Cumene: Preliminary Literature Search Strategy and List of References

A. Preliminary literature search strategy

This document identifies the data sources, search terms, and search strategies that were used to identify literature for the draft monograph on cumene (CASRN 98-82-8). The literature search strategy used for cumene involved several approaches designed to identify potentially useful information for the broad range of topics covered by a Report on Carcinogens (RoC) monograph, as listed below.

- Properties and Human Exposure (focusing on the U.S. population)
- Disposition (ADME) and Toxicokinetics
- Human Cancer Studies (if available)
- Experimental Studies of Tumors (in animals exposed to cumene)
- Mechanisms of Action
  - Genotoxicity
  - Toxicity as It Relates to Mechanisms
  - Mechanisms of Carcinogenicity

The methods for identifying the relevant literature for the draft cumene monograph including (1) the search strategy, (2) updating the literature search, and (3) review of citations using web-based systematic review software are discussed below and illustrated in Figure 1.

1) Search strategies: Relevant literature is identified using search terms, data sources, and strategies as discussed below.

a) General data search: This search covers a broad range of general data sources (see Table 1) for information relevant to many or all of the wide range of monograph topics pertaining to cumene.

b) Exposure-related data search: This search covers a broad range of potential sources (see Table 2) for exposure-related information and physical-chemical properties.

c) Database searches in PubMed, Scopus, and Web of Science: The majority of the primary literature used to draft the cumene monograph was identified from searches of these three extensive databases available through the NIEHS Library. Synonyms, metabolites, and the chemical class for cumene were identified from the sources listed in Table 3 and the search terms are listed in Table 4. Information on metabolites and structurally related chemicals may be important for evaluating potential mechanisms of carcinogenicity. These searches were combined with the search terms listed in Table 4 for each of the monograph topics listed above to create the specific literature searches in Table 5. See Table 4 for details on this approach and Table 5 for topic-specific search terms.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios that might result in exposure of people to cumene. For cumene, these exposure-related search terms were based on its use in the manufacture of acetone and phenol, and those search terms were combined with search terms specific for human cancer.

d) QUOSA library of occupational case-control studies: A search of the QUOSA-based library of approximately 6,000 occupational case-control studies, approximately 60% of which are currently available as searchable full-text pdfs, was conducted using the synonyms "cumene," "isopropylbenzene," and the CASRN number (98-82-8).

e) Special topic-focused searches: The two specific topics for which additional searches were conducted for cumene are listed below and described in Table 3.

- α_{2u}-Globulin-associated renal nephropathy
- Role of genotoxic mechanisms in K-*ras* mutations in mouse lung tumors

f) Secondary sources: Citations identified from authoritative reviews or from primary references located by literature search, together with publications citing key papers identified using the Web of Science "Cited Reference Search," were also added.

2) Updating the literature search

The literature search will be updated approximately every three months, and prior to submitting the draft monograph for interagency review. Monthly search alerts for cumene synonyms, metabolites, chemical class, exposure scenarios (human cancer), and topic-focused searches were created in PubMed, Scopus, and Web of Science, and the results of these searches from the closing date of the initial search will be downloaded for review.

3) Review of citations using web-based systematic review software

Citations retrieved from literature searches were uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature were conducted, with initial reviews (Level 1) based on titles and abstracts only to identify citations that could be excluded and to assign the included literature to one or more monograph topics; subsequent reviews (Level 2) for literature assigned to the various monograph topics were based on full-text (i.e., PDFs) of the papers and were carried out by the writer and scientific reviewer for each monograph section. Two reviewers, at least one of whom is a member of the ORoC at NIEHS, participated at each level of review. Human cancer studies and experimental animal studies undergo Level 3 reviews to assess the quality of the studies.

