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Study Title

H-25499 and H-25500: Subchronic Toxicity
90-Day Gavage Study in Male Rats

Laboratory Project ID: DuPont-11671

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PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of data obtained from this study.

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STUDY INFORMATION

Test Substance 1

Substance Tested: [REDACTED]

Synonyms/Codes: • H-25499 [REDACTED]
• H-24616 [REDACTED]

Haskell Number: 25499 / 24616

Purity: [REDACTED]

Physical Characteristics: Opaque tan liquid

Stability: The test substance appeared to be stable under the conditions of the study; no evidence of instability was observed.

Test Substance 2

Substance Tested: [REDACTED]

Synonyms/Codes: [REDACTED]
• H-25500 [REDACTED]

Haskell Number: 25500

Purity: [REDACTED]

Physical Characteristics: Clear liquid

Stability: The test substance appeared to be stable under the conditions of the study; no evidence of instability was observed.

Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Initiated/Completed: November 5, 2002 / (see report cover page)

SUMMARY

A 90-day oral study in rats was conducted to evaluate the potential nasal toxicity of H-25499^a [REDACTED] and H-25500 [REDACTED] in Crl:CD®(SD)BR rats. Groups of 15 male rats were administered daily dosages by oral gavage of the vehicle, 70 mg/kg H-25500, or 1000 mg/kg of H-25499 for 14, 28, or 91 days. Body weight was measured twice weekly. Clinical observations were evaluated throughout the study. After 14, 28, and 91 days of treatment, 5 rats per group per time point were sacrificed for evaluation of nasal histopathology.

Nasal lesions were produced in rats administered H-25499 and H-25500. The nasal lesions in rats administered H-25499 were characterized by degeneration/atrophy of the olfactory epithelium and degeneration/regeneration of the respiratory epithelium. The incidence of affected rats was low for animals sacrificed after 14 or 28 days of treatment, however; all the rats treated with H-25499 were affected after 91 days of treatment.

The nasal lesions in rats administered H-25500 were similar to those observed in rats treated with H-25499, with the additional finding that rats treated with H-25500 had adhesions in the nasal turbinates. The lesions observed in this study were similar to those observed in a previous 90-day study with H-24616 [REDACTED]. Based on the results of this study, the nasal lesions observed in the previous study with organofluoride urethane polymer with a surfactant can be attributed to the surfactant component of the material.

^a During the course of the study, a second lot (H-24616) of the same test substance was used due to an insufficient supply of H-25499.

INTRODUCTION

The test substance contains an [REDACTED] (H-25500), and is used as a carpet protectant. In a previous 90-day oral study, rats were administered daily dosages of 0, 50, 250, or 1000 mg/kg/day (based on active ingredient) of this same [REDACTED] product by gavage.⁽¹⁾ Nasal olfactory epithelium degeneration/necrosis was observed in male and female rats at all dosages, and inflammation of the olfactory epithelium was observed in male rats administered 250 or 1000 mg/kg/day. It was hypothesized that the surfactant in the product may have contributed to the nasal lesions. In order to test this hypothesis, in the current study, male rats were administered daily dosages of the vehicle (deionized water), 1000 mg/kg/day of [REDACTED] formulation (H-25499), or 70 mg/kg/day of the surfactant alone (H-25500). The dosage for the surfactant was based on the concentration of surfactant in the [REDACTED] formulation.

The study was originally initiated using test substance lot identified as H-25499. However, during the course of the study, the amount of H-25499 was determined to be insufficient for the remainder of the study. Therefore, H-24616 (a second lot of the test substance) was used to complete the 90-day treatment period. All references to the test substance in this report will use H-25499.

OBJECTIVE

The objective of this study is to compare the potential nasal toxicity of H-25499 and surfactant, H-25500, when administered by gavage to male rats. The oral route of administration was selected because it was the route of exposure in the previous studies.

