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IRIS Assessment Plan for Naphthalene (Scoping and Problem Formulation Materials)

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Integrated Risk Information System
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency

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ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
EPA	Environmental Protection Agency
HERO	Health and Environmental Research Online
IAP	IRIS Assessment Plan
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
NCEA	National Center for Environmental Assessment
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PECO	populations, exposures, comparators, and outcomes
RfC	reference concentration
RfD	reference dose

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1. INTRODUCTION

The Integrated Risk Information System (IRIS) Program is undertaking a reassessment of the health effects of naphthalene. This **IRIS Assessment Plan (IAP)** confirms the long-standing Agency priority for an assessment of naphthalene and aligns the assessment with the new documentation for systematic review in the IRIS program.

IRIS assessments provide high quality, publicly available information on the toxicity of chemicals to which the public might be exposed. These assessments are not regulations, but provide a critical part of the scientific foundation for decisions made in Environmental Protection Agency (EPA) program and regional offices to protect public health.

As part of the initial steps in assessment development, the IRIS Program undertakes scoping and initial problem formulation activities. During scoping activities, the IRIS Program consults with EPA program and regional offices to identify the nature of the hazard characterization needed, the most important exposure pathways, and the level of detail required to inform Agency decisions. A broad, preliminary literature survey may also be conducted to assist in identifying the extent of the evidence and health effects that have been studied for the chemical of interest. Based on the preliminary literature survey and the scope defined by EPA, the IRIS Program undertakes problem formulation activities to frame the scientific questions that will be the focus of the assessment. A summary of the IRIS Program's scoping and problem formulation conclusions are contained in the IAP.

The IAP is followed by development of a **Systematic Review Protocol**, which presents detailed methods for conducting the full systematic review and dose-response analysis, including any adjustments made to the IAP in response to public input. The IAP describes *what* will be assessed, and the chemical-specific protocol describes *how* the assessment will be conducted. Figure 1 graphically displays the context of the IAP and Systematic Review Protocol in the systematic review process.

This document presents the draft IAP for naphthalene—a summary of the IRIS Program's scoping and initial problem formulation conclusions. It describes the Agency need for the assessment; objectives and specific aims of the assessment; draft Populations, Exposures, Comparators, and Outcomes (PECO) criteria that outline the evidence considered most pertinent to the assessment; and identification of key areas of scientific complexity. Brief background information on uses and potential for human exposure is provided for context.

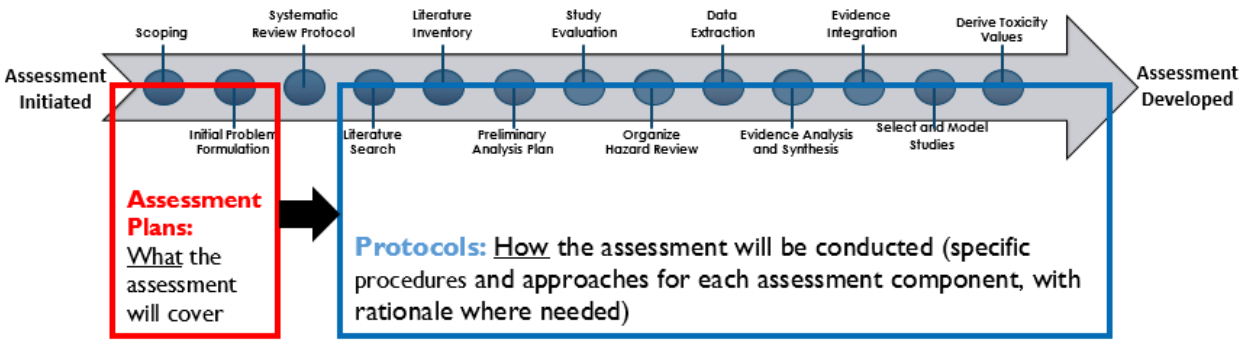

Figure 1. IRIS systematic review problem formulation and method documents.

