Report on Carcinogens (RoC) Concept: Cumene

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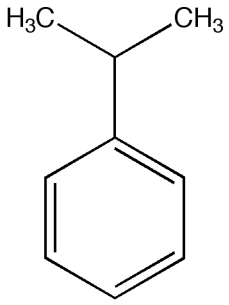

1. Rationale

Cumene (CASRN 98-82-8, isopropylbenzene) is an alkylated benzene found in fossil fuels, such as blended gasoline and kerosene, and products of incomplete combustion (IARC 2012). It has a gasoline-like odor and can exist as a vapor in ambient air. Cumene is structurally similar to benzene, toluene, styrene, xylene, and ethylbenzene. It is a high production volume chemical in the United States with the majority of its use in the synthesis of acetone and phenol. Cumene has been selected as a candidate substance[1] for the RoC based on widespread current U.S. exposure and an adequate database of cancer studies. Exposure to cumene comes from the use of fossil fuels, solvents, and cigarette smoke. The National Toxicology Program (NTP) completed a series of cumene inhalation toxicology and carcinogenesis studies (NTP 2009) and disposition and metabolism studies in rats and mice (Chen *et al*. 2011). Data on cumene were recently reviewed by the International Agency for Research on Cancer (IARC) which classified cumene as possibly carcinogenic to humans (Group 2B) (Grosse *et al.* 2011).

In January 2012, the NTP solicited information on cumene and other nominated substances (77FR2728, see *http://ntp.niehs.nih.gov/go/rocnom* for comments). No public comments were received on cumene.

The ORoC presented the draft concept document for cumene to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting[2] which provided an

[1]The scientific evaluation of cumene will be captured in the draft RoC monograph, which consists of a cancer evaluation component and draft substance profile (for more details see *http://ntp.niehs.nih.gov/go/rocprocess*). The proposed approach, delineated in this concept document, for preparing the cancer evaluation of the draft monograph is tailored to the nature, extent, and complexity of the scientific information on this chemical. This concept document also discusses information supporting the rationale and the proposed approach including (1) data on human exposure, (2) an overview of the nature and extent of the scientific information for evaluating carcinogenicity in humans and/or animals, (3) scientific issues and questions relevant to the evaluation of cumene carcinogenicity, (4) the proposed approach for conducting the cancer evaluation, including the literature search strategy, the scope and focus of the monograph, and the approaches for obtaining scientific and public input to address the key scientific questions and issues.

[2]Information on the NTP BSC June 21-22, 2012 meeting is available at *http://ntp.niehs.nih.gov/go/9741*.

opportunity for written and oral public comments. No public comments were received. The NTP Director approved cumene as a candidate substance and this concept was finalized based on review of the BSC's comments. The concept may be revised again if new information on cumene would lead to a change in the proposed approach for conducting the cancer evaluation.

2. Overview of Data Related to Human Exposure

Cumene is found in crude oil, coal tars, and other fossil fuels. People are exposed primarily through inhalation of ambient air near sources that contain and use fossil fuels as well as from workplace exposures through production/use of cumene in the chemical industry. The primary route of exposure to cumene is inhalation, although dermal and oral exposure can also occur. Cumene is released into the environment as a result of cumene production, processing, and transport, petroleum refining and the evaporation and combustion of petroleum products, the transportation and distribution of motor fuel, evaporation from gas stations, and the use of a variety of products containing cumene. The European Union estimates that daily release rates into ambient air from production/use are similar to the release rates from disperse sources (e.g., motor exhaust); however, gasoline usage is a more ubiquitous source of environmental exposure. In Los Angeles, California, 23,000 kg (53,600 lbs) of cumene per day (for 2 days) were released into the air in 1987 (Harley and Cass 1994). Cumene can also be released into the environment from oil spills; over 180 spill incidents involving cumene have been reported in the United States from 1990 to the present (NRC 2012). The European Union estimates that the greatest source of environmental exposure to humans is from contaminated air (EC 2001). People could also be exposed from cigarette smoke or ingestion of food, either from environmental contamination or from biogenic processes. Cumene has been detected in ambient air, effluent or wastewater, ground water, surface water, and sediments; however, contamination in drinking water is uncommon.