Figure 1. Literature search strategy and review

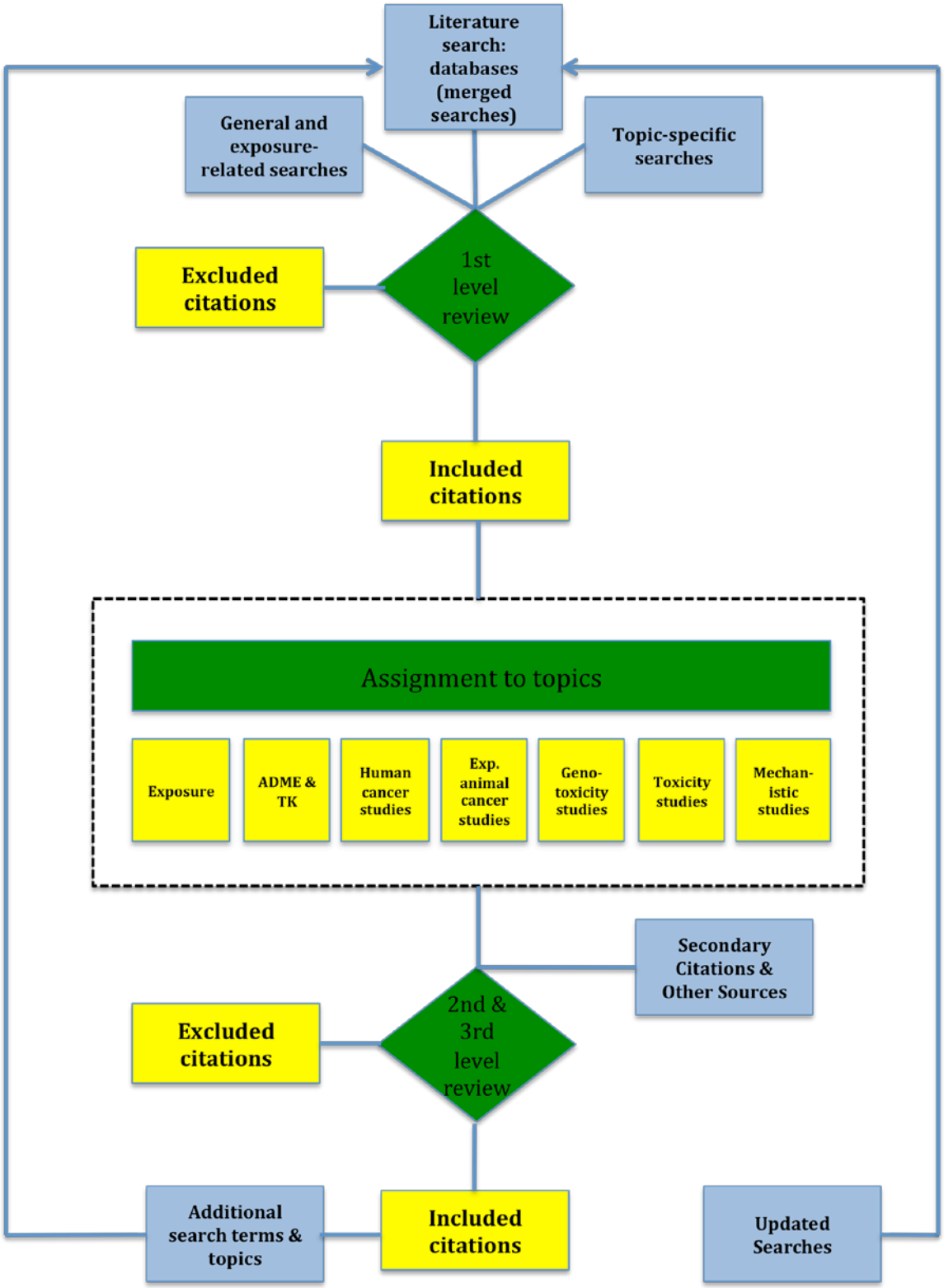

Table 1. General sources checklist for: Cumene

Source	Name of document
A) Comprehensive sources or reviews	
1) NTP technical reports	NTP2009
2) NTP nomination for toxicological evaluation documents	NTP1996
3) IARC monographs	--
4) ATSDR Toxicological Profiles	--
5) EPA IRIS	EPA1997
6) NAS Reports and Publications	--
7) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	WHO1999
b) EHC	--
c) HSGs	--
d) ICSCs	ICSC2004
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
8) California EPA Prop 65 hazard identification documents	CAEPA2010
10) New York State Department of Health- Health Topics A to Z	--
B) General information sources	
1) U.S. National Library of Medicine (NLM)- TOXNET	
a) HSDB	HSDB2005
b) CCRIS	CCRIS2011
c) GENETOX	GENETOX1991
d) ITER	ITER2012
e) LactMed	--
f) CPD	--
g) CTD	CTD2012
2) PubChem	PubChem2012
3) Kirk-Othmer Encyclopedia	HwangChen2010
4) USGS (Minerals)	--
C) European Union – sources to search	
1) International Uniform Chemical Information Database (IUCLID)	IUCLID2000
2) European Chemicals Agency	ECHA2012-EX UK2008-EX
3) The International Portal on Food Safety, Animal and Plant Health (IPFSAPH)	--
4) The European Food Safety Authority	--
5) European Centre for Disease Prevention and Control (ECDC)	--
6) European Monitoring Centre for Drugs and Drug Addiction	--

