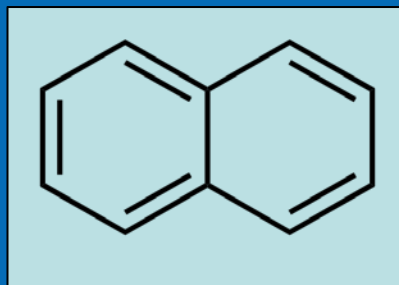


Problem Formulation for the IRIS Assessment of Naphthalene



(CAS Number: 91-20-3)

Assessment Manager: Channa Keshava



Production and Uses

- **Production**

- Naturally present in fossil fuels and commercially produced from coal tar and petroleum
- High Production Volume chemical (160 million lbs in US, 2012)

- **Uses**

- used in production of plasticizers, insect repellents, resins, phthalic anhydride, alkylated solvents, synthetic dyes
- consumer use – moth repellents, insecticide, toilet deodorant blocks, paint-related products
- present in certain jet fuels



- **Naphthalene is listed under several environmental acts**
 - Clean Air Act (CAA); Clean Water Act (CWA)
 - Federal Fungicide Insecticide and Rodenticide Act (FIFRA)
 - Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
 - Emergency Planning and Community Right-to-Know Act (EPCRA)
 - Resource Conservation and Recovery Act (RCRA)
- **Naphthalene is listed as a Hazardous Air Pollutant by EPA and is a contaminant found at >400 National Priorities List (NPL) sites**
- **Naphthalene is used as an inert ingredient and a fragrance in non-food use pesticide products regulated by EPA**



IRIS assessment of Naphthalene: Timeline

1998

Naphthalene Toxicological Review posted to the IRIS database

- *Classified as 'Group C, a possible human carcinogen'*
- *Includes RfD, RfC, and no IUR; no OSF*

2000

NTP 2-yr inhalation bioassay in rats

- *Increased incidence of non-neoplastic and neoplastic lesions in nasal cavity*

2004

External Peer Review draft of the IRIS assessment (inhalation carcinogenicity) is posted



IRIS assessment of Naphthalene: Timeline

- 2005** Peer Consultation Workshop on research needs related to the MOA of inhalation carcinogenicity

- 2014 (Jan)** IRIS conducts a “State-of-the-science workshop on chemically-induced mouse lung tumors”

- 2014 (July)** IRIS releases the scoping and problem formulation package



NRC Recommendations

- **NRC recommendation for problem formulation:**
 - literature survey to identify the possible health outcomes associated with the chemical
 - construction of a table to guide the formulation of specific questions that will be the subject of specific systemic reviews
 - examination of this table to determine which health outcomes warrant a systematic review and to define the systematic-review question

Health Outcomes Identified by the Preliminary Literature Survey

	Human Studies		Animal Studies		In Vitro Studies
	Oral	Inhalation	Oral	Inhalation	
Health Outcomes					
Body Weight			✓ (Subchronic)		
Cancer	✓ (Community)	✓ (Occupational)	✓ (Chronic)	✓ (Subchronic, Chronic)	
Cardiovascular			✓ (Subchronic)	✓ (Chronic)	
Dermatological		✓ (Occupational) ¹			
Developmental	✓ (Community)		✓		
Gastrointestinal	✓ (Community)	✓ (Community & Occupational)	✓ (Subchronic)	✓ (Chronic)	
Hematological	✓ (Community)	✓ (Community & Occupational)	✓ (Subchronic)		
Immunological	✓ (Community)		✓ (Subchronic)		
Hepatic	✓ (Community)	✓ (Community & Occupational)	✓ (Subchronic)	✓ (Chronic)	
Renal	✓ (Community)	✓ (Community)	✓ (Subchronic)	✓ (Chronic)	