MATERIALS AND METHODS

A. Test Substances

The test substance, H-25499 [REDACTED] was supplied by the sponsor as a opaque tan liquid. On test day 52, the quantity of H-25499 [REDACTED] was determined to be insufficient for the remainder of the study. Therefore, a second lot of the same test substance [REDACTED] was used until study termination.

The surfactant [REDACTED] was supplied by the sponsor as a clear liquid. The surfactant was assigned Haskell Laboratory Number H-25500 [REDACTED]

The test substances appeared to be stable under the conditions of the study. No evidence of instability, such as a change in color or physical state, was observed.

B. Test Species

Male Crl:CD[®](SD)IGS BR rats received from Charles River Laboratories, Inc., Raleigh, North Carolina were used on study.

The rat was selected for this study because it is the recommended species specified in the guidelines. The Crl:CD[®](SD)IGS BR strain was chosen because extensive background information is available from the literature, the supplier and previous studies at Haskell Laboratory. This species/strain also is considered suitable relative to longevity, hardiness, sensitivity to the test substance, and low incidence of spontaneous diseases.

C. Animal Husbandry

1. Housing

All rats were housed in stainless steel, wire-mesh cages suspended above cage boards. Rats were housed one per cage. Cage racks were relocated within the animal room each week and cages were repositioned on the racks every 2 weeks. Animal rooms were maintained on a 12-hour light/dark cycle (fluorescent light) and at a temperature of $22 \pm 3^{\circ}\text{C}$ and a relative humidity of $50 \pm 20\%$.

2. Feed and Water

Tap water was provided *ad libitum*. All rats were fed PMI[®] Nutrition International, LLC Certified Rodent LabDiet[®] 5002 *ad libitum*. During the test (exposure) period, test substance was incorporated into the food at concentrations specified by study design.

3. Identification

Prior to assignment to groups, each rat was temporarily identified by cage identification. After assignment to groups, an individual identification number was tattooed on the tail of each rat. The information on the cage labels included the unique 6-digit Haskell animal number and the individual identification number assigned to each rat.

4. Health Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore, and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed was used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program was administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

D. Quarantine and Pretest Period

Upon arrival at Haskell Laboratory, the rats were quarantined for at least 5 days. The rats were observed daily for any clinically apparent signs of disease or injury and weighed 3 times.

On the bases of acceptable body weight gains and clinical observations, all rats were released from quarantine by the laboratory animal veterinarian.

E. Study Design

Male	Number of Males	Daily Dosage	Dose Volume (mL/kg)
I	15	0 (Control) ^a	4.08
III	15	70 mg/kg Surfactant H-25500	1.00
V	15	1000 mg /kg H-25499 ^b	4.08

a Deionized water

b Group V received a second lot (H-24616) of the same test substance beginning on test day 52.

Study animals consisted of three subgroups: Subset 1 was sacrificed on test day 14 (5 rats/group), Subset 2 was sacrificed on test day 28 (5 rats/group), and Subset 3 was sacrificed on test day 91 (5 rats/group).

F. Assignment to Groups and Study Start

The rats were selected for study use on the bases of adequate body weight gain, freedom from any clinical signs of disease or injury, and a body weight within $\pm 20\%$ of the mean. The selected rats were distributed by computerized, stratified randomization so that there were no statistically significant differences among group body weight means.

Administration of test substances began on test day 0. The rats were between 6 and 8 weeks of age on test day 0.

G. Administration of Test Substances

H-25499 was administered undiluted, once daily by gavage to the study animals. Starting on test day 52, H-24616 replaced H-25499 and was administered daily to the study animals. H-25500 was diluted with deionized water and administered once daily by gavage. Animals designated for Subset 1 were dosed for 14 days. Animals designated for Subset 2 were dosed for 28 days. Animals designated for Subset 3 were dosed for 91 days. The volume of the test substances given to each rat daily was based on the most recently recorded weight. Control animals were similarly treated at the same dose volume of deionized water as the 1000 mg/kg H-25499 group.