The primary use of cumene is in the production of acetone and phenol. Occupational exposure can also occur in processes such as rubber vulcanization, solvent and paint manufacture, and in the pharmaceutical and textile industries (HSDB 2005). Contact with cumene might occur in activities related to collection of samples for analysis, loading of tanks, and cleaning or maintenance of containment areas (EC 2001). Occupational exposure might also occur from exposure to gasoline vapors, and some of the highest levels of cumene have been reported during car repair work (EC 2001). The recommended exposure limit and permissible exposure limit (10-hour time-weighted average) for cumene in air in the workplace are each 50 ppm [skin] (245 mg/m^3) (NIOSH 2010). The [skin] notation indicates that there is potential for dermal absorption.

Cumene is a high production volume chemical with U.S. production of > 1 billion pounds per year. In 2006, at least eight companies produced cumene in the United States (EPA 2006). U.S. EPA Toxics Release Inventory (TRI) total reported on- and off-site release of cumene was approximately 1,011,000 pounds from more than 300 facilities in 2010 (TRI 2012). In 2011, the United States exported over 127 million pounds (57.7 million kilograms) of cumene and imported 2.29 billion pounds (1.04 billion kilograms) (USITC 2011).

3. Overview of the Scientific Information Regarding Carcinogenicity

3.1. Human cancer studies

No epidemiological studies have been identified that examined the relationship between human cancer and exposure specifically to cumene.

3.2. Cancer studies in experimental animals

One cancer study was identified from the peer-reviewed literature. Cumene was tested for carcinogenicity in a 2-year inhalation study conducted by the NTP in both sexes of mice and rats (NTP 2009). NTP identified treatment-related effects. Male B6C3F_1 mice developed alveolar/bronchiolar adenomas and carcinomas (lung). Hemangiosarcomas (spleen and other organs) and thyroid gland adenomas may have been related to cumene exposure. Female mice developed alveolar/bronchiolar carcinomas (lung). Hepatocellular adenoma or carcinoma, combined (liver) were considered to be related to exposure to cumene. Male F344/N rats developed respiratory epithelial adenomas (nose), and renal tubule adenomas or carcinomas, combined (kidney). Interstitial-cell adenomas of the testes may have been related to cumene exposure. Female rats developed respiratory epithelial adenomas (nose).

3.3. Mechanistic and other relevant data

Studies in rodents demonstrate that cumene is well absorbed following oral, dermal, or inhalation exposure (WHO 1999, NTP 2009). It is readily absorbed in humans exposed by inhalation, metabolized to water-soluble metabolites, and excreted into the urine with no evidence of long-term retention within the body (EPA 1997). Toxicokinetic data are available from metabolism studies in rats and mice (WHO 1999, Chen *et al.* 2011). Cumene is metabolized by P450 oxidation of the alkane group or oxidation of the benzene ring. Sixteen metabolites have been identified, including alpha methyl styrene (AMS) and other metabolites that may be derived from an AMS-oxide intermediate (Chen *et al.* 2011); however, no specific enzymes involved in cumene metabolism have been identified. Cumene has been assayed for genotoxic effects in cultured cells and to a more limited extent in exposed rodents (NTP 2009). Studies have explored mouse lung tumors induced by cumene exposure for mutations in regulatory genes (*K-ras* and *p53*) and for loss of heterozygosity. No genetic toxicology studies in humans have been identified.

