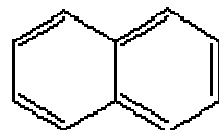


# Naphthalene



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## Use:

- ❖ Intermediate in the synthesis of anthranilic & phthalic acids, naphthols, naphthylamines etc.
- ❖ Ingredient in moth repellants & toilet bowl cleaner
- ❖ In veterinary medicine as antiseptic, lice control on livestock & poultry

## Human Exposure to Naphthalene

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- ❖ **Workers during production & use as a chemical intermediate**
- ❖ **General Public through breathing ambient air, smoking & use of products with naphthalene as a constituent**

## Evidence of Human Exposure

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- ❖ **Ambient air contains ~ 1µg naphthalene /m<sup>3</sup>**
- ❖ **Urine samples from 983 subjects in NHANES study contain naphthalene metabolites (1-naphthol:1 - 2500 µg/L; 2-naphthol:1 - 88 µg/L)**

## Rationale for Carcinogenicity Testing of Naphthalene

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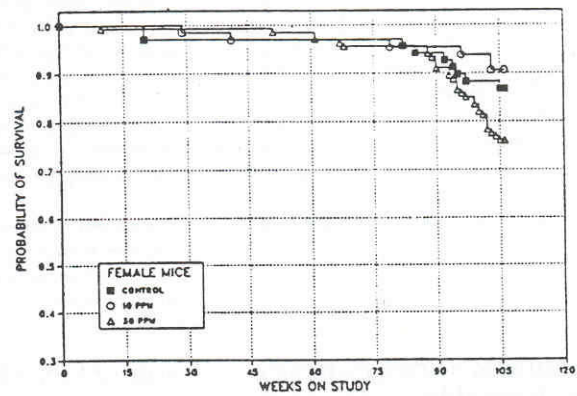
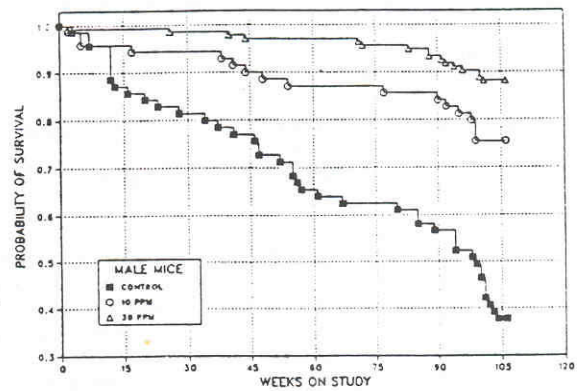
- ❖ **Widespread human exposure**
- ❖ **Lack of adequate cancer studies in animals**
- ❖ **Questionable study linking increased incidence of laryngeal cancer to exposure to naphthalene in naphthalene workers as compared to the general public in East Germany**

## **2-Year Inhalation Study With Naphthalene Mouse Study Design**

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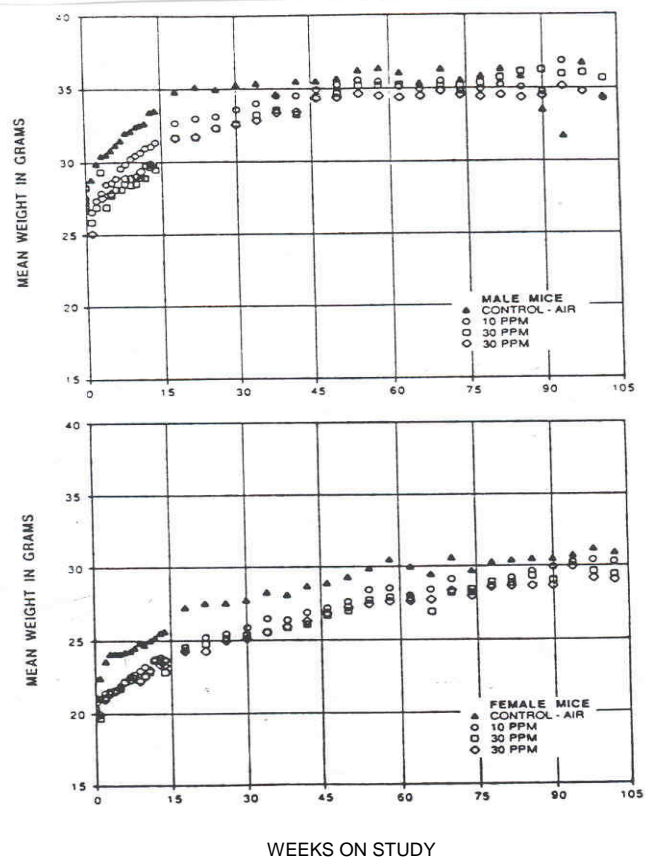
- ❖ **Animals: Male & Female B6C3F<sub>1</sub> Mice**
- ❖ **Group Size & Exposure Concentrations:**
- ❖ **75 at 0 ppm, 75 at 10 ppm & 150 at 30 ppm per sex**
- ❖ **Exposure Duration: 6 hrs./d, 5 d/wk for 103 weeks**