H. Body Weights

All rats were weighed twice per week.

I. Clinical Observations and Mortality

Cage-site examinations to detect moribund or dead rats and abnormal behavior and appearance among rats were conducted at least twice daily throughout the study. At every weighing, each rat was individually handled and examined for abnormal behavior and appearance.

J. Pathology Evaluations

Five animals from each group were sacrificed on test days 14, 28, and 91. Noses from all sacrificed animals were processed and microscopically evaluated.

RESULTS AND DISCUSSION

Nasal lesions were produced in rats administered [REDACTED] and in rats administered H-25500 (surfactant only). These lesions are summarized in Text Table 1.

TEXT TABLE 1
INCIDENCES OF COMPOUND-RELATED MICROSCOPIC LESIONS
IN THE NOSE OF MALE RATS^a

	Vehicle Control	H-25500 70 mg/kg/day	H-25499 1000 mg/kg/day
14 Days			
No abnormality detected	3	3	1
Degeneration/atrophy, olfactory mucosa	1	1	3
Degeneration/regeneration, respiratory mucosa.	1	1	2
Adhesion, turbinates.	-	1	-
Exudate, nasal cavity	-	1	1
28 Days			
No abnormality detected	4	2	2
Degeneration/atrophy, olfactory mucosa	1	1	2
Degeneration/regeneration, respiratory mucosa	-	-	1
Adhesions, turbinates	-	-	-
Exudate, nasal cavity	-	-	1
91 Days			
No abnormality detected	4	-	-
Degeneration/atrophy, olfactory mucosa	1	5	5
Degeneration/regeneration, respiratory mucosa.	-	1	-
Adhesion, turbinates.	-	5	-
Exudate, nasal cavity	-	-	1

^a 5 rats/group/time point

The primary finding in the nose of male rats administered 1000 mg/kg/day H-25499 by gavage was degeneration and atrophy of olfactory epithelium. Degeneration or regeneration of respiratory epithelium and exudates within the nasal cavity (composed of proteinaceous material and neutrophils) were also present in a few affected animals. Olfactory lesions were present in low incidences at 14 and 28 days, but all animals were affected after 91 days exposure. These lesions were characterized by disorganization and thinning of the olfactory epithelium especially along the ventral one-half of the nasal septum in the posterior nasal sections. Other areas more commonly affected included the medial extents of the ethmoturbonates. Minimal focal olfactory degeneration was noted in some controls; however, these lesions were randomly distributed and

thus distinguishable from the compound-induced lesions.^a The compound-related lesions observed in the current study following exposure to 1000 mg/kg/day of the [REDACTED] [REDACTED] are similar to those produced in a previous study with this material.⁽¹⁾

In animals administered 70 mg/kg/day surfactant alone (H-25500), olfactory changes similar to those observed with H-25499 were observed in the nose. However, in the surfactant only group, olfactory changes were also associated with fibrous adhesions between individual turbinates and between turbinates and the nasal septum. These adhesions were likely a sequela of focally more severe olfactory epithelial necrosis and ulceration. Thus, microscopic changes in the nose of rats in the surfactant-only group were qualitatively similar to those of rats in the polymer/surfactant group, although lesions in the surfactant-only group appear somewhat more severe based on the consistent presence of turbinate adhesions. The mechanism underlying this apparently greater severity is not known.

No studies have been conducted with the [REDACTED] alone, and thus its potential for nasal toxicity has not been determined. Nevertheless, based on the results of this study, the nasal lesions observed in a previous study with [REDACTED] [REDACTED] can be largely, if not completely, attributed to the surfactant component of the material.

RECORDS AND SAMPLE STORAGE

All data and records for analytical characterizations conducted by the sponsor will be retained by the sponsor. Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

A sample of the test substance will be collected for archive purposes and retained at Haskell Laboratory, Newark, Delaware. Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware or at Iron Mountain Records Management, Wilmington, Delaware.