Potential mechanisms of carcinogenesis of cumene have been published and include genetic (Hong *et al.* 2008) or epigenetic effects (Wakamatsu *et al.* 2008), formation of tissue-specific cytotoxic metabolites by a cyp2f2-specific mechanism in the mouse lung (Cruzan *et al.* 2009, Chen *et al.* 2011), or species-specific accumulation of α_{2u}-globulin in kidneys of male rats (Cushman *et al.* 1995, Chen *et al.* 2011).

4. Key Scientific Questions and Issues Relevant for the Cancer Evaluation

The key scientific questions concern results of studies in experimental animals and potential mechanisms of carcinogenicity.

- What is the level of evidence (sufficient or not sufficient) for the carcinogenicity of cumene from studies in experimental animals? What are the tissue sites?
- What are the potential modes of action by which cumene may cause cancer? Is there evidence that any mechanism is not relevant to humans?

- What is the level of evidence (strong, moderate, weak or insufficient data) that the renal tumors observed in male rats are caused by an α_{2u}-globulin-associated renal nephropathy mechanism? Are there other potential mechanisms by which cumene could cause renal cancer in male rats?

5. Proposed Approach for Conducting the Cancer Evaluation

5.1. Scope and focus of the draft RoC monograph

The ORoC will prepare the draft RoC monograph on cumene, which will consist of two parts, the cancer evaluation component and the substance profile. The cancer evaluation component of the draft monograph will review and assess the scientific literature, provide a discussion of scientific issues, and assess and integrate the relevant scientific evidence, applying the listing criteria to reach a preliminary RoC listing recommendation[3]. The substance profile of the draft monograph will give the NTP's preliminary listing recommendation and a summary of the key supportive evidence. Details on the methods for writing the draft RoC monograph and topics typically covered in the monograph are outlined in the NTP process for the preparation of the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*). Details of the preliminary literature search strategy including data sources and literature search terms that are consistent with this approach are discussed in Appendix 1.

A complete discussion and assessment of potential modes of action of cumene-induced neoplasia, including metabolic activation, cytotoxicity, genetic-related and epigenetic modes of action will be included in the monograph. The relevance to humans of respiratory, renal, and or other tumors observed in experimental animals will be discussed. A key issue for discussion is the accumulation of α_{2u}-globulin in kidneys of male rats as a species-specific mechanism in the development of renal tumors (see Section 5.2). Set criteria have been developed by IARC and U.S. EPA for assessing α_{2u}-globulin mediated neoplasia in rat kidneys. The draft monograph will apply these criteria to the body of evidence and discuss the relevance of these tumors to humans.

5.2. Proposed approaches for obtaining scientific and public input

Public comments on scientific issues have been requested[4] on cumene at several times prior to the development of the draft RoC monograph, including the request for information on the nomination, and the request for comment on the draft concept. The ORoC will consider this information and experts suggested by the public in drafting the cancer evaluation component of the draft monograph. The ORoC will create a webpage for the candidate substances currently under review. The webpage will typically include the following: (1) RoC documents related to the review of the substance (e.g., concept document, draft RoC monograph), (2) citations for references identified from literature searches, (3) public comments, (4) an input box for the public to provide information (such as new literature) or comment (such as the identification of additional scientific issues), and (5) information on public meetings or listening sessions. The NTP will communicate when new information is added or updated (such as updated literature searches) to the website via the NTP list

[3]A listing recommendation can be not to list, to list as *reasonably anticipated to be a human carcinogen*, or to list as *known to be a human carcinogen*.

[4]Federal Register notice is available at *http://ntp.niehs.nih.gov/go/rocnom*.

serve.[5] Additional scientific issues may be identified during the preparation of the monograph. Future forums (such as a listening session) for receiving public comment on any additional scientific issues may be considered depending on public interest; these would be announced via a *Federal Register* notice, the NTP list serve and the RoC website.

ORoC will consult with appropriate technical advisors, external or internal to the government, with knowledge related to cumene and/or alkylbenzenes. Sources for identifying these advisors include, but are not limited to, peer-reviewed literature databases, and recommendations from the scientific community and the public. Advisors with knowledge in genotoxicity and mechanisms of carcinogenesis will be consulted to help identify relevant literature and scientific issues and to provide critical comments on the ORoC assessment of the mechanistic data.