2. SCOPING AND INITIAL PROBLEM FORMULATION

2.1. BACKGROUND

Naphthalene is a polycyclic aromatic hydrocarbon that is a white crystalline solid with an aromatic odor. It is soluble in organic solvents and stable in closed containers under normal temperatures and pressures (NTP, 2011). Naphthalene is naturally occurring and is most abundantly found in coal tar, coal and petroleum (ToxNet Hazardous Substances Data Bank, 2017; ATSDR, 2005). The release of naphthalene may also occur because of its manufacture or use in the chemical industry. In the United States, naphthalene is considered a high production volume (HPV) chemical, though domestic production of naphthalene has decreased significantly from a peak of 900 million pounds in 1968 to an aggregate volume of 100–250 million pounds in 2015 (U.S. EPA, 2016). Naphthalene is also present in jet fuels, such as JP-8 (ATSDR, 2013). Naphthalene is mainly used in the manufacture of dyes, surfactants, leather tanning agents, dispersants, pesticides, resins, solvents, and chemical intermediates (ATSDR, 2005). Major consumer products containing naphthalene include moth repellents, in the form of mothballs or crystals, and toilet deodorant blocks (ATSDR, 2005). Naphthalene is used as fragrance in non-food-use pesticide products while naphthalene derivatives are also used as inert ingredients in non-food use pesticide products regulated by EPA (U.S. EPA, 2015, 2012). Lastly, naphthalene is also a constituent of tobacco smoke.

The general public can be exposed to naphthalene via inhalation, ingestion, and dermal routes. Inhalation is generally considered to be the predominant route of exposure (ToxNet Hazardous Substances Data Bank, 2017). Naphthalene is emitted into the atmosphere by industrial facilities, open burning and mobile sources. Naphthalene is a component of fuel oil and gasoline and is produced as a combustion by-product in vehicle exhaust. Exposure to naphthalene may also come from contact with contaminated land and water resulting from spills during storage, transportation and disposal of fuel oil, coal tar, etc. (CalEPA, 2004; IARC, 2002). Because tobacco smoke and numerous consumer products contain and release naphthalene, naphthalene is a contaminant of indoor air (CalEPA, 2004; IARC, 2002). For nonsmokers exposed to environmental tobacco smoke in their residences, the naphthalene intake rate is 1 to 3 μg day^{-1} (Jia and Batterman, 2010; Nazaroff and Singer, 2004). An estimate of the average total intake rate of naphthalene via inhalation in ambient and indoor air is 19 μg day^{-1} (Jia and Batterman, 2010; Howard, 1989). Children can receive additional exposure to naphthalene through ingestion of soil or food contaminated with naphthalene or through accidental ingestion of household products containing naphthalene, such as mothballs and deodorant blocks (ATSDR, 2005), that are sometimes mistaken for candy. Occupational exposure to naphthalene occurs through inhalation and dermal contact by workers in facilities where naphthalene is produced or used, such as mothball manufacturing

plants and creosote-impregnation facilities. High exposures to naphthalene have also been suggested to occur in forest firefighters (Robinson et al., 2008).

Naphthalene is readily absorbed into the systemic circulation following oral, dermal, or inhalation exposure and distributed by the blood throughout the body. It can be transferred to the developing fetus of pregnant women (Anziulewicz et al., 1959; Zinkham and Childs, 1958, 1957) and has been detected in human breast milk (Cok et al., 2012; Tsang et al., 2011; Pellizzari et al., 1982) and umbilical cord serum (Tsang et al., 2011). Naphthalene is rapidly metabolized into a wide array of metabolites, including reactive epoxide and quinone intermediates that may interact with cellular macromolecules such as proteins and DNA. Two major metabolic pathways for naphthalene have been identified: 1) a cytochrome P450 (CYP)-dependent pathway and 2) a glutathione-conjugation-dependent pathway. Metabolites pertaining to both major pathways have been identified in the blood and urine of occupationally-exposed individuals and in experimentally-exposed animals (ATSDR, 2005; CalEPA, 2004; IARC, 2002). The naphthalene metabolites 1-naphthol and 2-naphthol have been widely detected in the urine of the US general population, including in children aged 6-19 years old (CDC, 2018).

An assessment of naphthalene is currently available on the IRIS website at https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=436 (US EPA, 1998). This assessment, conducted using guidance from EPA's 1986 Cancer Guidelines (U.S. EPA, 1986), includes a review of inhalation studies which provide support for a reference concentration (RfC) of 3×10^{-3} mg/m^3 for noncancer effects based on hyperplasia and metaplasia in respiratory and olfactory epithelium in mice, and a review of oral studies which provide support for a reference dose (RfD) of 2×10^{-2} mg/kg-day for noncancer effects based on decreased body weight in male rats. EPA's 1998 IRIS assessment classified naphthalene as a Group C, possible human carcinogen. This classification was based on inadequate carcinogenicity data in humans exposed to naphthalene via the oral and inhalation routes, and limited evidence of carcinogenicity in animals exposed to naphthalene via inhalation. The assessment concluded that a genotoxic mechanism appeared unlikely, but hypothesized that the mechanism for tumorigenesis involves oxygenated reactive metabolites produced via the cytochrome P450 monooxygenase system.