REFERENCE

1. DuPont Haskell Laboratory (2001). H-24616: Subchronic Toxicity 90-Day Gavage Study in Rats with One-Generation Reproduction Evaluations. Unpublished report. [REDACTED]

^a Focal minimal degeneration of olfactory epithelium in one animal administered 1000 mg/kg/day H-25499 for 28 days (animal #665965) was similar to that seen in controls and thus may represent a spontaneous occurrence of this lesion. In addition, artifactual disruption of the olfactory mucosa precluded critical evaluation of the olfactory epithelium in this animal.

TABLES

TABLES

EXPLANATORY NOTES

STUDY DESIGN

Male	Number of Males	Daily Dosage	Dose Volume (mL/kg)
I	15	0 (Control) ^a	4.08
III	15	70 mg/kg Surfactant H-25500	1.00
V	15	1000 mg /kg H-25499 ^b	4.08

a Deionized water

b Group V received a second lot (H-24616) of the same test substance beginning on test day 52.

Study animals consisted of three subgroups: Subset 1 was sacrificed on test day 14 (5 rats/group), Subset 2 was sacrificed on test day 28 (5 rats/group), and Subset 3 was sacrificed on test day 91 (5 rats/group).

TABLE I
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
SUBSET ONE (DAY 14)

LESIONS	LESION INCIDENCE (#)				
	Males				
TREATMENT	0	70	1000		
	mg/kg	mg/kg ^a	mg/kg ^b		
	I	III	V		
NOSE	(5)	(5)	(5)		
NO ABNORMALITY DETECTED	5	5	5		

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

TABLE 2
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
SUBSET TWO (DAY 28)

LESIONS	LESION INCIDENCE (#)				
	Males				
TREATMENT	0	70	1000		
	mg/kg ^a	mg/kg ^a	mg/kg ^b		
	I	III	V		
NOSE	(5)	(5)	(5)		
NO ABNORMALITY DETECTED	5	5	5		

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

TABLE 3
INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS
SUBSET THREE (DAY 91)

LESIONS	LESION INCIDENCE (#)				
	Males				
TREATMENT	0	70	1000		
	mg/kg	mg/kg ^a	mg/kg ^b	I	V
	I	III	V		
NOSE	(5)	(5)	(5)		
NO ABNORMALITY DETECTED	5	5	5		

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

TABLE 4

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
SUBSET ONE (DAY 14)

LESIONS	LESION INCIDENCE (#)				
	Males				
	TREATMENT	0	70	1000	
		mg/kg I	mg/kg ^a III	mg/kg ^b V	
RESPIRATORY SYSTEM		(5)	(5)	(5)	
NOSE					
NO ABNORMALITY DETECTED		3	3	1	
INFLAMMATION, SUBACUTE/CHRONIC.		1	1		
EXUDATE, NASAL CAVITY.			1	1	
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.		1	1	2	
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.		1	1	3	
ADHESION, TURBINATES.			1		

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500

^b 1000 mg/kg H-25499

TABLE 5
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
SUBSET TWO (DAY 28)

LESIONS	TREATMENT					LESION INCIDENCE (#)				
						Males				
	0	70	1000							
	mg/kg	mg/kg ^a	mg/kg ^b							
	I	III	V							
RESPIRATORY SYSTEM										
NOSE										
NO ABNORMALITY DETECTED										
INFLAMMATION, SUBACUTE/CHRONIC, TOOTH.										
INFLAMMATION, SUBACUTE/CHRONIC.										
EXUDATE, NASAL CAVITY.										
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.										
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.										
	(5)	(5)	(5)							
	4	2	2							
		1	1							
		1	1							
	1	1	2							

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

TABLE 6
INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
SUBSET THREE (DAY 91)

