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Scoping and Problem Formulation for the Identification of Potential Health Hazards for the Integrated Risk Information System (IRIS) Toxicological Review of Naphthalene

[CASRN 91-20-3]

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NOTICE

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CONTENTS

PREFACE

The National Research Council's Review of EPA's Integrated Risk Information System (IRIS) Process (NRC, 2014) discussed scoping and problem formulation as they apply specifically to IRIS assessments. IRIS assessments evaluate the available scientific literature to identify potential human health hazards of a chemical and to characterize dose-response relationships for each hazard. Accordingly, the NRC discussed scoping and problem formulation for IRIS assessments as being restricted to scientific questions that pertain only to hazard identification and dose-response assessment. Exposure assessment and risk characterization (the other components of a risk assessment) are outside the scope of IRIS assessments, as are the legal, political, social, economic, and technical aspects of risk management.

During scoping, the IRIS program seeks input from EPA's program and regional offices to identify the information and level of detail needed to inform their decisions. This includes the exposure pathways and specific exposed groups that the assessment will consider. The NRC's Review of EPA's IRIS Process characterized this practice as consistent with the risk-assessment guidance in Science and Decisions (NRC, 2009).

During problem formulation, the IRIS program seeks input from the scientific community and the general public as it frames the specific scientific questions for the systematic reviews that it will conduct in the assessment. The NRC's Review of EPA's IRIS Process identified the major challenge of problem formulation as determining which adverse outcomes the assessment should evaluate. The NRC suggested a three-step process for conducting problem formulation for IRIS assessments: (1) a literature survey to identify the possible health outcomes associated with the chemical, (2) construction of a table to guide the formulation of specific questions that will be the subject of specific systematic reviews, and (3) examination of this table to determine which health outcomes warrant a systematic review and to define the systematic-review questions. As an example, the NRC provided the question, "Does exposure to chemical X result in neurotoxic effects?" In addition to identifying health outcomes for systematic review, the problem formulation section discusses key issues that the assessment will address.

This document begins with a brief background information on naphthalene, which will be the subject of an IRIS assessment. Next the three steps that the NRC suggested are presented along with the systematic-review questions and key issues.

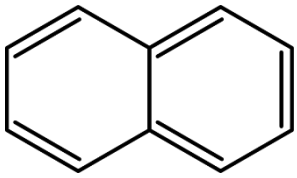
Early public involvement should increase the quality and transparency of IRIS assessments. Accordingly, the IRIS program is releasing this document in anticipation of a public science meeting focused on identifying the scientific information available for this assessment. The IRIS program encourages the scientific community and the general public to participate in this meeting.

1. BACKGROUND

1.1. Production and Use

Naphthalene is a polycyclic aromatic hydrocarbon chemical that is a white crystalline solid at room temperature with an aromatic odor. It is insoluble in water but soluble in many organic solvents. It is stable in closed containers under normal temperatures and pressures (NTP, 2011).

Naphthalene



CAS Number: 91-20-3

The largest source of naphthalene is fossil fuels, such as petroleum and coal (ATSDR, 2005). Naphthalene also occurs at high levels (~10%) in coal tar, which is a byproduct in the production of steel (HSDB, 2005).

Naphthalene is considered a High Production Volume chemical in the United States, though domestic production of naphthalene has decreased significantly from a peak of 900 million pounds in 1968 to 215 million pounds reported in 2004 (ATSDR, 2005) and 160 million pounds reported in 2012 (U.S. EPA, 2013a).

More than 60% of naphthalene in the U.S. is used in the production of phthalic anhydride, which is an intermediate in the production of phthalate plasticizers, resins, phthaleins, dyes, pharmaceuticals, insect repellents, and other materials (ATSDR, 2005). Naphthalene is also present in certain jet fuels, just as JP-8 (ATSDR, 2013). The major consumer products made from naphthalene are moth repellents, in the form of mothballs or crystals, and toilet deodorant blocks (ATSDR, 2005). However, the use of naphthalene as a moth repellent and insecticide is decreasing and it is being replaced by other compounds (HSDB, 2005). Other uses in consumer products include: aerosol paint concentrates and other paint-related products, agricultural chemicals,

herbicides, caulking compounds and sealants, automotive chemicals, repellants and attractants, synthetic resin and rubber adhesives, wall coverings, and wood office work surfaces (HSDB, 2005).

According to the U.S. EPA's Toxics Release Inventory (TRI) Program, the environmental release of naphthalene in the US from facilities required to report in 2012 was approximately 1.5 million pounds into the atmosphere from fugitive emissions and point sources; 2.2 million pounds to land from landfills, land treatment, underground injection and other land disposal sources; and 6,539 pounds to surface waters (U.S. EPA, 2013b).

1.2. Environmental Fate

Volatilization from soil is an important dissipation process for naphthalene. Based on its affinity to soil organic matter (soil organic partitioning ratios of approximately 1000), the mobility of naphthalene in soil is expected to be moderate to low (HSDB, 2005). The half-life of naphthalene in soil is estimated to be on the order of days to weeks (HSDB, 2005). In soils previously exposed to naphthalene or other PAHs, microbial degradation rates can be increased (HSDB, 2005).

In water, naphthalene tends to reversibly adsorb to suspended solids and sediment. Dissolved naphthalene can volatilize from surface water and photolysis may also occur in clear, sunlit surface waters with a half-life of about 3 days. Bioconcentration factors in aquatic organisms range from 23 to 168. The biodegradation half-life in water is estimated to range from a day to more than a month. No abiotic hydrolysis of naphthalene is expected to occur in natural water (HSDB, 2005).

In the atmosphere, naphthalene exists primarily as a gas and is degraded via reaction with photochemically-produced hydroxyl radicals with a half-life of about 18-60 hours (HSDB, 2005).

