

Draft Report  
I-5038.005

APPENDIX A

89355946

**PATHOLOGY REPORT**

**SIX-WEEK REPEATED SMOKE INHALATION IN MICE  
TO COMPARE HISTOPATHOLOGY AND SHORT-TERM ENDPOINTS  
USING TEST AND REFERENCE CIGARETTES (D33, D34 AND D36)  
STUDY NO. I-5038.005**

89355947

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APPENDIX 1 REPORTS CODE TABLE

APPENDIX 2 ABBREVIATIONS LIST

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**PATHOLOGY NARRATIVE**

**89355949**

PATHOLOGY REPORT

SIX WEEK REPEATED SMOKE INHALATION IN MICE  
TO COMPARE HISTOPATHOLOGY AND SHORT-TERM ENDPOINTS  
USING TEST AND REFERENCE CIGARETTES (D33, D34 AND D36)  
STUDY NO. I 5038.005

INTRODUCTION AND METHODS

Female B6C3F1 mice were divided into sham controls, a reference cigarette group, and 3 test cigarette groups and exposed to repeated doses of smoke by nose-only inhalation for 4, 15, or 30 exposure days over a period of 4, 23 or 44 days, respectively. Two of the test cigarette groups (D33 and D34) were terminated during the study and the tissues discarded. Four days after initiation, three mice from the remaining groups (Reference, D36 cigarette and Sham) were given colchicine (1mg/kg). Four hours later they were anesthetized with Metofane and killed by exsanguination in order to determine mitotic indices of the tracheal and intrapulmonary airway epithelium. Three additional mice from each group were killed in the same manner following 15 exposure days; the remainder (6 per group) were killed after 30 exposure days and necropsied. Lungs of all mice were weighed to the nearest milligram and fixed by perfusion with formalin to approximate the normal expanded state. The nasal passages were flushed with formalin and immersed in fixative. The remaining organs and tissues were removed from the animal and fixed in 10% neutral buffered formalin.

Nasal passages were decalcified and trimmed according to the procedures described by Young (1981). Lung lobes were sectioned and embedded longitudinally through the stem bronchus of each lobe (Dungworth, et al. 1976); trachea and mainstem bronchi were removed and embedded longitudinally. Three transverse sections were made of the larynx. All tissues were embedded in paraffin, sectioned at 6  $\mu$ m, and stained with hematoxylin, phloxine, and eosin.

The mitotic <sup>mice</sup> index was determined for the trachea and intrapulmonary airways of ~~rats~~ mice exposed to smoke for 4 days by counting the number of mitotic figures per 10 high power fields of airway epithelium. Respiratory tissues and gross lesions from ~~rats~~ mice of the 15 and 30 day sacrifices were examined microscopically.

## RESULTS

### GROSS NECROPSY FINDINGS

Treatment-related gross lesions characterized as brown discoloration of the lungs occurred in all smoke-exposed mice. The sham controls were free of discoloration. No difference was discerned between the reference and test cigarette groups. (Table of Gross vs. Micro Findings)

### MICROSCOPIC FINDINGS

Mitotic indices were increased in the tracheal epithelium of the reference cigarette group compared with the test and sham groups. The indices were similar among all groups for the intrapulmonary airways (Table I).

TABLE I  
The Mitotic Index (No. of Mitoses per 10 High Power Fields (HPF))  
of Tracheal or Intrapulmonary Airway (Bronchial) Epithelium

<u>Animal No.</u>	<u>Group</u>	<u>Trachea</u>	<u>Bronchi</u>	<u>Days of Test</u>
6075	1-Reference	14/10 HPF	0/10 HPF	4
6076	1-Reference	5/10 HPF	0/10 HPF	4
6077	1-Reference	6/10 HPF	2/10 HPF	4
6111	4-D36	2/10 HPF	1/10 HPF	4
6112	4-D36	1/10 HPF	1/10 HPF	4
6113	4-D36	0/10 HPF	0/10 HPF	4
6123	5-Sham	2/10 HPF	0/10 HPF	4
6124	5-Sham	2/10 HPF	0/10 HPF	4
6125	5-Sham	2/10 HPF	0/10 HPF	4

Mice treated for 30 days with smoke had increased numbers of alveolar foam cells in pulmonary alveoli. Fewer neutrophils were associated with them. A majority of these cells had a brownish cytosol and were most often

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observed in alveoli located near small airways. Most smoke-exposed mice had this response. This cellular response was graded as minimal. Mice of group 5 (sham controls) were free of this response. It was attributed to smoke inhalation. A difference was not observed among reference and test cigarettes. Foam cells were not observed in the lungs of mice treated for 15 exposure days.