LESIONS	LESION INCIDENCE (#)				
	Males				
TREATMENT	0	70	1000		
	mg/kg I	mg/kg ^a III	mg/kg ^b V		
RESPIRATORY SYSTEM					
NOSE		(5)	(5)	(5)	
NO ABNORMALITY DETECTED		4			
INFLAMMATION, SUBACUTE/CHRONIC.		1	1		
EXUDATE, NASAL CAVITY.					1
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.			1		
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.	1	5	5		
ADHESION, TURBINATES.			5		

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

TABLE 7
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS NON-NEOPLASTIC LESIONS
SUBSET ONE (DAY 14)

LESIONS	TREATMENT					Males					LESION INCIDENCE (#)				
	0	mg/kg	70	1000		I	III	V			I	III	V		
RESPIRATORY SYSTEM															
NOSE											(5)	(5)	(5)		
NO ABNORMALITY DETECTED											3	3	1		
INFLAMMATION, SUBACUTE/CHRONIC.															
minimal											1	1			
total observations per lesion											1	1			
EXUDATE, NASAL CAVITY.															
minimal															
total observations per lesion														1	
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.															
minimal											1				
mild															
total observations per lesion												1			
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.											1	1			
minimal															
moderate															
total observations per lesion											1	1			
ADHESION, TURBINATES.															
mild											1	1			
total observations per lesion														1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

TABLE 8
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS NON-NEOPLASTIC LESIONS
SUBSET TWO (DAY 28)

LESIONS	TREATMENT					Males		LESION INCIDENCE (#)
	0	mg/kg	70	mg/kg ^a	1000	I	V	
RESPIRATORY SYSTEM								
NOSE								
NO ABNORMALITY DETECTED								(5)
INFLAMMATION, SUBACUTE/CHRONIC, TOOTH.								4
mild								
total observations per lesion								1
INFLAMMATION, SUBACUTE/CHRONIC.								1
minimal								
total observations per lesion								1
EXUDATE, NASAL CAVITY.								1
moderate								
total observations per lesion								1
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.								
minimal								
total observations per lesion								1
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.								
minimal								
mild								
moderate								
total observations per lesion								1
								1
								2

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500

^b 1000 mg/kg H-25499

TABLE 9

	LESION INCIDENCE (#)					
	Males					
LESIONS	TREATMENT	0	70	1000		
		mg/kg	mg/kg ^a	mg/kg ^b		
		I	III	V		
RESPIRATORY SYSTEM						
NOSE		(5)	(5)	(5)		
NO ABNORMALITY DETECTED		4				
INFLAMMATION, SUBACUTE/CHRONIC.						
minimal						
total observations per lesion		1	1			
EXUDATE, NASAL CAVITY.		1	1			
mild						
total observations per lesion					1	
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.					1	
mild						
total observations per lesion						
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.						
minimal						
mild						
total observations per lesion		1	5	5		
ADHESION, TURBINATES.		1	5	5		
minimal						
mild						
total observations per lesion			2	3	5	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500^b 1000 mg/kg H-25499

APPENDICES

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EXPLANATORY NOTES

STUDY DESIGN

Male	Number of Males	Daily Dosage	Dose Volume (mL/kg)
I	15	0 (Control) ^a	4.08
III	15	70 mg/kg Surfactant H-25500	1.00
V	15	1000 mg /kg H-25499 ^b	4.08

a Deionized water

b Group V received a second lot (H-24616) of the same test substance beginning on test day 52.

Study animals consisted of three subgroups: Subset 1 was sacrificed on test day 14 (5 rats/group), Subset 2 was sacrificed on test day 28 (5 rats/group), and Subset 3 was sacrificed on test day 91 (5 rats/group).