1.3. Human Exposure Pathways

The general public can be exposed to naphthalene by inhalation, ingestion and dermal routes, but inhalation is generally considered to be the largest contributor to exposure (HSDB, 2005). Naphthalene has been measured in indoor and outdoor air. The highest indoor air concentrations generally occur in the homes of cigarette smokers, and the highest outdoor air concentrations have been found in the vicinity of certain industrial sources and hazardous waste sites (ATSDR, 2005).

Naphthalene has been detected infrequently in surface water and ground water (ATSDR, 2005; HSDB, 2005; U.S. EPA, 2003). Water concentrations are generally higher in urban areas and in the immediate vicinity of point sources of release, such as production factories and chemical waste sites (ATSDR, 2005). Detections in public drinking water systems are uncommon (U.S. EPA, 2003).

Dermal exposure to naphthalene may occur from handling naphthalene-containing products or wearing clothing stored in naphthalene-containing moth repellents (ATSDR, 2005).

Children can be exposed to naphthalene via soil ingestion, food ingestion, and accidental ingestion of household products containing naphthalene such as mothballs or deodorant blocks (ATSDR, 2005). Naphthalene has been detected in food as a contaminant (ATSDR, 2005) or as a result of food preparation (e.g., grilling and smoking) (HSDB, 2005).

Occupational exposure to naphthalene may occur through inhalation and dermal contact at workplaces where naphthalene is produced or used. The industries with the highest respiratory exposure to naphthalene are creosote impregnation, coal-tar processing, wood preserving, leather tanning, and asphalt production (IARC, 2002). Naphthalene levels in breath is used as a measure of occupational exposure to certain jet fuels (ATSDR, 2013).

Human exposure to naphthalene has been confirmed by detection of this compound in human tissues. Six of eight samples of mother's milk from four U.S. urban areas were found to contain naphthalene at detectable levels and 40% of human adipose tissue samples in a National Human Adipose Tissue Survey contained detectable levels of naphthalene (HSDB, 2005).

2. SCOPE OF THIS ASSESSMENT

EPA's previous IRIS assessment of naphthalene (U.S. EPA, 1998) included a reference concentration (RfC) for noncancer effects based on nasal effects and a reference dose (RfD) for noncancer effects based on decreased body weight in male rats, and classified naphthalene as Group C, a possible human carcinogen, based on inadequate data of carcinogenicity in humans exposed to naphthalene via the oral and inhalation routes. Since that time, a number of experimental animal and epidemiological studies have been published and the National Toxicology Program's Report on Carcinogens (NTP, 2011) listed naphthalene as, "reasonably anticipated to be a human carcinogen". Ethylbenzene and naphthalene oral bioassays with mice have both resulted in lung tumors and raised similar questions of their relevance to human health. An EPA peer consultation workshop on research needs related to mode of action for naphthalene-induced carcinogenicity was conducted in April 2005 to identify data gaps. Additionally, an EPA workshop on mouse lung tumors associated with exposure to several compounds, including ethylbenzene and naphthalene, was conducted in January 2014. The IRIS program is evaluating these two chemicals simultaneously due to their having some similar toxicological issues.

Naphthalene has been identified by EPA offices as a chemical for which an updated IRIS assessment would be useful, particularly focusing on oral and inhalation routes of exposure. Naphthalene is listed under several environmental acts that are implemented by EPA, including the Clean Water Act (CWA), Clean Air Act (CAA), Federal Fungicide Insecticide and Rodenticide Act (FIFRA), 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). The chemical is also listed as a Hazardous Air Pollutant by EPA and is a contaminant found at more than 400 National Priority List (Superfund) sites (U.S. EPA, 2014). Naphthalene is used as an inert ingredient and a fragrance in non-food use pesticide products regulated by EPA (U.S. EPA, 2012).

A new IRIS assessment will evaluate all potential human health hazards associated with naphthalene exposure through oral and inhalation routes of exposure. An assessment for the dermal route of exposure is not planned at this point because oral and inhalation exposure are generally considered the major routes of exposure and evaluating risk from dermal exposure was not identified as a priority need. Furthermore, although some occupational studies involving primarily inhalation exposures may have also included some dermal exposure, no dermal-only exposure studies in humans or experimental animals were identified.

3. PROBLEM FORMULATION

3.1. Preliminary Literature Survey

A preliminary literature survey was performed to identify health outcomes whose possible association with naphthalene has been investigated. This survey consisted of a search for health assessment information produced by other federal, state, and international health agencies, and an additional broad search of PubMed to locate more recent studies. The review of health assessment information results was used to narrow the list of potential health endpoints for consideration in the IRIS assessment and was supplemented by the PubMed search covering dates after the health assessments' publication. The PubMed search was not intended to be a comprehensive search of the available literature, but was intended to identify naphthalene health outcomes that had not been previously evaluated (*i.e.*, they were not a part of previous study designs) or were not observed in previous studies evaluated in prior health assessments. In addition, the preliminary literature survey was used to identify key scientific issues, including potential mode of action hypotheses that warrant evaluation in the assessment.