Other responses observed were minimal perivascular and peribronchiolar lymphocytic infiltrates, and occasionally peribronchiolar infiltrates of other inflammatory cells consisting of a mixture of neutrophils and mononuclear leukocytes (leukocytic infiltrates). The infiltrates were of similar incidence among all groups including the sham controls. Thus, their occurrence is incidental and not related to smoke. Their cause could not be determined. Antibody was not detectable to any of the viral or mycoplasmal agents common to mice.

In the nose, mucosal atrophy of olfactory epithelium (Sections III and IV) was observed in 1/6 reference cigarette-exposed mice, and respiratory epithelial metaplasia was observed focally in 1/6 D36 cigarette-exposed mice. The mucosal atrophy consisted of a focal reduction of cell numbers in the olfactory epithelium. Respiratory epithelial metaplasia was characterized by focal replacement of olfactory epithelium with respiratory mucociliary epithelium. The occurrence of the lesion in Sections III and/or IV of only 1/6 mice of each smoke-exposed group (reference and test) with no lesions in the more rostral Sections I and II suggest that they are incidental and unrelated to treatment. The cause of the lesions could not be determined. Lesions caused by exposure to cigarette smoke are most commonly observed in Sections I and II.

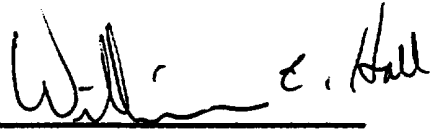
#### SUMMARY

The mitotic index was increased in the tracheal epithelium of mice exposed for 4 days to smoke from the reference cigarette (Group 1) compared with the test (D36) cigarette and sham controls (Groups 4 and 5, respectively). No difference in mitotic index was observed in bronchial epithelium.

In the lung, pigmented alveolar foam cells were found in mice exposed for 30 exposure days to smoke from the reference and D36 cigarette types, but not sham controls. Similar lesions were not observed in mice exposed for 15 days. Lesions were accompanied by slight infiltration of neutrophils. Other inflammatory changes consisting of perivascular and peribronchiolar

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lymphoid infiltrates, and/or peribronchiolar leukocytic infiltrates (neutrophils and lymphoid cells) were found in mice from all groups of both sacrifices and considered incidental. Nasal lesions were considered incidental. Changes attributable to test article cigarette smoke were not discerned.



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William C. Hall, V.M.D., Ph.D.  
Diplomate, A.C.V.P.  
April 29, 1986

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**PROJECT SUMMARY TABLE**

**89355954**

PATHOLOGY ASSOCIATES, INC.  
 SIX-WEEK REPEATED INHALATION STUDY  
 I-5038.005  
 FEMALE B6C3F1 MICE  
 MICROBIOLOGICAL ASSOCIATES, INC.

**Project Summary Table**  
 SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: 15038.005		FATES: ALL					
DAYS: ALL		SEX: FEMALE					
GROUP:		REF.15d	D36 15d	SHAM 15d	REF.30d	D36 30d	SHAM 30d
NUMBER OF ANIMALS:		3	3	3	6	6	6
NASAL, ORAL, PHARYNGEAL I	# Ex 3	3	3	3	6	6	6
NASAL, ORAL, PHARYNGEAL II	# Ex 3	3	3	3	6	6	6
NASAL, ORAL, PHARYNGEAL III	# Ex 3	3	3	3	6	6	6
ENDO T-MUCOSAL ATROPHY	0	0	0	0	1	0	0
NASAL, ORAL, PHARYNGEAL IV	# Ex 3	3	3	3	6	6	6
ENDO T-MUCOSAL ATROPHY	0	0	0	0	1	0	0
DNM-RESP. EPITH. METAPLASIA	0	0	0	0	0	1	0
TRACHEA	# Ex 3	3	3	3	6	6	6
HYPERPLASIA, EPITHELIAL	0	1	0	0	0	0	0
LARYNX	# Ex 3	3	3	3	6	6	6
LUNGS	# Ex 3	3	3	3	6	6	6
LYMPHOID INFILTRATE, PERIBR.	2	1	2	2	0	4	
LYMPHOID INFILTRATE, PERIVASC	1	3	0	2	6	3	
LEUKOCYTTIC INFILTRATE, PERIBR	0	0	0	1	1	0	
ALVEOLAR FOAM CELLS	0	0	0	6	4	0	