Health Outcomes Identified by the Preliminary Literature Survey

	Human Studies		Animal Studies		In Vitro Studies
	Oral	Inhalation	Oral	Inhalation	
Health Outcomes					
Musculoskeletal				✓ (Chronic)	
Neurological	✓ (Community)	✓ (Community & Occupational)	✓ (Subchronic)	✓ (Chronic)	
Ocular	✓ (Community)	✓ (Occupational)	✓ (Subchronic, Chronic)	✓ (Chronic)	
Reproductive			✓ (Subchronic)	✓ (Chronic)	
Respiratory	✓ (Community)	✓ (Occupational)	✓ (Subchronic)	✓ (Subchronic, Chronic)	
Other Data and Analyses					
ADME ²	✓	✓	✓	✓	✓
Toxicokinetic models			✓	✓	
Mode of action hypotheses			✓	✓	✓
Susceptibility data ³	✓	✓			
Genotoxicity			✓		✓
¹ Dermatological effects were observed in some occupational studies with possible dermal exposure. ² Absorption, distribution, metabolism and excretion (ADME) data also collected from animal dermal studies. ³ Individuals with glucose-6-phosphate dehydrogenase deficiency may be more susceptible to hematological, reproductive/developmental, and neurological effects. Hematological effects were also observed in dermal exposure studies in G6PD deficient infants. ✓ Checkmark without an associated descriptor indicate information from other types of studies.					



Key Science Issues

1. **Health outcomes**
2. **Toxicokinetics**
3. **Mode-of-action for mouse lung tumors**
4. **Mode-of-action for rat nasal tumors**
5. **Analysis of toxicogenomics data**
6. **Susceptibility factors**
7. **Data gaps, new studies, and research in progress**

Science issue 1: Health Outcomes

- The preliminary literature survey identified several health outcomes for systematic review:

Cancer

Reproductive

Hematological

Dermatological

Developmental

Respiratory

Immunological

Hepatic

Renal

Neurological

Ocular

Gastrointestinal

- Have any potential health outcomes been missed?
- Are there inter-relationships between some health outcomes that would warrant their being examined together?

Science issue 2: Toxicokinetics/ Species differences

Naphthalene is mainly metabolized through two metabolic pathways: (1) *CYP-450* pathway, (2) Glutathione conjugation pathway.

Qualitative and quantitative metabolic differences exist between humans and laboratory animals.

Toxicokinetic issues include:

- What is the chemical form responsible for the various toxicities reported?
- What are the relevant inter- and/or intra-species differences in toxicokinetics of naphthalene?
- Are there reliable PBPK models for interspecies or route-to-route extrapolation?



Science issue 3: Mode-of-action of mouse lung tumors

- EPA Mouse Lung Tumor Workshop (Jan 2014)
(<http://www.epa.gov/iris/irisworkshops/mltw/>)
- Are there newer data or additional perspectives that would be useful in understanding
 - the role of CYP450 enzymes in the metabolism of naphthalene
 - the contribution of naphthalene metabolites to the induction of lung tumors in mice, and
 - the respective roles of genotoxicity, cytotoxicity, and regenerative cell proliferation in the induction of lung tumors in mice

Science issue 4: Mode-of-action for rat nasal tumors

- Naphthalene has been associated with the induction of nasal cavity tumors in rats.
- What data would be useful in developing hypothesized mode(s)-of-action for rat nasal tumors?

Science issue 5: Analysis of Toxicogenomics Data

- Toxicogenomics data for naphthalene are available and might be informative
- How can toxicogenomics data be used to evaluate species and sex differences?

Science issue 6: Susceptibility factors

- Several reviews have discussed deficiency in the enzyme G6-PD as a potential susceptibility factor for the toxic effects of naphthalene
- It also has been noted that hematologic effects of naphthalene are more frequently seen in infants
- How can the available data be used to better characterize susceptibility?



Science issue 7: Data gaps, new studies and research in progress

- Are there any new studies published after Jun 2014 that are useful for naphthalene assessment?
- Are there any additional issues that require scientific discussion?

Thank You!