The following assessments, in addition to EPA's 1998 IRIS assessment (http://www.epa.gov/iris/subst/0436.htm; http://www.epa.gov/iris/toxreviews/0436tr.pdf), are available from several federal, state, and international health agencies (in reverse chronological order):

1. New Jersey Department of Environmental Protection (NJDEP), 2013, Site Remediation Program – Vapor intrusion – Naphthalene, http://www.nj.gov/dep/srp/guidance/vaporintrusion/
2. National Toxicology Program (NTP), 2011, NTP 12th Report on Carcinogens: Naphthalene, http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/naphthalene.pdf
3. Centers for Disease Control and Prevention (CDC), National Institute for Occupational Safety and Health (NIOSH), 2010, Pocket Guide to Chemical Hazards – Naphthalene, http://www.cdc.gov/niosh/npg/npgd0439.html
4. U.S. EPA, 2008, Office of Prevention, Pesticides and Toxic Substances. Reregistration Eligibility Decision for Naphthalene, EPA 738-R-07-010 http://www.epa.gov/pesticides/reregistration/REDs/naphthalene-red.pdf
5. Government of Canada, Environment Canada, Screening Assessment for the Challenge – Naphthalene, 2008, http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=F212515C-1

6. U.K. Health Protection Agency, Naphthalene Toxicological review, 2007, http://www.hpa.org.uk/webc/hpawebfile/hpaweb_c/1203084377981
7. Agency for Toxic Substances and Disease Registry (ATSDR), 2005, Toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, http://www.atsdr.cdc.gov/toxprofiles/tp67.pdf
8. California EPA (CalEPA), Office of Environmental Health Hazard Assessment, 2004, Air Toxic hot spots: Adoption of a unit risk value for naphthalene, http://www.oehha.org/air/hot_spots/naphth.html, http://www.oehha.org/air/hot_spots/pdf/naphth080304.pdf, http://oehha.ca.gov/air/chronic_rels/pdf/91203.pdf
9. U.S. EPA, 2003, Office of Water, Health Effects Support document for Naphthalene, http://water.epa.gov/action/advisories/drinking/upload/2003_03_05_support_cc1_naphthalene_healtheffects.pdf
10. European Chemicals Agency, 2003, European Union Risk Assessment Report – naphthalene, http://echa.europa.eu/documents/10162/4c955673-9744-4d1c-a812-2bf97863906a, EINECS no 202-049-5
11. International Agency for Research on Cancer (IARC), 2002, IARC Monograph on the Evaluation of Carcinogenic Risks to Humans: Some traditional herbal medicines, some mycotoxins, naphthalene and styrene, Vol 82, Lyon, France, http://monographs.iarc.fr/ENG/Monographs/vol82/mono82.pdf
12. International Programme on Chemical Safety (IPCS), 2001, Concise International Chemical Assessment Document 34, Chlorinated Naphthalenes, http://www.who.int/ipcs/publications/cicad/en/cicad34.pdf

3.2. Health Outcomes Identified by the Preliminary Literature Survey

The preliminary literature survey identified human, animal, and *in vitro* studies related to multiple health outcomes, mechanism of action, mode of action hypotheses, pharmacokinetics, and susceptible lifestages or subpopulations. Each row in Table 1 summarizes whether data are available on a particular health outcome or other toxicologically-relevant information, with each column indicating the types of studies that are available with respect to test system (human, animal, or *in vitro*) and exposure route (oral or inhalation, for *in vivo* studies). In addition, the table indicates whether animal studies of subchronic or chronic design are available, and whether the human studies are in an occupational, community, or clinical exposure setting. Studies that do not fall into any of these categories are indicated by checkmarks without an associated descriptor.

1 **Table 1. Naphthalene Studies**

	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)	
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.

3.3. Hazard Questions for Systematic Review

The health agency reviews listed in Section 3.1 were used to "prescreen" end points considered most relevant for assessment and the effects noted in these reviews are summarized below. Based on the availability of health endpoint information indicated in Table 1, systematic reviews of the available literature are proposed for multiple endpoints, including: cancer, cardiovascular, dermatological, gastrointestinal, hematological, immunological, hepatic, renal, neurological, ocular, respiratory, and reproductive and developmental effects. The summaries reflect characterizations provided by the other assessments and may differ from the final IRIS assessment's conclusions. The end points identified form the basis for developing the systematic review questions for a revised IRIS assessment. The systematic reviews would include analysis of available human, experimental animal, and *in vitro* studies. Systematic review questions were only developed where effects were noted.

Body weight effects

EPA's 1998 IRIS assessment derived a reference dose (RfD) for noncancer effects based on decreased mean terminal body weight in male rats in a subchronic oral rat study (BCL, 1980).

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in body weight effects in humans?

Cancer

EPA's 1998 IRIS assessment classified naphthalene as Group C, a possible human carcinogen, based on inadequate data of carcinogenicity in humans exposed to naphthalene via the oral and inhalation routes. Neither an inhalation unit risk nor an oral slope factor was derived because of a lack of information regarding the carcinogenic potential of naphthalene in humans. More recent reviews by federal (ATSDR, 2005) or international health agencies (IARC, 2002) have noted that experiments in rodents conducted by NTP (1992, 2000) reported increased incidences of cancers after inhalation exposure, and evaluated the carcinogenicity of naphthalene based on NTP (2000) and other studies. The International Agency for Research on Cancer (2002) has classified naphthalene as a 2B carcinogen (possibly carcinogenic to humans) based on inhalation data in animals (IARC, 2002). The National Toxicology Program's 12th Report on Carcinogens (2011) classified naphthalene as 'reasonably anticipated to be a human carcinogen' based on sufficient evidence from studies in experimental animals. CalEPA has derived an inhalation unit risk based on data for incidence of nasal respiratory epithelial adenoma and nasal olfactory

epithelial neuroblastoma in male rats (CalEPA, 2004). Additionally, some health agency reviews have discussed mechanistic studies investigating the role of mutagenicity and/or genotoxicity in inducing these cancers, as well as other mode of action hypotheses, including cytotoxicity and regenerative hyperplasia (IARC, 2002; ATSDR, 2005). The IRIS Program follows the Supplemental Cancer Guidelines that recommend an analysis of the available data for all carcinogenic chemicals to determine whether a mutagenic mode of action may be operational. This recommendation stems from a determination by the Agency that there is increased susceptibility for cancer when exposures occur early in life. If it is determined that naphthalene has human carcinogenic potential by the oral or inhalation routes of exposure, then a specific determination regarding the mode of action as per the Supplemental Cancer Guidelines will be made. Further mode of action information and key issues are discussed in section 3.4 below.

