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	5	4	4		4	2	4	3	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 45 cont. Individual histopathology data, lung section 2

Coded Animal Number		920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group		SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia							2			
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1	1	1	2	2	1	1	1
1002102	hypertrophy/hyperplasia										
	lumen										
1002201	macrophages without pigmentation	1						1			
1002202	macrophages with pigmentation							2	2	1	
1002203	pigmented macrophage nests							2	1		
1002204	lymphocytic infiltrates	1						1			
1002205	neutrophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	1									
1002302	thickened and cell-rich	2									
	blood vessels										
1002401	perivascular lymphocytic cells	3	1					3	5	3	3

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 45 cont. Individual histopathology data, lung section 2

Coded Animal Number		920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group		SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia					1					
	alveoli										
	epithelial findings		*								
1002101	alveolar emphysema	1	1	2	1	3	2	2	2	1	
1002102	hypertrophy/hyperplasia					2					
	lumen										
1002201	macrophages without pigmentation		1	1		4		2		1	
1002202	macrophages with pigmentation					5		3			
1002203	pigmented macrophage nests					2		3			
1002204	lymphocytic infiltrates		1	1		3		1		1	
1002205	neutrophilic granulocytes					2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					1					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1				4		4		2	

*: hyper-inflated area

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 46 Individual histopathology data, lung section 3

Coded Animal Number		920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group		SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1	1			1		
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus				1	1	7				
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	1	2	2	1		3	1	1
1002102	hypertrophy/hyperplasia				2	2			2		
	lumen										
1002201	macrophages without pigmentation	1		2	4	4			4	1	1
1002202	macrophages with pigmentation				4	4			4		2
1002203	pigmented macrophage nests				2	3			3		1
1002204	lymphocytic infiltrates	1		1	3	3			2		1
1002205	neutrophilic granulocytes				2	2			2		
1002206	XXL, PAS-positive macrophages	0	0	0	153	121	0	0	210	0	4
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells				2	2			2		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	4	1	2	4	4	2	4	3	2	4

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 46 cont. Individual histopathology data, lung section 3

Coded Animal Number		920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia			1				7	2		
1001002	BALT hyperplasia, main bronchus							7			
1001003	goblet cell hyperplasia, main bronchus							7	2		1
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	2			7	3	1	1
1002102	hypertrophy/hyperplasia		2					7	2		
	lumen										
1002201	macrophages without pigmentation		4				1	7	4	1	1
1002202	macrophages with pigmentation		5					7	5	2	
1002203	pigmented macrophage nests		1					7	1	1	
1002204	lymphocytic infiltrates		2				1	7	2	1	1
1002205	neutrophilic granulocytes		2					7	2		
1002206	XXL, PAS-positive macrophages	0	187	0	0	0	0	.	113	2	0
1002207	amorphous eosinophilic material							7			
1002210	brownisch deposits							7			
1002209	transudate / exudate							7			
1002208	erytrocytes							7			
	interstitium										
1002301	lymphocytic cells		2					7	1		
1002302	thickened and cell-rich							7			
	blood vessels										
1002401	perivascular lymphocytic cells	5	3		1		3	7	3	4	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 46 cont. Individual histopathology data, lung section 3

Coded Animal Number		920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group		3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						2				
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus	7			7		1				
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	1	1	4	1	2	1	2	3	1
1002102	hypertrophy/hyperplasia	2			7		1			2	
	lumen										
1002201	macrophages without pigmentation	4	1		4		4	1	2	4	
1002202	macrophages with pigmentation	4			4		5		1	4	
1002203	pigmented macrophage nests	2	2				2			4	
1002204	lymphocytic infiltrates	2	1		2		2		1	2	
1002205	neutrophilic granulocytes	2			2		2			2	
1002206	XXL, PAS-positive macrophages	98	4	0	.	0	67	0	0	37	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	2					2			2	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	3	4	3	4	3	4	1	4	3	4