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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**Project Summary Table**  
SUMMARY: Incidence of NEOPLASTIC and NON-NEOPLASTIC Microscopic Findings

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PROJECT ID. NO: 15038.005

FATES: ALL

DAYS: ALL

SEX: FEMALE

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GROUP:	REF.15d	036 15d	SHAM 15d	REF.30d	036 30d	SHAM 30d
NUMBER OF ANIMALS:	3	3	3	6	6	6

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OTHER TISSUES AND LESIONS:

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TABULATED ANIMAL DATA

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**PATHOLOGY ASSOCIATES, INC.**  
 SIX-WEEK REPEATED INHALATION STUDY  
 I-5038.005  
 FEMALE B6C3F1 MICE  
 MICROBIOLOGICAL ASSOCIATES, INC.

**Tabulated Animal Data**

PROJECT ID: 15038.005    GROUP: REF.15d    SEX: FEMALE    DAYS: ALL  
 PAGE 1                      FATES: ALL

ANIMAL ID. NO:	6878	6879	6880
NASAL, ORAL, PHARYNGEAL I	N	N	N
NASAL, ORAL, PHARYNGEAL II	N	N	N
NASAL, ORAL, PHARYNGEAL III	N	N	N
NASAL, ORAL, PHARYNGEAL IV	N	N	N
TRACHEA	N	N	N
LARYNX	N	N	N
LUNGS			N
LYMPHOID INFILTRATE, PERIBR.	1	1	-
LYMPHOID INFILTRATE, PERIVASC	1	-	-

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

Tabulated Animal Data

PROJECT ID: 15038.005    GROUP: REF.15d    SEX: FEMALE    DAYS: ALL  
PAGE 2    FATES: ALL

ANIMAL ID. NO:

6078    6079    6080

OTHER TISSUES AND LESIONS:

? ? ?  
Should there be  
an "N" for "done"  
see also p. III-4, 6, 8, 10, 12, 1

(End of Report)

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**PATHOLOGY ASSOCIATES, INC.**  
 SIX-WEEK REPEATED INHALATION STUDY  
 I-5838.005  
 FEMALE B6C3F1 MICE  
 MICROBIOLOGICAL ASSOCIATES, INC.

**Tabulated Animal Data**

PROJECT ID: 15038.005    GROUP: 036 15d    SEX: FEMALE    DAYS: ALL  
 PAGE 1                      FATES: ALL

ANIMAL ID. NO:	6114	6115	6116
NASAL, ORAL, PHARYNGEAL I	N	N	N
NASAL, ORAL, PHARYNGEAL II	N	N	N
NASAL, ORAL, PHARYNGEAL III	N	N	N
NASAL, ORAL, PHARYNGEAL IV	N	N	N
TRACHEA	N	N	
HYPERPLASIA, EPITHELIAL	-	-	1
LARYNX	N	N	N
LUNGS			
LYMPHOID INFILTRATE, PERIBR.	-	-	1
LYMPHOID INFILTRATE, PERIVASC	1	1	1

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Tabulated Animal Data

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PROJECT ID: I5038.005    GROUP: D36 15d    SEX: FEMALE    DAYS: ALL  
PAGE 2                    FATES: ALL

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ANIMAL ID. NO:                    6114    6115    6116

OTHER TISSUES AND LESIONS:

(End of Report)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

Tabulated Animal Data

PROJECT ID: 15038.005    GROUP: SHAM 15d    SEX: FEMALE    DAYS: ALL  
PAGE 1    FATES: ALL

ANIMAL ID. NO:	6126	6127	6128
NASAL, ORAL, PHARYNGEAL I	N	N	N
NASAL, ORAL, PHARYNGEAL II	N	N	N
NASAL, ORAL, PHARYNGEAL III	N	N	N
NASAL, ORAL, PHARYNGEAL IV	N	N	N
TRACHEA	N	N	N
LARYNX	N	N	N
LUNGS		N	
LYMPHOID INFILTRATE, PERIBR.	1	-	1

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
1-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Tabulated Animal Data

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PROJECT ID: 15038.005    GROUP: SHAM 15d    SEX: FEMALE    DAYS: ALL  
PAGE 2                      FATES: ALL

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ANIMAL ID. NO:                      6126    6127    6128

OTHER TISSUES AND LESIONS:

(End of Report)

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PATHOLOGY ASSOCIATES, INC.  
 SIX-WEEK REPEATED INHALATION STUDY  
 1-5038.005  
 FEMALE B6C3F1 MICE  
 MICROBIOLOGICAL ASSOCIATES, INC.