Systematic review questions: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in carcinogenesis in humans?

Is naphthalene exposure associated with genotoxic and/or mutagenic effects related to its potential carcinogenicity? And if so, under what conditions?

Cardiovascular effects

NTP (2000) conducted a comprehensive chronic inhalation bioassay in mice and rats that included evaluation of cardiovascular effects. However, neither NTP (2000) nor any of the available reviews by government health agencies and international health organizations noted consistent, treatment-related cardiovascular health effects from naphthalene exposure. This endpoint will not be evaluated further unless evidence of cardiovascular effects are identified in the comprehensive literature search.

Dermatological effects

IPCS (2001) reviewed cases of severe skin reactions following occupational exposure to naphthalene. However, reviews by other government health agencies and international health organizations did not note dermal health effects following oral or inhalation exposure to naphthalene.

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in dermatological effects in humans?

Gastrointestinal effects

Gastrointestinal effects in humans and animals were reviewed by IPCS (2001), ATSDR (2005), U.S. EPA (2008), and UK HPA (2007). Nausea, vomiting, abdominal pain, and diarrhea have been commonly documented in humans following inhalation or ingestion of naphthalene (ATSDR, 2005; U.S. EPA, 2008; IPCS, 2001). ATSDR (2005) summarized data indicating the formation of stomach lesions and discoloration of the intestines in rats following oral administration of naphthalene. U.S. EPA (2008) also noted diarrhea reported in orally exposed rabbits and rats.

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in gastrointestinal effects in humans?

Hematological effects

ATSDR (2005), CalEPA (2004), ECA (2003), UK HPA (2007), and U.S. EPA (2008) have summarized hematological effects observed in animal studies and humans. ATSDR (2005), UK HPA (2007), and U.S. EPA (2003) have reviewed hematological effects observed in animals. Although rats and mice do not appear to exhibit hemolytic effects, dogs orally exposed to naphthalene appeared to develop both hemolytic anemia and reticulocytosis (ATSDR, 2005; UK HPA, 2007; U.S. EPA, 2003).

Multiple reviews noted that human exposure to naphthalene by oral and inhalation is associated with intravascular haemolysis, which can cause anemia, leukocytosis, hematuria, and hemolytic anemia (IPCS, 2001; ATSDR, 2005; UK HPA, 2007; U.S. EPA, 2008). Hemolytic anemia, being the most common hematological effect seen in individuals exposed to naphthalene, is characterized by lowered hemoglobin, hematocrit, and erythrocyte values, elevated reticulocyte counts, reticulocytosis, Heinz bodies, elevated serum bilirubin, and fragmentation of erythrocytes (ATSDR, 2005). In severe cases, kernicterus was found to accompany hemolytic anemia (ECA, 2003). Observations of aplastic anemia in humans following ingestion or inhalation of naphthalene have also been noted (IPCS, 2001; ATSDR, 2005; UK HPA, 2007; U.S. EPA, 2000). More severe reactions, including the observation of Heinz body formation, hemoglobinuria and mild methemoglobinemia, have also been noted (ECA 2003). ATSDR (2005) noted reports of hemolytic anemia associated with dermal exposure to naphthalene. CalEPA (2004) noted that hematological effects following naphthalene exposure are frequently seen in neonates and infants, who appear to be more susceptible to hematological crises than adults due to their lower capacity for methemoglobin reduction. ATSDR (2005), ECA (2003), and UK HPA (2007) have also reviewed data identifying glucose-6-phosphate dehydrogenase deficiency as an additional factor that increases a subject's sensitivity to chemically-induced hemolysis.

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in hematological effects in humans?

Immunological effects

Immunologic effects in humans and animals were reviewed by U.S. EPA (1998, 2003) and ECA (2003). U.S. EPA (2003) noted a report documenting an enlarged spleen in one human subject following ingestion of naphthalene; however, it was suggested that this effect was associated with chemically-induced hemolysis. Reviews of immunological effects in rodent species orally exposed to naphthalene reported thymic lymphoid depletion and decreases in spleen weight (ECA, 2003; U.S. EPA, 1998, 2003).

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in immunological effects in humans?

Hepatic effects

ATSDR (2005) and ECA (2003) have summarized case studies of humans who experienced jaundice following exposure to naphthalene, although it was noted that this may be attributed to hemolytic anemia. Additionally, elevated levels of hepatic enzymes and liver enlargement were observed following oral exposure to naphthalene as reviewed by ATSDR (2005). Liver disease was seen in human subjects occupationally exposed to vapor-form naphthalene (IPCS, 2001), ATSDR (2005), U.S. EPA (1998), IPCS (2001) and ECA (2003) reviewed studies that observed hepatic effects, including evidence of liver damage and decreases in liver weight, in rodent species.

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in hepatic effects in humans?

Renal effects

Renal effects in humans and animals were reviewed by ECA (2003), ATSDR (2005), U.S. EPA (1998), and BCL (1980). ECA (2003) and ATSDR (2005) summarized reports of renal disease and kidney damage in humans after oral and inhalation exposure to naphthalene. Increases in kidney weight were documented following ingestion of naphthalene in rodent species (IPCS, 2001), as was kidney damage (BCL, 1980; U.S. EPA, 1998). No renal effects were seen in mice following a two year inhalation study (ATSDR, 2005).

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in renal effects in humans?

