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MR#306403

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August 2, 2007

TSCA Confidential Business Information Center (7407M)
EPA East - Room 6428 Attn: Section 8(e)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

CONTAIN NO CBI

Attn: TSCA Section 8(e) Coordinator

RE: Naphthalene (CAS#: 91-20-3) Preliminary Findings of an Acute Inhalation Study in Rats

ConocoPhillips Company is involved with an industry group that has sponsored an acute inhalation study in rats involving naphthalene. As a sponsor, ConocoPhillips has been provided with a preliminary draft of the pathology report. ConocoPhillips is submitting this draft study report in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA) because it includes findings that EPA may consider reportable. Toxicological endpoints observed in this study are not new; however, the naphthalene concentrations and duration of exposure in this study may be considered a new finding.

ConocoPhillips is submitting a preliminary rough draft of data on the acute effects of naphthalene vapors on nasal epithelial cells in rats. Two strains of rats, Fischer 344 (F344) and Sprague Dawley, were exposed to naphthalene vapors at the following target concentrations: 0, 0.1, 0.3, 1, 10 and 30 ppm for a single six hour period. A total of 30 animals of each sex per strain were exposed. The day following exposure, the animals were killed and nasal respiratory tissues were removed, processed with hematoxylin and eosin stains, and subsequently evaluated by light microscopy. Necrosis related to exposure to naphthalene was seen predominately in the olfactory epithelium. According to the preliminary pathology report, minimal effects were first observed in all groups exposed to a naphthalene vapor concentration of 1 ppm. Clear and strong pathological changes were observed in all groups exposed to vapor concentrations of 10 ppm and 30 ppm.

This study was conducted at the Hamner Institutes for Health Sciences under contract to the American Petroleum Institute. A copy of the preliminary rough draft pathology report provided to ConocoPhillips on July 11, 2007 is enclosed for your information. The study final report will be provided to EPA once it becomes available.

If you have any questions or require additional details, please contact Jesse McCoy at (918) 661-5090 or via email at jesse.h.mccoy@conocophillips.com

Sincerely,

Jesse H.McCoy, Jr.
TSCA Coordinator ConocoPhillips
1206 PB, Bartlesville, OK 74004

cc: Tracy Hammon
Donna Carvalho
Jennifer Galvin

Rough Draft

Hamner 304-427

Exposure Response Relationship and Threshold for Nasal Epithelial Effects in F344 and SD Rats Following Acute Inhalation Exposure of Naphthalene Vapor

Study Identification 07012

The purpose of this study was to establish an exposure-response and threshold for nasal epithelial effects in Fischer 344 and Sprague Dawley rat following an acute (6 hour) exposure to naphthalene vapor.

Six standard nose sections as typically done at the Hamner Institutes were processed and stained with H&E stains and evaluated by light microscopy. The sections (from anterior to posterior) are labeled Tip, Level I, Level II, Level III, Level IV and Level V. The Tip and Level I will have mostly squamous and respiratory epithelium. Olfactory epithelium is first observed along the dorsal meatus of Level II. Level III has olfactory epithelium lining the dorsal meatus, dorsal tips of a turbinate appearing in the dorsal meatus lumen and low in the nasal septum (probably the "septal olfactory organ"), the Levels IV and V has mostly olfactory epithelium dorsally lining the meatus, ethmoid turbinates and much of the nasal septum.

The attached tables show the group summary incidence data followed by approximate severity grade group averages for those animals that had the reported lesion.

Lesions related to exposure to naphthalene were observed in some of the respiratory epithelial locations but were seen predominately in the olfactory epithelium. The change related to exposure at this stage was necrosis. The necrosis was characterized by cytoplasmic vacuolation, loss of proper epithelial orientation, condensation of the cytoplasm, pkynotic and karyorrhectic nuclei and sloughing of the necrotic epithelium. Little inflammatory cell infiltration was present at this time. Some diagnoses in the tables represent spontaneous, nontreatment-related lesions (suppurative inflammation, foreign body granuloma).

Male F344 Rats

No significant lesions were observed in Control, Low (100 ppb), or Intermediate 1 (300 ppb) exposure levels. Focal olfactory epithelial necrosis was observed ventrally in the nasal septum of Nose Level III (possibly the septal olfactory organ) at Intermediate 2 (1 ppm) exposure concentration. Although minimal it was clearly and consistently present. At the Intermediate 3 exposure concentration (10 ppm) necrosis of the respiratory epithelium was minimal to mild, but clearly evident in the dorsal meatus of Nose Level I. Necrosis of the olfactory epithelium at this exposure level became marked and prominent in Nose Levels II, III, and IV. Necrosis of olfactory epithelium was widespread in the dorsal

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meatus, upper septum and on the medial aspects of ethmoid turbinates as they approach the septum.
Respiratory and olfactory epithelial necrosis observed in noses exposed to the High concentration (30 ppm) were similarly distributed as in the 10 ppm exposed rats, but olfactory epithelial necrosis was more prominent on the Nose Levels III and IV than at the 10 ppm concentration.