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 46 cont. Individual histopathology data, lung section 3

Coded Animal Number		920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group		SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus	1		1					7		2
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1					1	2	1	1	1
1002102	hypertrophy/hyperplasia										
	lumen										
1002201	macrophages without pigmentation	1						1	1	1	2
1002202	macrophages with pigmentation							2	2		
1002203	pigmented macrophage nests							2	1		
1002204	lymphocytic infiltrates	1						1	1	1	1
1002205	neutrophilic granulocytes										
1002206	XXL, PAS-positive macrophages	0	0	0	0	0	0	0	4	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich							1			1
	blood vessels										
1002401	perivascular lymphocytic cells	3	2	2				3	5		4

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 46 cont. Individual histopathology data, lung section 3

Coded Animal Number		920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group		SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
1001002	BALT hyperplasia, main bronchus										
1001003	goblet cell hyperplasia, main bronchus					1				1	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1	1	3	2	2	2	1	1
1002102	hypertrophy/hyperplasia					2					
	lumen										
1002201	macrophages without pigmentation					4		1			
1002202	macrophages with pigmentation					5		3			
1002203	pigmented macrophage nests					2		3			
1002204	lymphocytic infiltrates					2		1			
1002205	neutrophilic granulocytes					2					
1002206	XXL, PAS-positive macrophages	0	0	0	0	186	0	5	0	0	0
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					1					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1			4	4	5	1	4	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

XXL-macrophages: total number

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 47 Individual histopathology data, lung section 4

Coded Animal Number		920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposue Group		SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia				1						
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	2	3	3	1	1	3	1	1
1002102	hypertrophy/hyperplasia				2	2			2		
	lumen										
1002201	macrophages without pigmentation	1	1	2	4	4	1		4	1	
1002202	macrophages with pigmentation				4	4			4		
1002203	pigmented macrophage nests				4	4			2		
1002204	lymphocytic infiltrates			1	2	2	1		2		
1002205	neutrophilic granulocytes				2	2			2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells			1	3	2			2		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2	1	1	4	4	1	2	3	1	2

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 47 cont. Individual histopathology data, lung section 4

Coded Animal Number		920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposue Group		THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia		1					7	1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	2	2	1	2	7	3	2	2
1002102	hypertrophy/hyperplasia		2					7	2		
	lumen										
1002201	macrophages without pigmentation		4					7	4	1	
1002202	macrophages with pigmentation		5					7	5	3	
1002203	pigmented macrophage nests		1					7	3	2	
1002204	lymphocytic infiltrates		2					7	3	1	
1002205	neutrophilic granulocytes		2					7	2		
1002207	amorphous eosinophilic material							7			
1002210	brownisch deposits							7			
1002209	transudate / exudate							7			
1002208	erytrocytes							7			
	interstitium										
1002301	lymphocytic cells		1					7	1	1	
1002302	thickened and cell-rich							7			
	blood vessels										
1002401	perivascular lymphocytic cells	4	2	1			1	7	3	4	1

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 47 cont. Individual histopathology data, lung section 4

Coded Animal Number		920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposue Group		3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						2		1		
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	1	1	4	1	3	1	1	3	2
1002102	hypertrophy/hyperplasia	2			7		2			2	
	lumen										
1002201	macrophages without pigmentation	4		1	4	1	4		2	4	
1002202	macrophages with pigmentation	4		2	5	1	4		1	4	
1002203	pigmented macrophage nests	3		1	1		2			3	
1002204	lymphocytic infiltrates	2			2	1	2		1	3	
1002205	neutrophilic granulocytes	2			2		2			2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells	2					1			2	
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2	4	3	4	1	3	1	4	3	3

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 47 cont. Individual histopathology data, lung section 4