Since the posting of IRIS toxicological review of naphthalene in 1998 and the release, in 2005, of EPA's final cancer guidelines (U.S. EPA, 2005), new information on naphthalene has become available, including bioassay data, potency estimations, and physiologically-based pharmacokinetic (PBPK) models with potential to assist in performing route-to-route and animal-to-human extrapolations. More specifically, several significant studies on naphthalene toxicity have been published, including a 2-year inhalation study performed by NTP in which naphthalene-exposed rats showed an increased incidence of nasal tumors (NTP, 2000). In addition to this NTP study, numerous studies (>70) have been published which provide mechanistic information that informs the naphthalene mode of action, such as the involvement of specific cytochrome P450 subfamilies like CYP2F and CYP2A in the metabolism and possible activation of reactive

naphthalene intermediates (Buckpitt et al., 2013; Morris, 2013; Morris and Buckpitt, 2009; Carlson, 2008; Genter et al., 2006; Buckpitt et al., 2002; Su et al., 2000; Lanza et al., 1999; Shultz et al., 1999) that may interact with biological macromolecules such as proteins or DNA. These studies may help in further informing the naphthalene mode of action for cancer. Additionally, a PBPK model for naphthalene was developed using controlled human dermal and inhalation exposures to jet propulsion fuel 8, of which naphthalene is a component (Kim et al., 2007). The results of this more recent research will be evaluated using EPA's current cancer guidelines (U.S. EPA, 2005) and may provide new evidence to better inform naphthalene toxicity values.

2.2. SCOPING SUMMARY

Naphthalene is subject to regulation under several environmental statutes implemented by EPA, including the Clean Water Act (CWA), Clean Air Act (CAA), Federal Fungicide Insecticide and Rodenticide Act (FIFRA), Toxic Substances Control Act (TSCA); Emergency Planning and Community Right-to-Know Act (EPCRA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Resource Conservation and Recovery Act (RCRA). Naphthalene is also listed as a Hazardous Air Pollutant (HAP) by EPA and is a contaminant found at more than 400 National Priority List (Superfund) sites (U.S. EPA, 2014b).

During initial scoping, the IRIS Program met with EPA program and regional offices that had interest in an IRIS assessment for naphthalene to discuss specific assessment needs. Table 1 provides a summary of current programmatic interest. Additional programmatic and regional needs and interests will be reviewed and updated as the assessment progresses.

Table 1. EPA program interest in reassessment of naphthalene

EPA program	Oral	Inhalation	Statutes/regulations/policies	Anticipated uses/interest
OLEM	✓	✓	Comprehensive Environmental Response, Compensation and Liability Act (CERCLA); Emergency Planning and Community Right-to-Know Act (EPCRA); RCRA Subtitle I (Underground Storage Tanks)	Naphthalene toxicological information may be used to make risk determinations for response actions (e.g., short-term removals, long-term remedial response actions) under CERCLA and RCRA including Subtitle I leaking underground storage tanks. For example, CERCLA authorizes EPA to conduct short or long-term cleanups at Superfund sites and later recover cleanup costs from potentially responsible parties under section 107.
OLEM (Office of Land and Emergency Management)				

2.3. PROBLEM FORMULATION

A public science meeting on the scoping and problem formulation activities for naphthalene was held on September 3–4, 2014 (U.S. EPA, 2014a). The discussion from the public meeting indicated that a comprehensive assessment of naphthalene was warranted based on consideration of the amount of new evidence that had been generated regarding cancer- and non-cancer-related health risks, as well as the length of time that had passed since EPA conducted the last assessment.