APPENDIX A

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC OBSERVATIONS

INDIVIDUAL ANIMAL GROSS AND MICROSCOPIC OBSERVATIONS

EXPLANATORY NOTES

Lesion Grading

Histopathological changes are described according to their morphologic character, distribution and severity. The distribution (extent of tissue involvement) is indicated, where appropriate, by modifiers such as focal, multifocal, diffuse, unilateral, bilateral, etc.; A severity score, if appropriate, is also assigned as follows:

- Minimal: the amount of change present barely exceeds that which is considered to be within normal limits.
- Mild: in general, the lesion is easily identified but of limited severity. The lesion probably does not produce any functional impairment.
- Moderate: the lesion is prominent but there is significant potential for increased severity. Limited tissue or organ dysfunction is possible.
- Severe: the degree of change is either as complete as considered possible or great enough in intensity or extent to expect significant tissue or organ dysfunction.

Comment: grades minimal through severe represent progressive involvement/severity along a continuum with minimal lesions being the least severe and severe lesions being the most severe. While the grades refer to the morphological characteristics of lesions, they also indicate their relative biological significance.

Gross observations listing multiple masses for a tissue are distinguished with letters (i.e., a, b, c, d, etc.)

Neoplasm Designations

- *B: Benign neoplasm, primary site
- *M: Malignant neoplasm, primary site

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : I 0 mg/kg Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665927 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

665928 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 NOSE :
 DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.

665929 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : I 0 mg/kg Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665930 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665931 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA, minimal.

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : III 70 mg/kg Surfactant H-25500 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665942 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665943 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665944 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, moderate.
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA, mild.
ADHESION, TURBINATES, mild.
EXUDATE, NASAL CAVITY, minimal.

Individual Animal Listing

Showing animal data for individual animals
STUDY [REDACTED] male (* APPROVED PROTOCOL *)
Dose Group : III 70 mg/kg Surfactant H-25500 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665945 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

665946 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : V 1000 mg/kg H-25499 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665957 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.

665958 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA, minimal.
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.
EXUDATE, NASAL CAVITY, minimal.

665959 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA, minimal.

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : V 1000 mg/kg H-25499 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665960 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.

665961 Terminal Sacrifice
 Killed on Day : 14
 Exposure Group : Subset 1
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

Individual Animal Listing

Showing animal data for individual animals
STUDY [REDACTED] male (* APPROVED PROTOCOL *)
Dose Group : I 0 mg/kg Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665932 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665933 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.

665934 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : I 0 mg/kg Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665935 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

665936 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : III 70 mg/kg Surfactant H-25500 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665947 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

665948 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
INFLAMMATION, SUBACUTE/CHRONIC, TOOTH, mild.

665949 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.

Individual Animal Listing

Showing animal data for individual animals
STUDY [REDACTED] male (* APPROVED PROTOCOL *)
Dose Group : III 70 mg/kg Surfactant H-25500 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665950 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665951 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : V 1000 mg/kg H-25499 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665962 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, moderate.
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA, minimal.
EXUDATE, NASAL CAVITY, moderate.

665963 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665964 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : V 1000 mg/kg H-25499 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665965 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 NOSE :
 DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.

665966 Terminal Sacrifice
 Killed on Day : 28
 Exposure Group : Subset 2
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : I 0 mg/kg Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665937 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

665938 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

665939 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

 No Macroscopic Abnormality Observed :
 NOSE

Histopathology :

 No Microscopic Abnormality Observed :
 NOSE

Individual Animal Listing

Showing animal data for individual animals
STUDY [REDACTED] male (* APPROVED PROTOCOL *)
Dose Group : I 0 mg/kg Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665940 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

No Microscopic Abnormality Observed :
NOSE

665941 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, minimal.

Individual Animal Listing

Showing animal data for individual animals
STUDY : [REDACTED] male (* APPROVED PROTOCOL *)
Dose Group : III 70 mg/kg Surfactant H-25500 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665952 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.
ADHESION, TURBINATES, minimal.

665953 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.
ADHESION, TURBINATES, mild.

665954 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.
ADHESION, TURBINATES, mild.