One of the issues discussed in the cancer evaluation component of the draft monograph is whether the renal tumors observed in male rats are caused by a sex- and species-specific mechanism (α_{2u}-globulin nephropathy). The ORoC will convene a group of NTP scientists with specific expertise on cumene. They will independently review toxicology, renal pathology, and genotoxicity data relevant to cumene exposure in male rats. Toxicological, genotoxicity, or cancer data relevant to this assessment will be provided to the NTP scientists. At the meeting, each expert will independently provide comments related to applying the established IARC criteria (1999) and U.S. EPA (1991) mechanistic criteria to the available data. These individual assessments on the animal cancer data will be used by ORoC staff in drafting the mechanistic section and the overall synthesis of neoplastic findings in experimental animals with the mechanistic data in the draft monograph.

6. Public Release and Peer Review of the Draft Monograph

Once completed, the draft RoC monograph will undergo interagency review, and the NTP will release the draft monograph for public comment and public peer review. The NTP will convene an external peer-review scientific panel[6] to review the draft RoC monograph on cumene in a public forum (*http://ntp.niehs.nih.gov/go/rocprocess*). The panel will have expertise in disciplines relevant to the cancer evaluation of cumene such as toxicology and cancer assessment in experimental animals, inhalation toxicology, pathology, general metabolism/tissue-specific metabolism of alkylbenzenes, genotoxicity, and mechanisms of carcinogenesis. The NTP will also set aside time at the peer-review meeting for a discussion of scientific issues raised in the public comments.

[5]Persons can subscribe to the NTP list serve free-of-charge at *http://ntp.niehs.nih.gov/go/getnews*.

[6]NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166*.

References

1. Bakke OM, Scheline RR. 1970. Hydroxylation of aromatic hydrocarbons in the rat. *Toxicol Appl Pharmacol* 16(3): 691-700.
2. NIOSH. 2010. *NIOSH Pocket Guide to Chemical Hazards*. Centers for Disease control and Prevention. Updated on 11/18/10. *http://www.cdc.gov/niosh/npg/npgd0159.html*. Last accessed: 5/7/12.
3. Chen LJ, Wegerski CJ, Kramer DJ, Thomas LA, McDonald JD, Dix KJ, Sanders JM. 2011. Disposition and metabolism of cumene in F344 rats and B6C3F1 mice. *Drug Metab Dispos* 39(3): 498-509.
4. Cruzan G, Bus J, Banton M, Gingell R, Carlson G. 2009. Mouse specific lung tumors from CYP2F2-mediated cytotoxic metabolism: An endpoint/toxic response where data from multiple chemicals converge to support a mode of action. *Regul Toxicol Pharm* 55(2): 205-218.
5. Cushman JR, Norris JC, Dodd DE, Darmer KI, Morris CR. 1995. Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. *J Am Coll Toxicol* 14(2): 129-147.
6. EC. 2001. *European Union Risk Assessment Report: Cumene*. EUR 19726 EN. Luxembourg: European Commission. 95 pp.
7. EPA. 1991. *Alpha $_{2u}$-Globulin: Association with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat.* EPA/625/3-91/019F. Washington, D.C.: U.S. Environmental Protection Agency. 132 pp.
8. EPA. 1997. *Toxicological Review of Cumene (CAS No. 98-82-8)*. In Support of Summary Information on the Integrated Risk Information System. Washington, D.C.: U.S. Environmental Protection Agency. 35 pp.
9. EPA. 2006. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. *http://cfpub.epa.gov/iursearch/index.cfm* and search on CAS number.
10. Grosse Y, Baan R, Secretan-Lauby B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Islami F, Galichet L, Straif K. 2011. Carcinogenicity of chemicals in industrial and consumer products, food contaminants and flavourings, and water chlorination byproducts. *Lancet* 12: 328-329.
11. Harley RA, Cass GR. 1994. Modeling the concentrations of gas-phase toxic organic air pollutants: direct emissions and atmospheric formation. *Environ Sci Technol* 28(1): 88-98.
12. Henne KR, Fisher MB, Iyer KR, Lang DH, Trager WF, Rettie AE. 2001. Active site characteristics of CYP4B1 probed with aromatic ligands. *Biochemistry* 40(29): 8597-8605.
13. Hong HH, Ton TV, Kim Y, Wakamatsu N, Clayton NP, Chan PC, Sills RC, Lahousse SA. 2008. Genetic alterations in K-ras and p53 cancer genes in lung neoplasms from B6C3F1 mice exposed to cumene. *Toxicol Pathol* 36(5): 720-726.
14. HSDB. 2005. Hazardous Substances Data Bank. National Library of Medicine. Updated on 6/24/05. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB and search on CAS number or compound name. Last accessed: 11/28/11.
15. IARC. 1999. *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis,* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 147, Lyon, France: International Agency for Research on Cancer. pp. 1-14.
16. IARC. 2012. *A Review of Human Carcinogens: Some Chemicals in Industrial and Consumer Products. Food Contaminants and Flavourings, and Water Chlorination by-products. Cumene.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 101, Lyon, France: International Agency for Research on Cancer. pp. 1-24.