A preliminary literature survey was performed during the 2014 scoping and problem formulation activities to identify health outcomes resulting from exposure to naphthalene (U.S. EPA, 2014a). This survey consisted of a search for health assessment information produced by other federal, state, and international health agencies, and a broad search of literature from multiple science databases including PubMed, Web of Science, Toxline, and TSCATS. This literature search was updated in October 2017. The results of the literature search and subsequent preliminary screening were documented and can be found on the Health and Environmental Research Online (HERO) website on the naphthalene project page (https://hero.epa.gov/hero/index.cfm/project/page/project_id/367). Following the literature search and preliminary screening, studies were manually screened by title/abstract for relevance against the PECO (Population, Exposure, Comparator, Outcome) criteria as described in Section 3. Reviewed studies were sorted into bins according to the type(s) of health outcomes and/or health effects reported. In this way, human health hazards associated with naphthalene exposure were identified. These hazards included the following toxicities: hematological (e.g. hemolytic anemia), immune system, respiratory system, reproductive system, developmental, cancer and other toxicities. This was done to direct the studies to the appropriate subject matter experts for the next stages in the IRIS Assessment Development Process, namely study evaluation, data extraction, evidence synthesis and integration, and dose-response analysis. The initial results of the binning are shown below and show the number of studies for each endpoint/health outcome category for human and animal studies (Tables 2-4). Many studies reported more than one health effect/outcome category; therefore, there is not a one-to-one correspondence between the total number of studies across the endpoints and the total number of studies identified in the screening process.

1 **Table 2. Survey of Naphthalene Inhalation Studies**

	Human Studies				Animal Studies					
	Occupational Epidemiological Studies	General Population Epidemiological Studies	Controlled Exposure Studies	Case Reports/Case Series	Chronic	Subchronic	Short-term	Acute	Multigenerational	Gestational
Inhalation Exposure										
Cardiovascular					2	1				
Dermal					2					
Developmental				3						
Endocrine/Exocrine					2	1				
Gastrointestinal	1			4	2					
Hematological				6	2					
Hepatic				4	2	1		1		
Immunological	1	3			2	1				
Nasal					3	1	2	4		
Neurological				3	2	1				
Pulmonary	1	1		1	3			4		
Renal				1	2	1				
Reproductive				2	2	1				
Ocular				4	2					
Other effects[a]					3	1	2			

[a]Other effects include body weight, clinical signs, and other observations

NOTE: The numbers represent the numbers of studies that investigated a particular health effect, not the number of studies that identified a positive association with exposure to naphthalene. If a journal article or report included, for example, a study in both rats and mice, it was counted as two studies. Blanks indicate that no studies were identified in the systematic literature search and screening for that specific effect category.

1 **Table 3. Survey of Naphthalene Oral Exposure Studies**

	Human Studies				Animal Studies					
	Occupational Epidemiological Studies	General Population Epidemiological Studies	Controlled Exposure Studies	Case Reports/Case Series	Chronic	Subchronic	Short-term	Acute	Multigenerational	Gestational
Oral Exposure										
Cardiovascular				9		3				
Dermal										
Developmental				1						
Endocrine/Exocrine						2				
Gastrointestinal				17		2				
Hematological				31		4	1	1		
Hepatic				22		7	6	1		
Immunological						3	1	1		
Nasal										
Neurological				5		4	1			
Pulmonary				9		4	1			
Renal				29		6	2			
Reproductive				1		3	1			
Ocular				4		29	20	1		
Other effects[a]				27		15	5	9		

[a]Other effects include body weight, clinical signs, and other observations

NOTE: The numbers represent the numbers of studies that investigated a particular health effect, not the number of studies that identified a positive association with exposure to naphthalene. If a journal article or report included, for example, a study in both rats and mice, it was counted as two studies. Blanks indicate that no studies were identified in the systematic literature search and screening for that specific effect category.

2

Table 4. Survey of Naphthalene Studies with Dermal or Multiple/Unknown (Biomarker) Routes of Exposure

	Human Studies				Animal Studies					
	Occupational Epidemiological Studies	General Population Epidemiological Studies	Controlled Exposure Studies	Case Reports/Case Series	Chronic	Subchronic	Short-term	Acute	Multigenerational	Gestational
Dermal or Multiple/Unknown (Biomarker) Routes of Exposure										
Cardiovascular		2		3						
Dermal				2			2	2		
Developmental		1		2						
Endocrine/Exocrine		3					1			
Gastrointestinal	1			2						
Hematological		2		12		1	1			
Hepatic		3		11			1			
Immunological		3				1				
Nasal										
Neurological	1	1		4						
Pulmonary				3						
Renal				8			1			
Reproductive		7		1		1	1			
Ocular	1			2		1	1	1[b]		
Other effects[a]	2	2		9		1	1			

[a]Other effects include body weight, clinical signs, and other observations. [b]One animal study that evaluated ocular exposure is recorded here; all other animal studies in this table evaluated dermal exposure.