# Survival Curves of Mice in the Inhalation Study of Naphthalene



... .. female and female mice administered naphthalene

# Growth Curves of Mice in the Inhalation Study of Naphthalene



## Lung Tumor Incidence of Mice in the Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm
<b>MALES</b>			
Alveolar/Bronchiolar Adenoma <sup>a</sup>	7/69 (10%)	15/69 (22%)	27/135 (20%)
Alveolar/Bronchiolar Carcinoma <sup>a</sup>	0/69 (0%)	3/69 (4%)	7/135 (5%)
Alveolar/Bronchiolar Adenoma or Carcinoma <sup>a</sup>	7/69 (10%)	17/69 (25%)	31/135 (23%)
<b>FEMALES</b>			
Alveolar/Bronchiolar Adenoma <sup>a</sup>	5/68 (7%)	2/64 (3%)	28/134 (21%)**
Alveolar/Bronchiolar Carcinoma	0/68 (0%)	0/64 (0%)	1/134 (1%)
Alveolar/Bronchiolar Adenoma or Carcinoma <sup>a</sup>	5/68 (7%)	2/64 (3%)	29/134 (22%)**

<sup>a</sup> Positive trend (p < 0.001)

\*\* Greater than control (p < 0.01)

Historical rate for all lung tumors combined: males: 94/478 (20%; range 10% - 30%);  
females: 39/466 (8%; range 0% - 10%)

## Incidence of Lung Lesions of Mice in the 2- Year Inhalation Study of Naphthalene

Lesion	0 ppm	10 ppm	30 ppm
<b>MALES</b>			
Infiltration cellular, histiocyte <sup>a</sup>	1/70 (1%)	12/69 (17%)**	16/135 (12%)**
Inflammation, chronic <sup>a</sup>	0/70 (0%)	21/69 (30%)**	56/135 (41%)**
Inflammation, granulomatous	0/70 (0%)	19/69 (28%)**	15/135 (11%)**
<b>FEMALES</b>			
Infiltration cellular, lymphocyte <sup>a</sup>	11/68 (16%)	21/64 (33%)*	46/134 (34%)**
Inflammation, chronic <sup>a</sup>	3/68 (4%)	13/64 (20%)**	52/134 (39%)**
Inflammation, granulomatous <sup>a</sup>	0/68 (0%)	38/64 (59%)**	42/134 (31%)**
Glands, inflammation <sup>a</sup>	1/68 (1%)	3/64 (5%)	15/134 (11%)**

<sup>a</sup> Significant positive trend (p < 0.01)

\* Greater than control (p < 0.05)

\*\* Greater than control (p < 0.01)

## Incidence of Nonneoplastic Nasal Lesions in Mice in the Inhalation of Naphthalene

Lesion	0 ppm	10 ppm	30 ppm
<b>MALES</b>			
Inflammation <sup>a</sup>	0/69 (0%)	67/69 (97%)**	133/135 (99%)**
Olfactory epithelium, metaplasia <sup>a</sup>	0/69 (0%)	66/69 (96)**	134/135(99%)**
Respiratory epithelium, hyperplasia <sup>a</sup>	0/69 (0%)	66/69 (96%)**	134/135 (99%)**
<b>FEMALES</b>			
Inflammation <sup>a</sup>	1/68 (1%)	64/64 (100%)**	134/134 (100)**
Olfactory epithelium, metaplasia <sup>a</sup>	0/68 (0%)	64/64 (100%)**	134/134(100%)**
Respiratory epithelium, hyperplasia <sup>a</sup>	0/68 (0%)	64/64 (100%)**	134/134 (!00)**

<sup>a</sup> Significant positive trend (p < 0.001)