Coded Animal Number		920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposue Group		SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										*
1002101	alveolar emphysema	2		1	1	1	1	1	1	1	
1002102	hypertrophy/hyperplasia										
	lumen										
1002201	macrophages without pigmentation	1						1			
1002202	macrophages with pigmentation							2			
1002203	pigmented macrophage nests							3			
1002204	lymphocytic infiltrates	1						1			
1002205	neutrophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	2					2		4	2	

*: bronchiolo-alveolar adenoma

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 47 cont. Individual histopathology data, lung section 4

Coded Animal Number		920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposue Group		SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia										
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1		1	1	3	1	2	1	1	
1002102	hypertrophy/hyperplasia					2					
	lumen										
1002201	macrophages without pigmentation					4		1		1	
1002202	macrophages with pigmentation					5		3			
1002203	pigmented macrophage nests					3		3			
1002204	lymphocytic infiltrates					2		1		1	
1002205	neutrophilic granulocytes					2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytic cells					2					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells		1			4		4		3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

Table 48 Individual histopathology data, lung section 5

Coded Animal Number		920011	920020	920110	920115	920138	920140	920147	920197	920218	920220
Exposure Group		SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	3R4F_CONT	Cessation	THS 2.2_CONT	3R4F_CONT	THS 2.2_CONT	Cessation
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia					7					
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	1	3	3	2	1	2	1	1
1002102	hypertrophy/hyperplasia				2	2			2		
	lumen										
1002201	marophages without pigmentation		1	1	4	4	1		4		
1002202	macrophages with pigmentation				4	4			4		1
1002203	pigmented macrophage nests				2	2			3		
1002204	lymphocytic infiltrates		1	1	2	2	1		2		
1002205	neurophilic granulocytes				2	2			2		
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells				1	2			1		
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells			1	3	2			3	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 48 cont. Individual histopathology data, lung section 5

Coded Animal Number		920251	920261	920266	920282	920330	920339	920369	920379	920400	920448
Exposure Group		THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_Switch	SHAM	THS 2.2_CONT	Cessation	3R4F_CONT	Cessation	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	7		7				7	1	7	7
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	3	1	2		2	7	3	2	1
1002102	hypertrophy/hyperplasia		2					7	2		
	lumen										
1002201	marophages without pigmentation		4		1			7	4	1	1
1002202	macrophages with pigmentation		4					7	5	1	
1002203	pigmented macrophage nests		2					7	3		
1002204	lymphocytic infiltrates		2					7	2	1	1
1002205	neurophilic granulocytes		2					7	2		
1002207	amorphous eosinophilic material							7			
1002210	brownisch deposits							7			
1002209	transudate / exudate							7			
1002208	erytrocytes							7			
	interstitium										
1002301	lymphocytis cells							7	1		
1002302	thickened and cell-rich							7			
	blood vessels										
1002401	perivascular lymphocytic cells	1	2					7	3	3	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 48 cont. Individual histopathology data, lung section 5

Coded Animal Number		920556	920601	920617	920627	920632	920646	920700	920709	920722	920762
Exposure Group		3R4F_CONT	Cessation	THS 2.2_Switch	3R4F_CONT	Cessation	3R4F_CONT	Cessation	Cessation	3R4F_CONT	THS 2.2_Switch
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	7	7	7	1		7		7	7	7
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	3	2	1	4	2	3	1	1	2	1
1002102	hypertrophy/hyperplasia	2			7		2			1	
	lumen										
1002201	marophages without pigmentation	3	2	1	4		4	1	2	4	
1002202	macrophages with pigmentation	3	1		4		4		1	4	
1002203	pigmented macrophage nests	1			2		1			1	
1002204	lymphocytic infiltrates	2	1		2		2		1	2	
1002205	neurophilic granulocytes	2			2		2			2	
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells		1								
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1	4		3		2		2	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 48 cont. Individual histopathology data, lung section 5