Musculoskeletal effects

ATSDR (2005) reviewed the comprehensive chronic inhalation bioassays conducted by NTP (1992, 2000) in mice and rats that included evaluation of musculoskeletal effects. However, neither NTP (1992, 2000) nor any of the available reviews by government health agencies and international health organizations noted compound-related musculoskeletal health effects from naphthalene exposure. This endpoint will not be evaluated further unless evidence of musculoskeletal effects are identified in the comprehensive literature search.

Neurological effects

Neurological effects in humans and animals were noted in reviews by IPCS (2001), ATSDR (2005), and ECA (2003). Studies following inhalation exposure to naphthalene in humans document fatigue, headache, malaise, confusion, and listlessness (IPCS, 2001; ATSDR, 2005). In addition to those effects, altered sensorium, lethargy, vertigo, muscle twitching, convulsions, decreased responses to painful stimuli, and coma were reported after ingestion of naphthalene (ATSDR, 2005; IPCS, 2001). Some neurological effects, including kernicterus in children and infants, have been suggested to be secondary to hemolytic effects of naphthalene (ATSDR, 2005). Effects in rodents, including decreases in absolute brain or accumulation of ammonia, have been noted by ECA (2003).

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in neurological effects in humans?

Ocular effects

Ocular effects were noted in humans and animals in reviews by CDC (2010), UK HPA (2007), ECA (2003), ATSDR (2005), IPCS (2001), IARC (2002), and U.S. EPA (2008). IARC (2002), ECA (2003), UK HPA (2007), CDC (2010), and U.S. EPA (2003 & 2008) have summarized data on occupational exposure resulting in cataract formation, retinal hemorrhaging, chorioretinitis, eye irritation, lens opacity, decreased vision, corneal damage, and optical neuritis. Animal studies reviewed by U.S. EPA (2003, 2008), UK HPA (2007), ECA (2003), IPCS (2001), and IARC (2002) in rats, mice, and rabbits have shown similar effects as those exhibited in humans, specifically cataract formation, lens opacity, irritation, focal lesions, and increased ocular density. Some of these

reviews have noted other ocular effects in animal models, such as ocular discharge, retinal degeneration, yellowing of eye fluids, conjunctival reddening and swelling, and retinal damage (U.S. EPA 2003, 2008; ATSDR, 2005).

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in ocular effects in humans?

Reproductive/Developmental Effects

IARC (2002), ATSDR (2005), and ECA (2003) have summarized reproductive and developmental toxicity studies via the oral or inhalation route. Several studies have documented hemolytic anemia as the primary adverse effect in newborns following gestational exposure although sensorineural hearing loss and severe neonatal jaundice have also been reported (IARC, 2002; ATSDR, 2005; ECA, 2003. It was noted that in some of these cases the child or mother was glucose-6-phosphate dehydrogenase deficient (IARC, 2002; ECA, 2003). IARC (2002), ATSDR (2005), IRIS (1998), and U.S. EPA (2003, 2008) reviewed adverse effects in animal developmental and reproductive studies that included reductions in the number of live pups per litter and decreased maternal and fetal body weight in rodent species following oral exposure. IPCS (2001) reviewed studies that found accelerated onset of spermatogenesis in male offspring in rats orally administered naphthalene and reproductive abnormalities in cattle, pigs, and sheep exposed to PCNs. An increased percentage of adversely affected implants per litter and increased incidence of visceral malformations, especially enlarged ventricles of the brain, were reported in rats by IARC (2002). IARC (2002) also reported a study that documented lowered glutathione levels in the testes and epididymides in rats intraperitoneally injected with naphthalene. U.S. EPA (2003) reviewed a study that documented increases in delayed cranial ossification and heart development in rat fetuses following gestational exposure to naphthalene. ATSDR (2005) and U.S. EPA (2003) summarized studies in rabbits that reported increases in fused sternebrae in female pups, increased maternal mortality, increased rates of abortions, and other signs of maternal toxicity that included lethargy and bloody vaginal discharge.

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in developmental effects in humans?

Respiratory effects

EPA's 1998 IRIS assessment derived a reference concentration (RfC) for noncancer effects based on nasal effects (hyperplasia and metaplasia in respiratory and olfactory epithelium) in a chronic mouse inhalation study (NTP, 1992). Since that time, NTP (2000) has conducted a

comprehensive chronic inhalation bioassay in rats. Respiratory effects in humans and animals were summarized and reported by IARC (2002), ATSDR (2005), CalEPA (2004), ECA (2003), UK HPA (2007), and U.S. EPA (2003, 2008). ATSDR (2005) and U.S. EPA (2008) reviewed reports of rhinopharyngolaryngitis observed in humans exposed to naphthalene via inhalation. Inhalation and oral exposure reportedly also produced hypoxia or pulmonary edema in humans, although these respiratory effects were stated as being secondary to hemolysis. Reports summarized by NTP (1992, 2000) illustrated pulmonary necrosis and necrosis of bronchial epithelial cells following intraperitoneal (ip) injection in mice. IARC (2002) evaluated studies done in mice, rats, and hamsters that documented swelling, vacuolization, exfoliation, and/ or necrosis of tracheobronchial epithelium following i.p. injection of naphthalene. Additionally, IARC (2002) reviewed studies done in mice observing pulmonary neuroendocrine-cell hyperplasia and injury to distal and proximal conductivity airways. Reviews of respiratory effects in rodent species orally exposed to naphthalene noted increase in lung weight, lung injury, slow respiration, periods of apnea, and necrosis and exfoliation in nasal olfactory epithelium (UK HPA, 2007; ECA, 2003). ECA (2003) also reviewed studies showing vacuolation in lobar bronchus cells and necrosis of olfactory epithelium in hamsters. Several animal studies observing respiratory effects following inhalation exposure have been summarized by IARC (2002), ATSDR (2005), CalEPA (2004), ECA (2003), UK HPA (2007), and U.S. EPA (2003, 2008). The nose and lungs are commonly reported to be the most sensitive toxicity targets in rodent species. Nonneoplastic lesions of the nose included chronic inflammation, metaplasia of the olfactory epithelium, atypical hyperplasia, atrophy, hyaline degeneration of the olfactory epithelium, hyperplasia of the respiratory epithelium of the nose, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium, glandular hyperplasia, and loss of Bowmans' glands as reported by IARC (2002), ATSDR (2005), CalEPA (2004), ECA (2003), UK HPA (2007), and U.S. EPA (2003, 2008). IARC (2002), CalEPA (2004), ECA (2003), UK HPA (2007) and U.S. EPA (2003, 2008) reviewed reports of lung injury including chronic inflammation, injury to the proximal and distal conducting airways, damage to ciliated and Clara cells of bronchial epithelium, alveolar epithelial hyperplasia, interstitial fibrosis, necrosis of Clara cells in proximal airways, and the formation of granuloma. No reviews identified studies of respiratory effects in humans from oral or dermal exposure to naphthalene.