17. Ishida T, Matsumoto T. 1992. Enantioselective metabolism of cumene. *Xenobiotica* 22(11): 1291-1298.
18. NRC. 2012. National Response Center Database. United States Coast Guard. *http://www.nrc.uscg.mil/foia.html*. Last accessed: 3/15/12.
19. NTP. 2009. *Toxicology and Carcinogenesis Studies of Cumene (CAS No. 98-82-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies)*. NTP TR 542, NIH Publication No. 09-5885. Research Triangle Park, NC: National Toxicology Program. 206 pp.
20. Robinson D, Smith JN, Williams RT. 1955. Studies in detoxication. 60. The metabolism of alkylbenzenes: isopropylbenzene (cumene) and derivatives of hydratropic acid. *Biochem J* 59(1): 153-159.
21. TRI. 2012. TRI Explorer Chemical Report. U.S. Environmental Protection Agency. *http://www.epa.gov/triexplorer* and select Cumene. Last accessed: 3/7/12.
22. USITC. 2011. USITC Interactive Tariff and Trade Dataweb. United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2902700000. Last accessed: 4/13/11.
23. Wakamatsu N, Collins JB, Parker JS, Tessema M, Clayton NP, Ton TV, Hong HH, Belinsky S, Devereux TR, Sills RC, Lahousse SA. 2008. Gene expression studies demonstrate that the K-ras/Erk MAP kinase signal transduction pathway and other novel pathways contribute to the pathogenesis of cumene-induced lung tumors. *Toxicol Pathol* 36(5): 743-752.
24. WHO. 1999. *Concise International Chemical Assessment Document 18: Cumene*. Geneva, Switzerland: World Health Organization. 32 pp.

Appendix 1

Preliminary Literature Search Strategy: Cumene

This document identifies the data sources, search terms and preliminary search strategies for identifying literature for the draft monograph on cumene. The literature search will be updated approximately every three months, and prior to submitting the draft monograph for interagency review. Additional literature searches will be conducted as needed to identify information to address scientific issues that arise during the review. Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature are conducted, with initial reviews based on titles and abstracts only, and later reviews based on full-text.