Tabulated Animal Data

PROJECT ID: 15038.005    GROUP: REF.30d    SEX: FEMALE    DAYS: ALL  
 PAGE 1                      FATES: ALL

ANIMAL ID. NO:	6081	6082	6083	6084	6085	6086
NASAL, ORAL, PHARYNGEAL I	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL II	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL III ENDO T-MUCOSAL ATROPHY	N	N	N	N	N	2
NASAL, ORAL, PHARYNGEAL IV ENDO T-MUCOSAL ATROPHY	N	N	N	N	N	2
TRACHEA	N	N	N	N	N	N
LARYNX	N	N	N	N	N	N
LUNGS						
LYMPHOID INFILTRATE, PERIBR.	-	1	1	-	-	-
LYMPHOID INFILTRATE, PERIVASC	-	-	-	-	1	1
LEUKOCYTTIC INFILTRATE, PERIBR	-	-	-	1	-	-
ALVEOLAR FOAM CELLS	1	1	1	1	1	1

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Tabulated Animal Data

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PROJECT ID: 15038.005    GROUP: REF.30d    SEX: FEMALE    DAYS: ALL  
PAGE 2                            FATES: ALL

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ANIMAL ID. NO:                    6081    6082    6083    6084    6085    6086

OTHER TISSUES AND LESIONS:

(End of Report)

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**PATHOLOGY ASSOCIATES, INC.**  
**SIX-WEEK REPEATED INHALATION STUDY**  
**1-5838.005**  
**FEMALE B6C3F1 MICE**  
**MICROBIOLOGICAL ASSOCIATES, INC.**

**Tabulated Animal Data**

**PROJECT ID: 15838.005    GROUP: D36 30d    SEX: FEMALE    DAYS: ALL**  
**PAGE 1                            FATES: ALL**

ANIMAL ID. NO:	6117	6118	6119	6120	6121	6122
NASAL, ORAL, PHARYNGEAL I	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL II	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL III	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL IV DNM-RESP. EPITH. METAPLASIA	N	N	N	2	N	N
TRACHEA	N	N	N	N	N	N
LARYNX	N	N	N	N	N	N
LUNGS						
LYMPHOID INFILTRATE, PERIVASC	1	1	1	1	1	1
LEUKOCYTIC INFILTRATE, PERIBR	-	-	1	-	-	-
ALVEOLAR FOAM CELLS	-	1	-	1	1	1

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Tabulated Animal Data

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PROJECT ID: 15038.005    GROUP: 036 38d    SEX: FEMALE    DAYS: ALL  
PAGE 2                      FATES: ALL

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ANIMAL ID. NO:                      6117    6118    6119    6120    6121    6122

OTHER TISSUES AND LESIONS:

(End of Report)

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**PATHOLOGY ASSOCIATES, INC.**  
 SIX-WEEK REPEATED INHALATION STUDY  
 I-5038.005  
 FEMALE B6C3F1 MICE  
 MICROBIOLOGICAL ASSOCIATES, INC.

**Tabulated Animal Data**

PROJECT ID: I5038.005    GROUP: SHAM 30d    SEX: FEMALE    DAYS: ALL  
 PAGE 1                      FATES: ALL

ANIMAL ID. NO:	6129	6130	6131	6132	6133	6134
NASAL, ORAL, PHARYNGEAL I	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL II	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL III	N	N	N	N	N	N
NASAL, ORAL, PHARYNGEAL IV	N	N	N	N	N	N
TRACHEA	N	N	N	N	N	N
LARYNX	N	N	N	N	N	N
LUNGS						
LYMPHOID INFILTRATE, PERIBR.	1	1	1	-	-	1
LYMPHOID INFILTRATE, PERIVASC	-	-	-	1	1	1

(Report Continued)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Tabulated Animal Data

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PROJECT ID: 15038.005    GROUP: SHAM 30d    SEX: FEMALE    DAYS: ALL  
PAGE 2    FATES: ALL

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ANIMAL ID. NO:                    6129   6130   6131   6132   6133   6134

OTHER TISSUES AND LESIONS:

(End of Report)

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**GROSS VS. MICROSCOPIC FINDINGS**

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

*Shall have  
to info later?*

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005      GROUP: SHAM 30d      SEX: FEMALE      DAYS: ALL  
PAGE 1      FATES: ALL

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ANIMAL NO: 6129      PATHOLOGY ID. NO: MB0011      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:

>NGL      ?