Systematic review question: Integrating the human, animal, and mechanistic evidence, what is the potential for naphthalene exposure to result in respiratory tract effects in humans?

3.4. Key Issues

Toxicokinetics of Naphthalene

ATSDR (2005), IARC (2002), Cal EPA (2004) have reviewed the absorption, distribution, metabolism and excretion (ADME) of naphthalene. Briefly, exposure to naphthalene occurs mainly through inhalation, oral and dermal routes. Naphthalene is readily absorbed into the systemic circulation following exposure by any of these routes. Absorbed naphthalene and its metabolites are distributed by the blood throughout the body. Naphthalene is rapidly metabolized in a number of tissues to a wide array of metabolites, including epoxide and quinone intermediates that may react with cellular macromolecules such as proteins and DNA. Two major metabolic pathways have been identified: one dependent on cytochrome P450 (CYP) and another involving glutathione conjugation. Multiple metabolites have been identified in urine and blood of workers exposed to naphthalene and in experimental animal studies.

Studies are available comparing the rate and extent of metabolism of naphthalene in different tissues and in different animal species; and these are important for evaluating differences across tissues and across species in naphthalene-related toxicity. For instance, lung specific expression patterns of cytochrome P450 enzymes, particularly CYP2F, have been investigated as potential explanations for differences in respiratory tract toxicity and cancer. In human tissues (based on in vitro metabolism studies of liver microsomes) other enzymes may be involved. Overall, inter- and intraspecies differences in metabolism could impact the extrapolation of rodent bioassay data to humans and the identification of potential susceptible subpopulations.

Based on the available data, some key issues EPA will evaluate regarding the toxicokinetics of naphthalene include:

- The chemical form (naphthalene or a metabolite) responsible for the various toxicities reported.
- Available information on inter- and/or intraspecies differences in the toxicokinetics relevant to naphthalene or its metabolites.
- The availability, evaluation, and further development (within assessment resources and time constraints) of PBPK models for reliable route-to-route, interspecies, and/or intraspecies extrapolation.

Mode of Action for Respiratory Tract Tumors

As discussed previously, several reviews have discussed mechanistic studies investigating the role of mutagenicity and/or genotoxicity in inducing respiratory tract tumors in rodents (IARC, 2002; ATSDR, 2005). For instance, the potential for mutagenicity and/or genotoxicity of

naphthalene metabolites such as 1,2- and 1,4-naphthaquinone has been noted. Others have suggested a dual mode of action involving mutation and sustained cytotoxicity-induced, regenerative cell proliferation and hyperplasia for naphthalene-induced nasal tumors in rats (Bogen et al., 2008). Based on EPA's Cancer Guidelines and Supplemental Guidance (U.S. EPA, 2005a,b), the current understanding of biology of cancer indicates that mutagenic chemicals are expected to exhibit a greater effect in early life exposure versus later life exposure. If a determination were made that a mutagenic mode of action were operative for naphthalene-induced respiratory tract tumors, then Age-Dependent Adjustment Factors would be applied to the cancer toxicity values to account for early-life susceptibility. Therefore, as for all IRIS assessments, evaluation of a potential mutagenic mode of action for naphthalene-induced rodent respiratory tract tumors has important implications.

Several investigators have evaluated other potential modes of action for chemically-induced mouse lung tumors such as those observed from naphthalene exposure (NTP, 1992; Bogen et al., 2008; Cruzan, 2009, Rhomberg et al., 2010). In addition, mode of action workshops (see below) and a peer-consultation workshop[1] have been conducted previously on the topic of mode of action of naphthalene-induced carcinogenicity. Because of the importance of evaluating all existing information on this topic, recently EPA conducted a "State-of-the-science workshop on chemically-induced mouse lung tumors: applications to human health assessment" on January 7-8, 2014, RTP, NC. The focus of this workshop was to discuss the available data and interpretation of results from studies of mouse bronchiolar-alveolar adenomas and carcinomas (lung tumors) following exposure to naphthalene, styrene or ethylbenzene, and the relevance of such tumors in mice to human cancer risk. Several panels of scientists discussed the available studies of human cancer epidemiology and pathophysiology, comparative pathology, biological mechanisms and evidence for cellular, genetic and molecular toxicology. The panelists included experts from academia, industry, government and nongovernmental organizations. The aim of the workshop was not to have the panel reach consensus on any particular topic, but to foster discussion across the different areas of expertise and viewpoints so that both EPA and the public could become better informed of the issues. Workshop materials can be obtained at http://www.epa.gov/iris/irisworkshops/mltw/. The workshop materials and topics discussed during this meeting will be used to inform the development of the naphthalene assessment. In addition, another similar workshop was conducted recently by the Styrene Information and Research Center to highlight mode of action research related to mouse lung tumors and human relevance (http://styrene.org/2013-mode-of-action-workshop).