NOTE: The numbers represent the numbers of studies that investigated a particular health effect, not the number of studies that identified a positive association with exposure to naphthalene. If a journal article or report included, for example, a study in both rats and mice, it was counted as two studies. Blanks indicate that no studies were identified in the systematic literature search and screening for that specific effect category.

Based on the literature searches and screening done to date, EPA anticipates conducting a systematic review for the following health effect categories:

- Hematological,
- Immune system,
- Respiratory system,
- Reproductive/developmental system,
- Cancer, and
- Other toxicities

2.4. KEY SCIENCE ISSUES

Based on the preliminary literature survey, the following key scientific issues and potential mode-of-action (MOA) hypotheses were identified that warrant evaluation in this assessment.

Species differences:

- Differences in metabolism: Naphthalene toxicity is related to protein binding by naphthalene quinone metabolites and/or the participation of naphthalene quinone metabolites in redox cycles leading to oxidative stress and DNA damage (O'Brien, 1991). These quinone intermediates are produced via cytochrome P450 (CYP)-dependent metabolism, and may specifically involve the CYPF subfamily. While much progress has been made in the characterization of the mouse CYP2F2, the CYP thought to be primarily involved in naphthalene metabolism in mice, characterizing the relative contribution of P450 oxidizing enzymes to naphthalene metabolism in rats and humans has been more difficult (Buckpitt et al., 2002; Shultz et al., 1999). Recent studies show that, in addition to the CYPF subfamily, the CYP2A class also plays an important role in naphthalene-induced lung toxicity and may be the more pertinent enzyme in naphthalene metabolism in humans (Li et al., 2017; Su et al., 2000).

- Health effects: The results available at present indicate that there are likely major interspecies catalytic differences between mouse, rat and human CYPF enzyme homologs. As an example, studies have shown that chronic naphthalene exposure of rats and mice results in nasal non-neoplastic lesions, nasal cytotoxicity and degeneration of the nasal olfactory epithelium in both species; additionally, chronic naphthalene exposure also leads to the development of nasal tumors in rats, but lung tumors in mice. The rate and extent of metabolism of naphthalene in various tissues and in different animal species along with anatomical differences in the nasal turbinates between species will be important considerations in evaluating differences in naphthalene metabolism across species.

- Evaluation of the current and available naphthalene PBPK models for reliable route-to-route, interspecies, and/or intraspecies extrapolation is needed. If necessary, further development of PBPK models will also be considered.

- Mode of action: Multiple animal and in vitro studies published since the 1998 IRIS Toxicological Review have provided mechanistic information and postulated the involvement of several biological processes in the development of naphthalene-induced tumor formation. These proposed processes include genotoxicity, cytotoxicity, and sustained regenerative cell proliferation. Among the key events identified by these studies are the depletion of glutathione and the formation of reactive naphthalene quinone metabolites via the cytochrome P450 pathway. These quinone metabolites may lead to oxidative stress and DNA damage. The role and biological plausibility of each of these proposed mechanisms occurring in humans and their role in the formation of naphthalene-induced tumors will need to be evaluated. Differences in enzyme activities between human and rodent tissues exist; therefore, evaluation of the cancer MOA in the context of toxic metabolite formation and the relevance of these toxic metabolites to human cancer hazard will also need to be evaluated.

3. OVERALL OBJECTIVE, SPECIFIC AIMS, AND DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO)

The overall objective of this assessment is to identify adverse health effects and characterize exposure-response relationships for these effects of naphthalene to derive toxicity values (e.g., reference doses [RfDs], reference concentrations [RfCs], cancer risk estimates) as supported by the available data. This assessment will use systematic review methods to evaluate the epidemiological and toxicological literature for naphthalene, including consideration of relevant mechanistic evidence. The evaluation conducted in this assessment will be consistent with relevant EPA guidance.[1] The systematic review protocol will be disseminated after review of the draft assessment plan and will reflect changes made to the specific aims and PECO in response to public input.

3.1. SPECIFIC AIMS

- Identify epidemiological (i.e., human) and toxicological (i.e., experimental animal) literature reporting effects of exposure to naphthalene as outlined in the PECO.

- Use an iterative approach to determine which mechanistic studies are most important to summarize, based on factors such as robustness of the evidence in humans and animals, likelihood to impact evidence synthesis conclusions for human health, and directness or relevance of the model systems for understanding potential human health hazards. When summarizing individual mechanistic studies is deemed not critical, other published authoritative sources, such as public health agency reports and expert review articles, will be relied upon for this information.