Female F344 Rats
The female rats were affected nearly the same as the male rats with slight variances. Just the like the males the first changes observed were minimal and in the olfactory epithelium low in the nasal septum of Nose Level III in 4 of the 5 rats exposed to Intermediate concentration 2 (1ppm).
Females exposed to Intermediate concentration 3 (10 ppm) or High (30 ppm) had lesion distribution similar to the males with slight variances in severities. Females had no olfactory epithelial necrosis of Nose Level IV at 10 ppm.

Male Sprague Dawley Rats
Control animals were normal. Two males exposed to Low (100 ppb) had minimal olfactory epithelial necrosis in Nose Level III. In one animal the section anterior to it had a foreign body granuloma (can cause secondary epithelial changes). That these olfactory lesions are related to exposure is not convincing. No other lesions are present.
In male SD rats exposed to Intermediate concentration 1 (300 ppb) there are three rats that have minimal olfactory epithelial necrosis at Nose Level III and one of those has a foreign body granuloma in the section anterior to it. However, it is beginning to seem like this is the weak beginning of an effective exposure concentration since focus of necrosis is also seen in the Nose Level IV of one male rat.
Male SD rats exposed to Intermediate concentration 2 (1ppm) have the minimal but consistent presence of olfactory epithelial necrosis on the nasal septum. This plus a focus of respiratory epithelial necrosis and another focus of olfactory necrosis at another site in the nose indicates that this could be a clearer effect level similar to the F344 rats.
Male SD rats exposed to Intermediate concentration 3 (10 ppm) or High concentration (30 ppm) had marked lesions similar to the F344 males.

Female Sprague Dawley Rats
Like the male SD rats the females had a mild olfactory epithelial necrosis diagnosis in one Low (100 ppb) female rat Nose Level III and two instances of minimal olfactory epithelial necrosis of Nose Level III in the Intermediate concentration 1 (300 ppb) exposure group. However, the presence of mild olfactory epithelial necrosis in one control female in Nose Level III makes the possibility that the lesions seen at 100 ppb and 300 ppb less likely to be exposure related.
As in the males SD and F344 males and females, the minimal but consistent olfactory epithelial necrosis observed in Nose Level III and Intermediate concentration 2 (1ppm), seems to be the clear start of exposure-related lesion induction.
Female SD rats exposed to Intermediate concentration 3 and the High concentration have lesions roughly similar in severity, incidence and distribution of the male SD rats and male and female F344 rats.

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Summary.

The clear, albeit minimal, effects of exposure to naphthalene were first observed in all groups exposed to the Intermediate concentration 2 (1 ppm). Clear and strong pathological changes were observed in all groups exposed to Intermediate concentration 3 (10 ppm) or High (30 ppm).
There is a hint of exposure –related lesions in Sprague-Dawley males and females occurring at the two lowest exposure concentrations but the evidence is weak.

For the tables grading is presented as incidence (number with lesion/number examined) + lesion grade, where 1= minimal, 2=mild, 3=moderate, 4=marked.

Rough Draft

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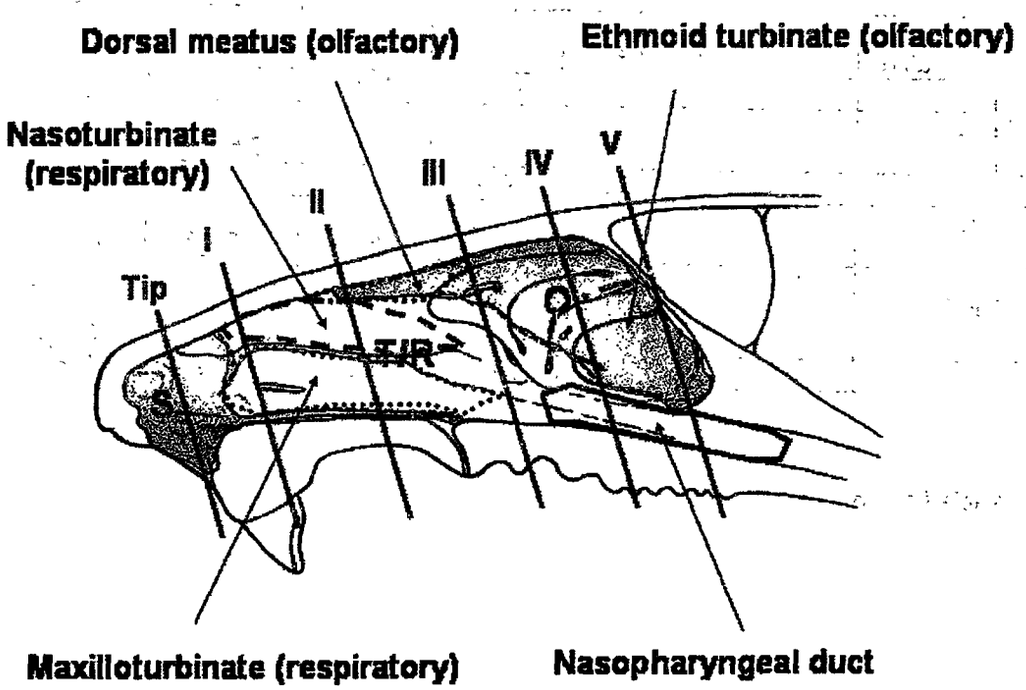
Parasagittal view of the rodent nasal cavity showing the approximate location of transverse sections used for microscopic examination, squamous epithelium (S), transitional/respiratory epithelium (T/R), and olfactory epithelium (O).