[1] http://www.epa.gov/EPA-MEETINGS/2005/March/Day-08/m4472.htm

Toxicogenomic data are available on naphthalene that might inform naphthalene toxicokinetics and/or toxicodynamics (Thomas et al., 2009, 2011). As discussed in U.S. EPA (2009), gene and protein expression, and other transcriptional and translational data can provide important information on absorption, distribution, metabolism, and excretion (ADME), mechanism of action, and human relevance information in the weight of evidence analysis. Specifically for naphthalene, types and levels of gene expression in the toxicogenomics data may inform species and gender differences in tissues such as nose and lung. Lastly, evaluations of the available mode of action information have recently been conducted, including a hypothesis-based weight-of-evidence analysis that was used as a tool for evaluating strengths and uncertainties associated with the mode of action data for naphthalene (Rhomberg et al., 2010, Piccirillo et al., 2012)

Based on the available data, the key issues for naphthalene mode of action include (but are not limited to):

- Identification of key events leading to the development of tumors in rats (nose) and mice (lung)
- Role of reactive metabolites (epoxides, quinones and/or ROS) in naphthalene-induced tumors
- The potential role of genotoxicity and/or mutagenicity in the mode of action of naphthalene-induced tumors, including site-specific DNA damage
- Role of cytotoxicity and sustained regenerative cell proliferation in the mode of action of naphthalene-induced tumors
- Role of cytochrome P-450 enzymes in the development of tumors
- Exceedance of detoxification capacity (e.g., GSH depletion) and the potential for covalent modification of key proteins
- Role of species differences observed in the development of naphthalene-induced tumors. For example,
    - increased incidence of nasal tumors following inhalation exposure in rats but not mice, whereas both rats and mice exhibit nasal cytotoxicity and degeneration of the nasal olfactory epithelium
    - increased incidence of nonneoplastic lung lesions (e.g. clara cell necrosis) and lung tumors in mice but not in rats
- Species differences in enzyme activities (e.g., epoxide hydrolase, aldo-keto reductases) and naphthalene toxicity

Based on the U.S. EPA (2005) Cancer Guidelines framework for evaluation of mode of action, the following will be considered after a systematic review:

- Identification of mode of action hypotheses to be considered in the assessment
- Identification of the key events for each hypothesized mode of action
- Evaluation of experimental support for each hypothesized mode of action

- Sufficient support for each hypothesized mode of action in test animals
- Human relevance of hypothesized modes of action
- Populations or lifestages that are particularly susceptible to each hypothesized mode of action

Human Susceptibility

Human susceptibility has already been discussed above in the context of toxicokinetics and mode of action, but in addition, several reviews have identified deficiency in glucose-6-phosphate dehydrogenase (G6-PD) as a potential susceptibility factor for the toxic effects of naphthalene (IARC, 2002; ATSDR 2005; ECA 2003; UK HPA 2007; U.S. EPA 2008). Therefore, an additional key issue regarding susceptibility is to identify the end points (and related evidence) for which G6-PD deficiency is associated with increased susceptibility to naphthalene toxicity.

CalEPA (2004) noted that hematological effects following naphthalene exposure are frequently seen in neonates and infants, who are seemingly more susceptible to hematological crises than adults due to their lower capacity for methemoglobin reduction.

REFERENCES

Abdo KM, Grumbein S, Chou BJ, Herbert R. (2001) Toxicity and carcinogenicity study in F344 rats following 2 years of whole-body exposure to naphthalene vapors. Inhalation Toxicology 13:931-950.

Adkins B Jr., Van Stee EW, Simmons, JE, Eustis SL. (1986) Oncogenic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 17(2-3):311-322.

ATSDR (Agency for Toxic Substances and Disease Registry), (2005), Toxicological profile for naphthalene, 1-methylnaphthalene, and 2-methylnaphthalene, http://www.atsdr.cdc.gov/toxprofiles/tp67.pdf

ATSDR (Agency for Toxic Substance and Disease Registry) (2013) Addendum to Toxicological profile for jet fuels (JP-5 and JP-9). http://www.atsdr.cdc.gov/toxprofiles/jet_fuels_addendum.pdf

BCL (Battelle's Columbus Laboratories), (1980) Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle Laboratories under NTP Subcontract No. 76-34-106002.

Bogen KT, (2008) An adjustment factor for mode-of-action uncertainty with dual-mode carcinogens: the case of naphthalene-induced nasal tumors in rats. Risk Anal. 28:1033-51.

CalEPA (California EPA), (2004) Air Toxic hot spots: Adoption of a unit risk value for naphthalene, http://www.oehha.org/air/hot_spots/naphth.html, http://www.oehha.org/air/hot_spots/pdf/naphth080304.pdf

CDC (Centers for Disease Control and Prevention), National Institute for Occupational Safety and Health (NIOSH), (2010) Pocket Guide to Chemical Hazards – Naphthalene. http://www.cdc.gov/niosh/npg/npgd0439.html

Cruzan G, Bus J, Banton M, Gingell R, Carlson G. (2009) Mouse specific lung tumors from CYP2F2-mediated cytotoxic metabolism: anendpoint/toxic response where data from multiple chemicals converge to support a mode of action. Regul Toxicol Pharmacol. 55:205-18.