Coded Animal Number		920791	920793	920800	920816	920830	920835	920856	920865	920896	920911
Exposure Group		SHAM	SHAM	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch	THS 2.2_CONT	Cessation	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia						7				7
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	2		1	1	1	1	2		1	1
1002102	hypertrophy/hyperplasia										
	lumen										
1002201	marophages without pigmentation	1								1	
1002202	macrophages with pigmentation							1		1	
1002203	pigmented macrophage nests										
1002204	lymphocytic infiltrates									1	
1002205	neurophilic granulocytes										
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells										
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells	1							4	1	

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

Table 48 cont. Individual histopathology data, lung section 5

Coded Animal Number		920921	920936	920955	920970	921001	921019	921031	921060	921062	921070
Exposure Group		SHAM	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_CONT	3R4F_CONT	Cessation	THS 2.2_Switch	THS 2.2_CONT	SHAM	SHAM
	Site / Finding										
Code	**bronchi**										
1001001	reserve cell hyperplasia	7				7	7	7	7	7	
	alveoli										
	epithelial findings										
1002101	alveolar emphysema	1	1	2	1	2	2	1	2	1	1
1002102	hypertrophy/hyperplasia					2					
	lumen										
1002201	marophages without pigmentation			1		4		1			
1002202	macrophages with pigmentation					4		2			
1002203	pigmented macrophage nests					3					
1002204	lymphocytic infiltrates			1		2		1			
1002205	neurophilic granulocytes					2					
1002207	amorphous eosinophilic material										
1002210	brownisch deposits										
1002209	transudate / exudate										
1002208	erytrocytes										
	interstitium										
1002301	lymphocytis cells					1					
1002302	thickened and cell-rich										
	blood vessels										
1002401	perivascular lymphocytic cells					3		1			

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)

-: not applicable
+: mild artifacts
++: moderate artifacts
+++: severe artifacts

LIVER

Table 49 **Individual histopathology data, liver**

Coded Animal Number			920019	920023	920038	920041	920050	920114	920121	920172	920216	920230
Exposure Group			THS 2.2_Switch	SHAM	THS 2.2_Switch	3R4F_CONT	THS 2.2_Switch	THS 2.2_Switch	THS 2.2_Switch	3R4F_CONT	SHAM	THS 2.2_CONT
	Site / Finding	Staining										
Code	**parenchyma**										**	
4000001	micro-granuloma with micro-hemorrhage	HE	2	1	2		2	1	2	1	2	1
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	4	4	2	1	3	4	2	5	2	3
4000003	hyperchromasia, hepatocytes	HE						3	3		2	
4000004	mono-nuclear inflammatory cells	HE				1		1			1	
4000005	neutrophlic granulocytes	HE						1				
4000006	amount of fat	OR	5	3	3	3	5	5	3	4	2	3
4000007	amount of glycogen	PAS	3	3	1	2	2	1	3	4	4	2
4000008	hemorrhage	HE									2	
4000009	degeneration/necrosis, hepatocytes	HE	2	3				2		1	2	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	2	2	2	3	2	3	3	2	1
4000014	brownish pigment	HE	1							1		
4000012	bile duct hyperplasia	HE	2	2	3	2	2	2	2	2	3*	2
4000013	increase of collagen fibers	HE	1	2	3	1	3	2	2	3	2	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

*: dilatation of bile ducts
**: cyst formation

Table 49 cont. Individual histopathology data, liver

Coded Animal Number			920287	920346	920351	920408	920452	920461	920520	920532	920579	920591
Exposure Group			SHAM	3R4F_CONT	THS 2.2_CONT	SHAM	SHAM	Cessation	Cessation	Cessation	Cessation	Cessation
	Site / Finding	Staining										
Code	**parenchyma**											
4000001	micro-granuloma with micro-hemorrhage	HE	1		1		3*	1	1	1	3	2
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	4	1	2	4	2	4	2	3	4	2
4000003	hyperchromasia, hepatocytes	HE		2	2		3		2		2	
4000004	mono-nuclear inflammatory cells	HE					1					
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	4	2	4	3	2	3	4	3	3	4
4000007	amount of glycogen	PAS	3	3	4	2	3	3	2	3	2	3
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE	2	2	1	2		1	2	2	3	
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	3	2	3	5	2	2	3	3	2
4000014	brownish pigment	HE	2	2	1		3	2		1	1	1
4000012	bile duct hyperplasia	HE	1	2	1	2	2	1	2	1	2	2
4000013	increase of collagen fibers	HE	1	3	2	3	3	2	3	2	3	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