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : III 70 mg/kg Surfactant H-25500 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665955 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.
ADHESION, TURBINATES, mild.

665956 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
INFLAMMATION, SUBACUTE/CHRONIC, minimal.
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA, mild.
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.
ADHESION, TURBINATES, minimal.

Individual Animal Listing

Showing animal data for individual animals
STUDY : [REDACTED] male (* APPROVED PROTOCOL *)
Dose Group : V 1000 mg/kg H-25499 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665967 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.

665968 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.

665969 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.

Individual Animal Listing

STUDY [REDACTED] Showing animal data for individual animals
male (* APPROVED PROTOCOL *)
Dose Group : V 1000 mg/kg H-25499 Sex: Males

Animal Ref Microscopic & Macroscopic Findings

665970 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.

665971 Terminal Sacrifice
 Killed on Day : 91
 Exposure Group : Subset 3
 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
NOSE

Histopathology :

NOSE :
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA, mild.
EXUDATE, NASAL CAVITY, mild.

APPENDIX B

INDIVIDUAL ANIMAL MICROSCOPIC OBSERVATIONS LISTING INDIVIDUAL ANIMALS AFFECTED

MICROSCOPIC OBSERVATIONS IN MALE RATS LISTING INDIVIDUAL ANIMALS AFFECTED
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
SUBSET 1 (DAY 14)

LESIONS	LESION INCIDENCE (#)			
	Males			
	TREATMENT	0 mg/kg I	70 mg/kg ^a III	1000 mg/kg ^b V
RESPIRATORY SYSTEM				
NOSE		(5)	(5)	(5)
NO ABNORMALITY DETECTED		665927	665942	665961
		665929	665943	
INFLAMMATION, SUBACUTE/CHRONIC. EXUDATE, NASAL CAVITY.		665930	665946	
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.		665931	665945	
			665944	665958
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.		665931	665944	665958
		665928	665944	665959
				665957
ADHESION, TURBINATES.				665958
			665944	665960

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500

^b 1000 mg/kg H-25499

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
SUBSET 2 (DAY 28)

LESIONS	TREATMENT				LESION INCIDENCE (An	
	0	70	1000	Males		
	mg/kg I	mg/kg ^a III	mg/kg ^b V			
RESPIRATORY SYSTEM						
NOSE	(5)	(5)	(5)			
NO ABNORMALITY DETECTED	665932	665950	665963			
	665934	665951	665966			
	665935					
	665936					
INFLAMMATION, SUBACUTE/CHRONIC, TOOTH.		665948				
INFLAMMATION, SUBACUTE/CHRONIC.		665947	665964			
EXUDATE, NASAL CAVITY.			665962			
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA.			665962			
DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.	665933	665949	665962			
			665965			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500
^b 1000 mg/kg H-25499

INCIDENCES OF MICROSCOPIC OBSERVATIONS IN MALE RATS
NEOPLASTIC AND NON-NEOPLASTIC LESIONS
SUBSET 3 (DAY 91)

LESIONS	TREATMENT				LESION INCIDENCE (An)			
					Males			
	0	70	1000		0	70	1000	
	mg/kg	mg/kg ^a	mg/kg ^b		I	III	V	
RESPIRATORY SYSTEM								
NOSE				(5)	(5)		(5)	
NO ABNORMALITY DETECTED				665937				
				665938				
				665939				
				665940				
INFLAMMATION, SUBACUTE/CHRONIC. EXUDATE, NASAL CAVITY.				665941	665956			665971
DEGENERATION/REGENERATION, RESPIRATORY, MUCOSA. DEGENERATION/ATROPHY, OLFACTORY, MUCOSA.				665941	665956			665967
					665952	665953	665968	
					665954	665969		
					665955	665970		
ADHESION, TURBINATES.					665956	665971		
					665952			
					665953			
					665954			
					665955			
					665956			

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

^a 70 mg/kg Surfactant H-25500

^b 1000 mg/kg H-25499