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EPL PROJECT NO. 304-427
F344 MALE

NOSE	CONTROL	LOW 100 ppb	I1 300 ppb	I2 1 ppm	I3 10 ppm	HIGH 30 ppm
Tip	NRL	NRL	NRL	NRL		
Respiratory epithelial necrosis					1/5 + 1	1/5 + 1
LI	NRL	NRL	NRL	NRL		
Respiratory epithelial necrosis					5/5 +~ 2.5	5/5 +~ 1.2
Respiratory epithelial inflammation suppurative	2/5	1/5				
LII			NRL	NRL		
Olfactory epithelial necrosis					5/5 + 4	5/5 + 4
LIII	NRL	NRL	NRL			
Olfactory epithelial necrosis				5/5 + 1	5/5 + 3	5/5 + 4
LIV	NRL	NRL	NRL	NRL		
Olfactory epithelial necrosis					4/5 +~ 1.5	5/5 + 3.2
LV	NRL	NRL	NRL	NRL	NRL	NRL

L = Level
I = Intermediate
NRL = No Remarkable Lesion

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EPL PROJECT NO. 304-427
F344 FEMALE

NOSE	CONTROL	LOW 100 ppb	I1 300 ppb	I2 1 ppm	I3 10 ppm	HIGH 30 ppm
Tip	NRL	NRL	NRL	NRL		
Respiratory epithelial necrosis					5/5 + 2.2	5/5 + 1.2
LI	NRL	NRL	NRL	NRL		
Respiratory epithelial necrosis					5/5 + 2.6	4/5 + 2
LII	NRL	NRL	NRL	NRL		
Olfactory epithelial necrosis					5/5 + 3.8	5/5 + 4
LIII	NRL	NRL	NRL			
Olfactory epithelial necrosis				4/5 + 1	5/5 + 2	5/5 + 3.5
LIV	NRL	NRL	NRL	NRL	NRL	
Olfactory epithelial necrosis						3/5 + 2.6
LV	NRL	NRL	NRL	NRL	NRL	NRL

L = Level
I = Intermediate
NRL = No Remarkable Lesion

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EPL PROJECT NO. 304-427
SD MALE

NOSE	CONTROL	LOW 100 ppb	I1 300 ppb	I2 1 ppm	I3 10 ppm	HIGH 30 ppm
TIp	NRL	NRL	NRL	NRL	NRL	NRL
Respiratory epithelial necrosis						
LI	NRL	NRL	NRL			
Respiratory epithelial necrosis				1/5 + 1	5/5 + 2.4	5/5 + 1.8
LII	NRL					
Olfactory epithelial necrosis				1/5 + 1	5/5 + 4	5/5 + 4
Foreign body granuloma		1/5 + 2	1/5 + 2			
LIII	NRL					
Olfactory epithelial necrosis		2/5 + 1	3/5 + 1	4/5 + 1	5/5 +~ 3.6	5/5 + 3.8
LIV	NRL	NRL		NRL		
Olfactory epithelial necrosis			1/5 + 1		5/5 + 1.8	5/5 + 3
LV	NRL	NRL	NRL	NRL		
Olfactory epithelial necrosis					1/5 + 1	1/5 + 2

L = Level
I = Intermediate
NRL = No Remarkable Lesion

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EPL PROJECT NO. 304-427
SD FEMALE

NOSE	CONTROL	LOW 100 ppb	I1 300 ppb	I2 1 ppm	I3 10 ppm	HIGH 30 ppm
Tip	NRL	NRL	NRL	NRL		
Respiratory epithelial necrosis					1/5 + 3	2/5 + 1.5
LI	NRL	NRL	NRL	NRL		
Respiratory epithelial necrosis					5/5 + 2	5/5 + 1.2
LII	NRL	NRL	NRL	NRL		
Olfactory epithelial necrosis					5/5 + 4	5/5 + 4
LIII						
Olfactory epithelial necrosis	1/5 + 2	1/5 + 2	2/5 + 1	4/5 + 1	5/5 + 2.4	5/5 + 3.8
LIV	NRL	NRL	NRL	NRL		
Olfactory epithelial necrosis					1/5 + 2	5/5 + 2.4
LV	NRL	NRL	NRL	NRL	NRL	NRL

L = Level
I = Intermediate
NRL = No Remarkable Lesion

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