*: brownish pigment

Table 49 cont. Individual histopathology data, liver

Coded Animal Number			920648	920662	920686	920721	920727	920732	920735	920780	920831	920841
Exposure Group			THS 2.2_Switch	Cessation	THS 2.2_CONT	Cessation	3R4F_CONT	3R4F_CONT	THS 2.2_Switch	Cessation	THS 2.2_CONT	3R4F_CONT
	Site / Finding	Staining										
Code	**parenchyma**											
4000001	micro-granuloma with micro-hemorrhage	HE	1	1	1		1	2	2	2		
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	3	3	3	3	3		4	2	4	4
4000003	hyperchromasia, hepatocytes	HE				2		3			2	2
4000004	mono-nuclear inflammatory cells	HE		1				2	1	2	1	
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	3	4	4	5	5	3	4	4	3	3
4000007	amount of glycogen	PAS	3	2	2	3	2	3	3	2	3	3
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE				2		2		2		
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	4	3	2	2	2	2	2	2	4	2
4000014	brownish pigment	HE	1									
4000012	bile duct hyperplasia	HE	3	2	1	1	2	2	2	2	2	2
4000013	increase of collagen fibers	HE	3	2	2	2	2	3	3	3	2	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

Table 49 cont. Individual histopathology data, liver

Coded Animal Number			920852	920861	920885	920899	920904	920971	920984	921005	921024	921102
Exposure Group			3R4F_CONT	SHAM	SHAM	THS 2.2_CONT	SHAM	3R4F_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_CONT	THS 2.2_Switch
	Site / Finding	Staining										
Code	**parenchyma**											
4000001	micro-granuloma with micro-hemorrhage	HE		2	1	1	2	2	2	1	2	2
4000002	cytoplasmatic vacuolisation, hepatocytes	HE	3	3	3	3	4	1	4	3	4	3
4000003	hyperchromasia, hepatocytes	HE		2	2							
4000004	mono-nuclear inflammatory cells	HE			1				1			
4000005	neutrophlic granulocytes	HE										
4000006	amount of fat	OR	2	4	4	5	4	2	4	4	4	3
4000007	amount of glycogen	PAS	2	4	2	3	4	1	2	3	3	3
4000008	hemorrhage	HE										
4000009	degeneration/necrosis, hepatocytes	HE		3		2	2	2	2	2	3	3
	periportal/interstitial area											
4000011	mono-nuclear inflammatory cells	HE	2	3	2	3	2	3	2	2	5	3
4000014	brownish pigment	HE	1					2		1		
4000012	bile duct hyperplasia	HE	1	2	1	2	2	2	2	1	2	2
4000013	increase of collagen fibers	HE	2	2	2	3	3	3	3	2	2	2

Error code: a: corrected/changed entry
b: entry in wrong cell
c: other with explanation

Data Entry: 1-5: severity grading
6: incidence
7: invalid (insufficient quality of slide)
0: finding not observed

MORPHOMETRY DATA

Table 50 Individual morphometrical data and histopathology data of alveolar emphysema