ECA (European Chemicals Agency), (2003) European Union Risk Assessment Report – naphthalene. http://echa.europa.eu/documents/10162/4c955673-9744-4d1c-a812- 2bf97863906a, EINECS no 202-049-5

Government of Canada, Environment Canada, Health Canada, (2008) Screening Assessment for the Challenge Naphthalene, CAS No. 91-20-3. http://www.ec.gc.ca/eseees/default.asp?lang=En&n=F212515C-1

HSDB (2005). Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB; accessed May 14, 2014.

IARC (International Agency for Research on Cancer), (2002) IARC Monographs on the Evaluation of Carcinogenic risks to humans: Some traditional herbal medicines, some mycotoxins, naphthalene and styrene, Vol 82, Lyon, France. Available online: http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-8.pdf

IPCS (International Programme of Chemical Safety), (2001) Concise International Chemical Assessment Document 34, Chlorinated Naphthalenes, http://www.who.int/ipcs/publications/cicad/en/cicad34.pdf

New Jersey Department of Environmental Protection (NJDEP), 2013, Site Remediation Program – Vapor intrusion – Naphthalene, http://www.nj.gov/dep/srp/guidance/vaporintrusion/

National Toxicology Program (NTP), 2011, NTP 12th Report on Carcinogens: Naphthalene, http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/naphthalene.pdf

NRC (National Research Council), (2009) Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press. http://www.nap.edu/openbook.php?record_id=12209

NRC (2014) Review of EPA's Integrated Risk Information System (IRIS) Process: National Research Council. The National Academies Press http://www.nap.edu/openbook.php?record_id=18764.

NTP (National Toxicology Program), (1991) Developmental toxicity of naphthalene (CAS No. 91-20-3) administered by gavage to Sprague-Dawley (CD) rats on gestational days 6 through 15. Final study report and appendix. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. TER91006.

NTP (1992) Toxicology and carcinogenesis studies of naphthalene in B6C3F1 mice (inhalation studies). Technical Report Series No. 410. NIH Publication No. 92-3141.

NTP (2000) Toxicology and carcinogenesis studies of naphthalene (CASD no. 91-20-3) in F344/N rats (inhalation studies). National Toxicology Program. U.S. Department of Health and Human Services, National Institutes of Health, Rockville, MD. Technical report series no. 500.

NTP (2011). Report on carcinogens. 12th ed. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. Available online: http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/naphthalene.pdf

Piccirillo VJ, Bird MG, Lewis RJ, Bover WJ (2012). Preliminary Evaluation of the Human Relevancy of Respiratory Tumors Observed in Rodents Exposed to Naphthalene. Regulatory Toxicology and Pharmacology. 62: 3, 433-440.

Rhomberg LR, Bailer LA, Goodman JE, (2010). Hypothesis-based weight of evidence – a tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a potential carcinogenic mode of action – Naphthalene as an example. Critical Reviews in Toxicology. 40:8, 671-696.

UK HPA (U.K. Health Protection Agency), (2007) Naphthalene Toxicological review. http://www.hpa.org.uk/webc/hpawebfile/hpaweb_c/1203084377981

U.S. EPA (U.S. Environmental Protection Agency), (1998) Toxicological Review of Naphthalene. http://www.epa.gov/iris/toxreviews/0436tr.pdf

U.S. EPA (2003). Health Effects Support Document for Naphthalene. U.S. Environmental Protection Agency, Office of Water. Available online: www.epa.gov/safewater/ccl/pdf/naphthalene.pdf

U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Washington, DC, EPA/630/P-03/001F, 2005.

U.S. EPA (2005b) Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. U.S. Environmental Protection Agency, Washington, DC, EPA/630/R-03/003F, 2005.

U.S. EPA (2008) Office of Prevention, Pesticides and Toxic Substances. Reregistration Eligibility Decision for Naphthalene, EPA 738-R-07-010 http://www.epa.gov/pesticides/reregistration/REDs/naphthalene-red.pdf

U.S. EPA (2009) An Approach to Using Toxicogenomic Data in U.S. EPA Human Health Risk Assessments: A Dibutyl Phthalate Case Study (Final Report). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/028F, 2009.

U.S. EPA (2011). National-scale Air Toxics Assessment. U.S Environmental Protection Agency. Office of Air and Radiation. http://www.epa.gov/ttn/atw/nata2005/index.html Accessed May 22, 2014

U.S. EPA (2012). Inert Use Information. U.S. Environmental Protection Agency. Office ofPesticide Program, http://iaspub.epa.gov/apex/pesticides/f?p=101:1: Accessed May 22, 2014

U.S. EPA (2013a). Chemical Data Reporting. U.S. Environmental Protection Agency. Office ofChemical Safety and Pollution Prevention. http://www.epa.gov/oppt/cdr/index.html Accessed May 22, 2014

U.S. EPA (2013b). Toxic Release Inventory. U.S. Environmental Protection Agency. Toxic Release Inventory Program. http://iaspub.epa.gov/triexplorer/tri_release.chemical Accessed May 22, 2014

U.S. EPA (2014). The Superfund Enterprise Management System (SEMS). U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. http://www.epa.gov/superfund/sites/siteinfo.htm Accessed June 27, 2014

Thomas RS, Bao W, Chu T, Bessarabova, Nikolskaya T, Nikolskya Y, Andersen ME, Wolfinger RD. (2009) Use of Short-term Transcriptional Profiles to Assess the Long-term Cancer-Related Safety of Environmental and Industrial Chemicals. Toxicological Sciences 112(2), 311–321.

Thomas RS, Clewell RJ, Allen BC, Wesselkamper SC, Wang NC, Lambert JC, Hess-Wilson JK, Zhao QJ, Andersen ME. (2011) Application of Transcriptional Benchmark Dose Values In Quantitative Cancer and Noncancer Risk Assessment. Toxicological Sciences 120(1), 194–205.