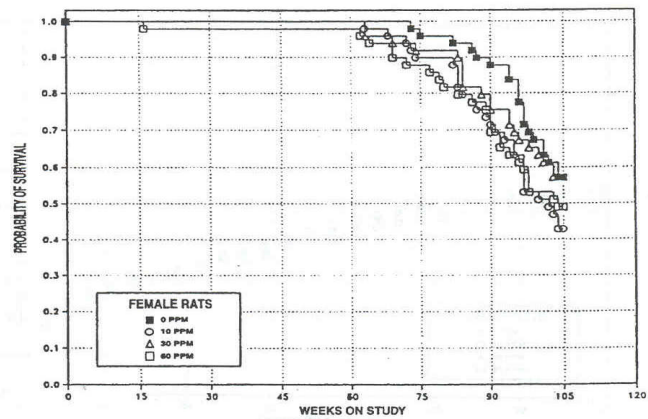
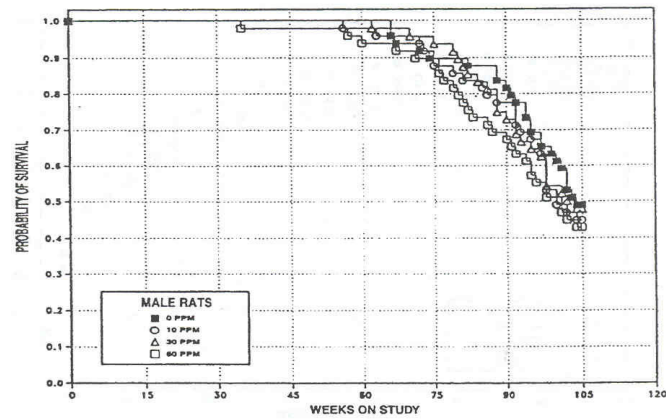
\*\* Greater than control (p < 0.001)

# Rat Study Design

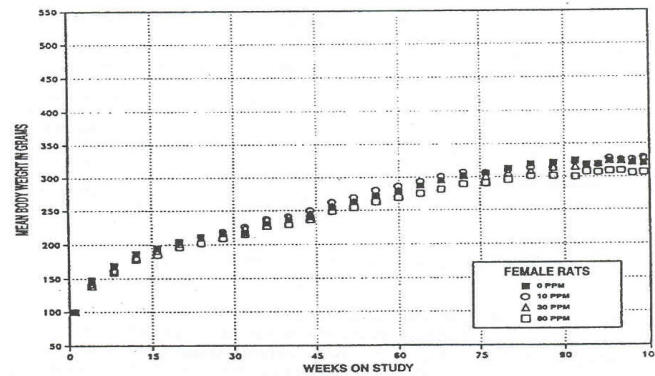
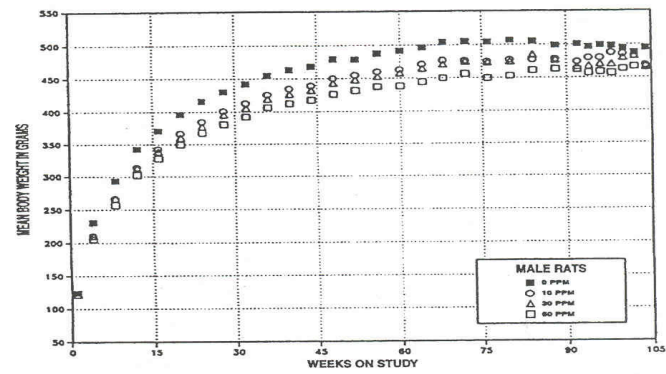
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- ❖ **Animals: Male & Female F344/N Rats**
- ❖ **Group Size: 49 Males and 49 Females**
- ❖ **Exposure Concentrations: 0,10, 30 or 60 ppm**
- ❖ **Exposure Duration: 6 hrs./day/ 5 days a week for 105 weeks**

# Survival Curves of Rats in the Inhalation Study of Naphthalene



# Growth Curves of Rats in the Inhalation Study of Naphthalene



## Nasal Tumor Incidence of Rats in the Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm	60 ppm
<b>MALES</b>				
Respiratory Epithelial Adenoma <sup>a</sup>	0/49 (0%)	6/49 (12%)**	8/48 (17%)**	15/48 (31%)**
Olfactory Epithelial Neuroblastoma <sup>b</sup>	0/49 (0%)	0/49 (0%)	4/48 (8%)	3/48 (6%)
<b>FEMALES</b>				
Respiratory Epithelial Adenoma	0/49 (0%)	0/49 (0%)	4/49 (8%)	2/49 (4%)
Olfactory Epithelial Neuroblastoma <sup>a</sup>	0/49 (0%)	2/49 (4%)	3/49 (6%)	12/49 (24%)**