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ANIMAL NO: 6130      PATHOLOGY ID. NO: MB0011      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:

>NGL

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ANIMAL NO: 6131      PATHOLOGY ID. NO: MB0011      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:

>NGL

---

ANIMAL NO: 6132      PATHOLOGY ID. NO: MB0011      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:

>NGL

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SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: SHAM 30d    SEX: FEMALE    DAYS: ALL  
PAGE 2    FATES: ALL

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ANIMAL NO: 6133    PATHOLOGY ID. NO: MB001I    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:

>NGL

---

ANIMAL NO: 6134    PATHOLOGY ID. NO: MB001I    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:

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(End of Report)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005      GROUP: D36 30d      SEX: FEMALE      DAYS: ALL  
PAGE 1      FATES: ALL

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ANIMAL NO: 6117      PATHOLOGY ID. NO: MB001I      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION      NO COROLLARY CHANGE DETECTED

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ANIMAL NO: 6118      PATHOLOGY ID. NO: MB001I      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION      LUNGS- ALVEOLAR FOAM CELLS

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ANIMAL NO: 6119      PATHOLOGY ID. NO: MB001I      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION      NO COROLLARY CHANGE DETECTED

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ANIMAL NO: 6120      PATHOLOGY ID. NO: MB001I      PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:      DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:      RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION      LUNGS- ALVEOLAR FOAM CELLS

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: D36 30d    SEX: FEMALE    DAYS: ALL  
PAGE 2    FATES: ALL

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ANIMAL NO: 6121    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

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ANIMAL NO: 6122    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: FOUND DEAD  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 30

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

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(End of Report)

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PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: REF.30d    SEX: FEMALE    DAYS: ALL  
PAGE 1    FATES: ALL

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ANIMAL NO: 6081    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: FOUND DEAD  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 38

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

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ANIMAL NO: 6082    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

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ANIMAL NO: 6083    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

---

ANIMAL NO: 6084    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
> LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

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89355875

PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: REF.30d    SEX: FEMALE    DAYS: ALL  
PAGE 2    FATES: ALL

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ANIMAL NO: 6085    PATHOLOGY ID. NO: MB001I    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

---

ANIMAL NO: 6086    PATHOLOGY ID. NO: MB001I    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 44

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
.NGS-BROWN DISCOLORATION    LUNGS- ALVEOLAR FOAM CELLS

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(End of Report)

89355976

PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

info?  
✓

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: SHAM 15d    SEX: FEMALE    DAYS: ALL  
PAGE 1    FATES: ALL

---

ANIMAL NO: 6126    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23  
REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:    /  
>NGL

---

ANIMAL NO: 6127    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23  
REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>NGL

---

ANIMAL NO: 6128    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23  
REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>NGL

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(End of Report)

89355977



PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: D36 15d    SEX: FEMALE    DAYS: ALL  
PAGE 1    FATES: ALL

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ANIMAL NO: 6114    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:    /  
>LUNGS-SLIGHT BROWN DISCOLORATION    NO COROLLARY CHANGE DETECTED

---

ANIMAL NO: 6115    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-SLIGHT BROWN DISCOLORATION    NO COROLLARY CHANGE DETECTED

---

ANIMAL NO: 6116    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-SLIGHT BROWN DISCOLORATION    NO COROLLARY CHANGE DETECTED

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(End of Report)

89355978

PATHOLOGY ASSOCIATES, INC.  
SIX-WEEK REPEATED INHALATION STUDY  
I-5038.005  
FEMALE B6C3F1 MICE  
MICROBIOLOGICAL ASSOCIATES, INC.

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Correlation of Gross & Micro Findings

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PROJECT ID: I5038.005    GROUP: REF.15d    SEX: FEMALE    DAYS: ALL  
PAGE 1    FATES: ALL

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ANIMAL NO: 6078    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:    /  
>LUNGS-SLIGHT BROWN DISCOLORATION    NO COROLLARY CHANGE DETECTED

---

ANIMAL NO: 6079    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-SLIGHT BROWN DISCOLORATION    NO COROLLARY CHANGE DETECTED

---

ANIMAL NO: 6080    PATHOLOGY ID. NO: MB0011    PATHOLOGIST: WCH  
ANIMAL FATE: SCHEDULED SACRIFICE  
PROBABLE CAUSE OF DEATH:    DAYS ON TEST: 23

REFERENCE TO NECROPSY RECORD:    RELATED HISTOPATHOLOGY:  
>LUNGS-SLIGHT BROWN DISCOLORATION    NO COROLLARY CHANGE DETECTED  
>    LARYNX AND TRACHEA RECEIVED  
DISTORTED.