- Conduct study evaluations (risk of bias and sensitivity) for individual epidemiological and toxicological studies. Studies with critical deficiencies will generally be considered uninformative, and will generally not be considered further.

- Extract data on relevant health outcomes from epidemiological and toxicological studies included based on study evaluation.

- Synthesize the evidence across studies, assessing similar health outcomes using a narrative approach or meta-analysis (if appropriate).

[1]EPA guidance documents: http://www.epa.gov/iris/basic-information-about-integrated-risk-information-system#guidance/

- Evaluate each evidence stream (human and animal) separately. Determine the confidence in conclusions for each health outcome from across studies (or subsets of studies) within human and animal evidence streams.

- For each health outcome, integrate results across evidence streams (human and animal) to conclude whether a substance is hazardous to humans. Identify and discuss issues concerning potentially susceptible populations and life stages. Biological support from mechanistic studies and nonmammalian model systems will be considered based on the iterative prioritization approach outlined in the PECO.

- Derive toxicity values (e.g., reference doses [RfDs], reference concentrations [RfCs], cancer risk estimates) as supported by the available data. Quantitative toxicity values for dermal exposure will not be derived, although dermal exposure studies will be evaluated and used to inform hazard identification when available (noting that a PBPK model for dermal naphthalene exposure is available).

- Characterize uncertainties and identify key data gaps and research needs, such as limitations of the evidence base, limitations of the systematic review, and consideration of dose relevance and pharmacokinetic differences when extrapolating findings from higher dose animal studies to lower levels of human exposure.

3.2. DRAFT POPULATIONS, EXPOSURES, COMPARATORS, AND OUTCOMES (PECO)

A PECO is used as an aid to focus the research question(s), search terms, and inclusion/exclusion criteria in a systematic review. The draft PECO for naphthalene (Table 5) was based on: (1) nomination of the chemical for assessment, (2) discussions with scientists in EPA program and regional offices to determine the scope of the assessment that will best meet Agency needs, and (3) preliminary review of the health effects literature for naphthalene (primarily reviews and authoritative health assessment documents) to identify the major health hazards associated with exposure to naphthalene and key areas of scientific complexity.

Table 5. Draft PECO criteria for the naphthalene assessment

PECO element	Evidence
Populations[a]	**Human:** Any population and lifestage (occupational or general population, including children and other sensitive populations). The following study designs will be considered most informative: controlled exposure, cohort, case-control, cross-sectional, and ecological. Note: Case reports and case series will be tracked during study screening, but are not the primary focus of this assessment. They may be retrieved for full-text review and subsequent evidence synthesis if no or few informative study designs are available. Case reports also can be used as supportive information to establish biologic plausibility for some target organs and health outcomes.
	Animal: Nonhuman mammalian animal species (whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).
Exposures	**Human:** Any exposure to naphthalene (CASRN 91-20-3), including occupational exposures, via oral, inhalation, or dermal route[s]. Exposures quantified by either biomonitoring or occupational exposure history are preferred.
	Animal: Any exposure to naphthalene (CASRN 91-20-3) via oral, inhalation, or dermal route[s]. Studies employing chronic exposures or short-term, developmental-only exposures will be considered the most informative. Studies involving exposures to mixtures will be included only if they include an arm with exposure to naphthalene alone. Other exposure routes, including injection, will be tracked during title and abstract screening and tagged as "supplemental information."
	Studies describing physiologically-based pharmacokinetic (PBPK) models for naphthalene will be included.
Comparators	**Human:** A comparison or referent population exposed to lower levels (or no exposure/exposure below detection limits) of naphthalene, or exposure to naphthalene for shorter periods of time.
	Animal: A concurrent control group exposed to vehicle-only treatment.
Outcomes	All health outcomes (both cancer and noncancer). In general, endpoints related to clinical diagnostic criteria, disease outcomes, histopathological examination, or other apical/phenotypic outcomes will be prioritized for evidence synthesis over outcomes such as biochemical measures. As discussed above, based on preliminary screening work, EPA anticipates that a systematic review for health effect categories other than those identified (i.e., hematological, immune system, respiratory system, reproductive/developmental system, and cancer) will not be undertaken unless a significant amount of new evidence is found upon review of references during the comprehensive literature search.

[a]Evidence from in vitro, in silico, and other types of mechanistic studies will be prioritized based on likelihood to impact evidence synthesis conclusions for human health. For naphthalene, mechanistic studies will only be considered for evaluation if they are essential for answering questions identified during the human and animal evidence synthesis.

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