1. Data Sources

Identification of synonyms and metabolites for cumene (CASRN 98-82-8)

- *Synonyms*- National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Bank)
- *Metabolites*- Robinson *et al.* (1955), Bakke and Scheline (1970), Ishida and Matsumoto (1992), Henne *et al.* (2001)

Citation databases (searches titles, abstracts, and key words)

- PubMed
- Web of Science
- Scopus

Additional data sources:

- Authoritative reviews or general sources for exposure and other information (e.g., Toxnet; U.S. Government agencies websites, publications and databases; International Agency for Research on Cancer)
- Citations in authoritative reviews or in primary references located by literature search
- QUOSA library of occupational case-control studies (full text search for cumene and RN: 98-82-8)

Data sources: α_{2u}-globulin-associated renal nephropathy

- IARC Scientific Publications No. 147, Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis (1999).
- U.S. EPA, Alpha$_{2u}$-Globulin-Associated Renal Nephropathy with Chemically Induced Renal Toxicity and Neoplasia in the Male Rat. Prepared for the Risk Assessment Forum. EPA/625/3-91/019F, Washington, DC, September 1991.

2. Preliminary Literature Searches

Literature searches in the three databases (see Data Sources, Section 1) are conducted using search terms specific for cumene (synonyms, chemical class, metabolites, and exposure scenario) and for the topics covered by the monograph (see Table 1). Search terms for the specific topics have been developed in consultation with an information specialist. The

specific literature searches are constructed to answer the key questions of the monograph, as a result, not all topic-specific searches will include all the different types of substance-specific search terms; for example, searches for exposure information will only be combined with search terms for cumene synonyms since information on exposure to cumene metabolites is beyond the scope of this document.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios in which people may be exposed to cumene in addition to search terms specific for cumene. For cumene, these include terms related to its use in manufacturing and production of acetone and phenol. In addition to the human cancer studies identified from the above searches, a full-text search for cumene is conducted using a QUOSA library of occupational case-control studies.

Appendix 1

Table 1: Preliminary literature search approach for cumene

Substance	Search terms	Topics (combined with)[a]
Cumene synonyms	cumene OR 98-82-8 OR isopropylbenzene OR isopropylbenzol OR (1-methylethyl)benzene OR 2-phenylpropane NOT cumene hydroperoxide[b]	Human Exposure Toxicokinetics Human Cancer Studies Cancer Studies in Experimental Animals Genotoxicity Toxicity Mechanism
Alkylated benzene synonyms	alkylated benzene OR alkylated benzenes	Cancer Studies in Experimental Animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Cumene metabolites synonyms	2-phenyl-2-propanol, 2-phenyl-1,2-propanediol, 2-phenylpropanoic acid, 2-phenylmalonic acid, 2-hydroxy-2-phenylpropionic acid, dihydroxycumene monosulfate, 2-(2-hydroxy-2-propyl)phenylsulfate, 2-hydroxy-2-phenylpropylsulfate, 2-phenyl-1,2-propandiol monoglucuronide, 2-phenyl-1,2-propandiol 1-glucuronide, 2-phenyl-2-propanol glucuronide, 2-phenylpropionylglucuronide, 2-phenylpropionylglycine, S-(2-hydroxy-2-phenylpropyl)-N-acetylcysteine, 2-phenyl-1-propanol glucuronide, 2-phenyl-1-propanol	Human Cancer Studies Cancer Studies in Experimental Animals (for the mechanistic section) Genotoxicity Toxicity Mechanism
Exposure scenario (Phenol/ Acetone manufacturing)	("phenol" and (manufacturing or manufacture or production)) or (acetone and (manufacturing or manufacture or production))	Human Cancer Studies

[a]Search terms for each of these topics are developed in consultation with an informational specialist.

[b]Note: Searches for cumene synonyms bring up a large number of citations for cumene hydroperoxide. Cumene hydroperoxide is an intermediate in the synthesis of acetone and phenol from cumene and is used in other reactions as an epoxidation reagent for allylic alcohols and fatty acid esters, or as an initiator for radical polymerization. It has not been identified as a metabolite of cumene in any biological system. The term NOT or AND NOT "cumene hydroperoxide" was used to eliminate these citations from the database search results.