<sup>a</sup> Significant positive trend (p < 0.001)

<sup>b</sup> Significant positive trend (p = 0.027)

\*\* Greater than control (p ≤ 0.013)

Historical rate for nasal tumors: 0/299 (0%)

## Incidence of Nonneoplastic Nasal Lesions of Male Rats in the Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm	60 ppm
<b>Olfactory Epithelium</b>				
Hyperplasia, Atypical	0/49 (0%)	48/49 (98%)**	45/48 (94%)**	46/48 (96%)**
Atrophy	3/49 (6%)	49/49 (100%)**	48/48 (100%)**	47/48 (98%)**
Inflammation, Chronic	0/49 (0%)	49/49 (100%)**	48/48 (100%)**	48/48 (100%)**
<b>Respiratory Epithelium</b>				
Hyperplasia	3/49 (6%)	21/49 (43%)**	29/48 (60%)**	29/48 (60%)**
Metaplasia, Squamous	0/49 (0%)	15/49 (31%)**	23/48 (48%)**	18/48 (38%)**
Goblet Cell, Hyperplasia	0/49 (0%)	49/49 (100%)**	29/48 (60%)**	26/48 (54%)**
<b>Glands</b>				
Hyperplasia	1/49 (2%)	49/49 (100%)**	48/48 (100%)**	48/48 (100%)**
Metaplasia, Squamous	0/49 (0%)	3/49 (6%)	14/48 (29%)**	26/48 (54%)**

\*\* Significantly greater than control (p < 0.01)

## Incidence of Nonneoplastic Nasal Lesions of Female Rats in the Inhalation Study of Naphthalene

	0 ppm	10 ppm	30 ppm	60 ppm
<b>Olfactory Epithelium</b>				
Hyperplasia, Atypical	0/49 (0%)	48/49 (98%)**	48/49 (98%)**	43/49 (88%)**
Atrophy	0/49 (0%)	49/49 (100%)**	49/49 (100%)**	47/49 (96%)**
Inflammation, Chronic	0/49 (0%)	47/49 (96%)**	47/49 (96%)**	45/49 (92%)**
<b>Respiratory Epithelium</b>				
Hyperplasia	0/49 (0%)	18/49 (37%)**	22/49 (45%)**	23/49 (47%)**
Metaplasia, Squamous	0/49 (0%)	21/49 (43%)**	17/49 (35%)**	15/49 (31%)**
Goblet Cell, Hyperplasia	0/49 (0%)	16/49 (33%)**	29/49 (59%)**	20/49 (41%)**
<b>Glands</b>				
Hyperplasia	0/49 (0%)	48/49 (98%)**	48/49 (98%)**	42/49 (86%)**
Metaplasia, Squamous	0/49 (0%)	2/49 (4%)	20/49 (41%)**	20/49 (41%)**

\*\* Greater than control (p < 0.01)

# Genetic Toxicology of Naphthalene

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- ❖ **Salmonella Typhimurium Gene Mutations:**  
**Negative with and without S9**
- ❖ **Sister chromatid exchange**  
**Cultured Chinese Hamster ovary cells *in vitro*: Positive with or without S9**
- ❖ **Chromosomal aberrations:**  
**Cultured Chinese Hamster ovary cells *in vitro*: Positive with, negative without S9**
- ❖

# Conclusion

## Mouse Study of Naphthalene

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### **Carcinogenicity:**

- ❖ **Males: Non-carcinogenic**
- ❖ **Females: Carcinogenic causing increased incidence of pulmonary alveolar/bronchiolar adenoma**

### **Other Effects:**

- ❖ **Increased incidence of nonneoplastic lesions of the nose and lung of mice of each sex.**

# Conclusion

## Rat Study of Naphthalene

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### **Carcinogenicity**

- ❖ **Males: Carcinogenic – Increased incidence of Nasal Respiratory epithelium adenoma and Olfactory epithelium neuroblastoma**
- ❖ **Females: Carcinogenic - Increased incidence of Nasal Respiratory epithelium adenoma and Olfactory epithelium neuroblastoma**

### **Other Effects:**

- ❖ **Increased incidence of nonneoplastic nasal lesions of rats of each sex.**