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(End of Report)

89355979

**QUALITY ASSURANCE REPORT**

**89355980**

## QUALITY ASSURANCE STATEMENT

This histopathology project has been conducted in compliance with Good Laboratory Practice regulations promulgated by the U. S. Food and Drug Administration and the U. S. Environmental Protection Agency. Pathology Associates, Incorporated has a functioning and responsive quality assurance unit which has conducted appropriate inspections and reported all findings to management. The following is a record of those inspections and reports:

<u>Date of Inspection<sup>1</sup></u>	<u>Phase Inspected</u>	<u>Date Findings Reported to Management / and Study Pathologist</u>
* 02-21-86	Trimming	02-24-86
* 03-12-86	Processing	03-12-86
* 03-12-86	Embedding	03-12-86
* 03-14-86	Microtomy	03-17-86
* 03-11-86	Staining	03-11-86
* 03-11-86	Coverslipping	03-11-86
* 03-11-86	Labeling	03-11-86
** 03-29-86	Individual Animal Data	03-30-86
** 03-29-86	Data Entry	03-30-86
** 03-29-86	Computer Validation	03-30-86
** 03-30-86	Draft Pathology Report	03-30-86

- \* General monthly phase inspection
- \*\* Inspection specific for Study Number

<sup>1</sup>In accordance with the PAI Quality Assurance Division's Standard Operating Procedures, phase inspections are routinely conducted on a random basis at a minimum of monthly. Dates of inspection are reported for each study according to the most recent phase inspection conducted during that period.

  
\_\_\_\_\_  
Director, Quality Assurance Unit

April 30, 1986

\_\_\_\_\_  
Date

Six Week Repeated Smoke Inhalation in Mice to Compare Histopathology and Short-term Endpoints Using Test and Reference Cigarettes (D33, D34 and D36) Study No. I 5038.005.

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**APPENDIX 1**

**89355982**

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**Reports Code Table**

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**N** Tissues within normal histological limits  
**A** Autolysis precluding adequate evaluation  
**U** Tissues unavailable/unsuitable for evaluation  
**S** Tissues not applicable to animal  
**\*** Tissues not examined/not required by protocol

---

**1** minimal  
**2** mild  
**3** moderate  
**4** severe  
**>** focal  
**J** diffuse  
**>** multifocal  
**P** Present  
**B** Neoplasm, Benign  
**M** Neoplasm, Malignant without Metastasis  
**C** Neoplasm, Malignant with Metastasis  
**X** Metastatic Site (+)

(End of Report)

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**APPENDIX 2**

**89355984**

## ABBREVIATIONS LIST

ENDO T	ENDOTURBINATE
DNM	DORSAL NASAL MEATUS
RESP	RESPIRATORY
EPITH	EPITHELIUM
PERIBR	PERIBRONCHIOLAR
PERIVASC	PERIVASCULAR

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Draft Report  
I-5038.005

APPENDIX B

89355986

APPENDIX B  
WEEKLY TPM DETERMINATIONS

Cigarette Type	RTD (mm H <sub>2</sub> O)	Butt Length (mm)	TPM (mg)
	Week 1		
Reference II	103	51	12.9
	97	51	11.0
D36	86	49	15.4
	94	40	17.4
	Week 2		
Reference II	98	52	13.8
	99	55	13.3
D36	76	38	23.5
	89	37	24.4
	Week 3		
Reference II	105	60	6.5
	105	56	8.2
D36	92	47	16.1
	92	47	15.2

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APPENDIX B (Cont'd)  
WEEKLY TPM DETERMINATIONS

Cigarette Type	RTD (mm H <sub>2</sub> O)	Butt Length (mm)	TPM (mg)
-----			
Week 4			
Reference II	89	50	5.5
	87	51	3.6
D36	85	49	5.4
	94	51	6.5
Week 5			
Reference II	92	42	17.7
	84	39	19.2
D36	82	44	16.2
	78	40	17.6
Week 6			
Reference II	104	57	8.8
	110	55	9.9
D36	90	47	13.1
	81	42	21.0
	89	50	13.2
Week 7			
Reference II	103	49	14.9
	98	51	13.6
D36	88	44	17.2
	91	50	16.0
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89355989