Animal ID	Exposure group	LM	DI	BA	Lung Volume	Emphysema
920011	SHAM	52,1	16,4	14,18	160,2	1,0
920110	SHAM	52,4	17	14,35	189,2	1,3
920266	SHAM	42,9	14,9	13,61	153,4	1,2
920330	SHAM	47,1	13	11,50	179,4	1,0
920448	SHAM	50	12,2	10,30	195,1	1,5
920791	SHAM	46,6	15,2	12,43	153,8	1,4
920793	SHAM	51,2	11,3	12,25	180,9	0,0
920921	SHAM	48,4	6,9	13,35	158,3	1,0
921062	SHAM	51,9	14,4	13,03	179,9	1,0
921070	SHAM	49,1	22,3	14,79	198,1	1,0
920115	3R4F_CONT	59,3	42,2	11,50	204,0	2,8
920138	3R4F_CONT	64	50	10,90	163,7	2,6
920197	3R4F_CONT	65,9	46,9	12,02	198,6	2,8
920261	3R4F_CONT	65,4	47,5	10,24	212,3	3,2
920379	3R4F_CONT	64,9	43,8	9,83	174,0	3,0
920556	3R4F_CONT	60,3	37,8	12,02	174,0	3,2
920627	3R4F_CONT	invalid	invalid	invalid	invalid	4,0
920646	3R4F_CONT	62,1	45,2	10,02	167,6	2,6
920722	3R4F_CONT	59,4	39,4	11,85	159,3	2,6
921001	3R4F_CONT	63,3	53,3	9,80	245,3	2,6
920020	THS 2.2_CONT	47,9	9,4	14,68	179,4	1,0
920147	THS 2.2_CONT	49,6	19,4	12,43	154,3	1,0
920218	THS 2.2_CONT	50,7	19,2	12,87	169,1	1,0
920339	THS 2.2_CONT	44,1	11,2	11,03	173,0	1,5
920800	THS 2.2_CONT	52,7	8,9	12,33	141,1	1,0
920816	THS 2.2_CONT	46,3	17,3	12,53	171,5	1,0
920835	THS 2.2_CONT	48,8	16,8	14,21	194,6	1,2
920911	THS 2.2_CONT	49,1	6	12,73	193,7	1,0
920970	THS 2.2_CONT	44,8	7,3	15,71	226,1	1,0
921060	THS 2.2_CONT	50,9	16,7	13,36	195,6	1,6

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

Table 50 cont Individual morphometrical data and histopathology data of alveolar emphysema

Animal ID	Exposure group	LM	DI	BA	Lung Volume	Emphysema
920140	Cessation	52,6	15	13,29	206,9	1,3
920220	Cessation	56,1	19,7	12,84	156,3	1,2
920369	Cessation	invalid	invalid	invalid	invalid	invalid
920400	Cessation	49,2	17,9	13,29	150,4	1,4
920601	Cessation	51,3	23,7	14,17	147,0	1,6
920632	Cessation	52,4	15,3	13,73	167,1	1,2
920700	Cessation	51,2	11,3	14,59	180,4	2,4
920709	Cessation	54,7	16,4	11,18	182,8	1,4
920856	Cessation	53,8	18,9	12,77	227,6	1,8
921019	Cessation	60,7	17,4	12,33	152,9	1,8
920251	THS 2.2_Switch	53,7	18,8	11,38	171,0	1,0
920282	THS 2.2_Switch	49,1	15,2	13,07	155,8	1,8
920617	THS 2.2_Switch	51,5	14,7	13,68	181,9	1,0
920762	THS 2.2_Switch	52,6	12,9	12,22	174,0	1,6
920830	THS 2.2_Switch	52,5	9,8	13,18	167,6	1,0
920865	THS 2.2_Switch	48,1	13	14,61	164,7	1,0
920896	THS 2.2_Switch	52,8	11,1	12,06	190,2	1,0
920936	THS 2.2_Switch	53,1	7,3	12,43	227,1	1,0
920955	THS 2.2_Switch	48,4	17,4	13,50	172,0	1,6
921031	THS 2.2_Switch	59,5	30,4	14,01	204,0	1,6

LM: mean chord length (µm) DI: destructive index (%) BA: bronchiolar attachments (n/mm)
Lung Volume (mm^3) Emphysema: mean value of histopathology scores of five lung sections

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