Table 2. Exposure-related sources checklist for: Cumene

Source	Name of document
Exposure- and properties-specific sources	
1) U.S. National Library of Medicine (NLM)- TOXNET	
a) ChemIDplus	ChemIDPlus202
b) Haz-Map	HAZMAP2012-EX
c) HPDB	HPDB2012
d) TOXMAP	TOXMAP2012
2) Akron database	Akron2010
3) SRI Directory of Chemical Producers	SRI2011
4) Chem Sources Suppliers	ChemSources2011
5) National Health and Nutrition Examination Survey (NHANES) data studies	NHANES2012-EX
6) National Occupational Exposure Survey (NOES) (1981-1983)	NIOSH1990
7) National Institute for Occupational Safety and Health (NIOSH) - Health Hazard Evaluations	NIOSH-HHE2002
8) National Response Center (NRC) Database	NRC2010
9) U.S. International Trade Commission (USITC)- Import/Export data	USITC2011
10) EPA Toxics Release Inventory (TRI)	TRI2012
11) EPA AP-42, Compilation of Air Pollutant Emission Factors	--
12) EPA Enforcement and Compliance History Online (ECHO) Database	--
13) EPA EJView Database	EPA2012
14) EPA HPV Challenge Program Chemical List	--
15) EPA Inventory Update Rule (IUR)	EPA2011a
16) EPA Locating and Estimating (L&E) documents	--
17) EPA/Office of Pesticide Programs (OPP) Chemical Ingredients Database	--
18) Food and Drug Administration (FDA) Pesticide Monitoring Database	--
19) FDA Orange Book	--
20) FDA Total Diet Study	FDA_TDS-91-03-EX FDA_TDS-04-05-EX
21) Medline Plus	--
22) United States Patent Office	USPTO2012-EX
23) Trademark Electronic Search System (TESS)	TESS2007
24) Material Safety Data Sheets (MSDS)	Citgo2005 MSDS-Xchange2012-EX
25) Dow Chemical Product Safety Assessments	--

Table 3. Data sources for cumene searches

Information type	Data sources
Synonyms	National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Base)
Metabolites	Robinson *et al.* (1955), Bakke and Scheline (1970), Ishida and Matsumoto (1992), Henne *et al.* (2001)
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
K-*ras* mutations in mouse lung tumors	Additional publications were identified from literature cited in the NTP (2009) technical report and in other publications (e.g., Hong *et al.* 2008, Wakamatsu *et al.* 2008, Hoenerhoff *et al.* 2009) identified from the search for information on potential mechanisms of carcinogenicity. Information and additional publications were also obtained from the NTP's Genetic Alterations in Cancer (GAC) database (http://www.niehs.nih.gov/research/resources/databases/gac/description/index.cfm).

Table 4: 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 *Combine with-* NOT cumene hydroperoxide[b]	Human exposure Toxicokinetics Human cancer studies Cancer studies in experimental animals Genotoxicity Toxicity Mechanism
Cumene metabolites and their 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
Chemical class (alkylated benzene) synonyms	alkylated benzene OR alkylated benzenes	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 were 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.

Table 5: Search terms for monograph topics for cumene

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
Exposure	exposure OR occurrence OR oral OR dermal OR air OR water OR food OR soil OR environmental pollut* OR environmental exposure* OR occupational exposure*	("Environmental Pollutants" [MeSH] OR "Environmental Pollution" [MeSH])

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
ADME/ Toxicokinetics	*Toxicokinetic search terms*- administration OR absorption OR distribution OR tissue distribution OR bioavailab* OR biological availability OR metaboli* OR biotransform* OR activat* OR bioactivat* OR detoxif* OR excret* OR clearance OR eliminat* OR kinetic* OR pharmacokinetic* OR toxicokinetic* OR cytochrome P450 *Combine with AND* *Animal study search terms*- in vivo OR animal* OR mouse OR mice OR rat OR hamster OR guinea pig OR rabbit OR monkey OR dog	*Toxicokinetic search terms*- "Pharmacokinetics"[Mesh]) OR "Metabolism"[Mesh]) OR "Cytochrome P-450 Enzyme System"[Mesh]
Human Cancer	((cumene OR ("phenol" AND (manufacturing OR manufacture OR production)) OR (acetone AND (manufacturing OR manufacture OR production))) AND (cancer OR mortality OR follow-up OR incidence) AND (epidemiogic* OR workers OR case-control OR cohort OR case-report OR case-series))	None
Animal Tumors	*Cancer search terms*- cancer OR neoplasm* OR carcinogen* OR malignan* OR oncogene* OR tumor* OR tumour* *Combine with AND* *Animal study search terms*- animal* OR mouse OR mice OR rat OR hamster OR "guinea pig" OR rabbit OR monkey OR dog	*Cancer search terms*- "Neoplasms"[Mesh]) OR "Carcinogens"[Mesh]
Genotoxicity	genetic toxicology" OR clastogen* OR "DNA strand break*" OR "unscheduled DNA synthesis" OR "UDS" OR aneuploid OR aneuploid* OR polyploid OR polyploid* OR "neoplastic cell transformation" OR "chromosom* aberration*" OR cytogenetic OR cytogenetic* OR "DNA adduct*" OR "DNA damage" OR "DNA repair" OR crosslink* OR "germ-line mutation" OR micronucle* OR mutagen OR mutagen* OR mutation OR mutation* OR oncogen* OR "sister chromatid exchange" OR "SCE" OR "SOS response*" OR "Ames test" OR "gene expression" OR "cell proliferation" OR cytotoxic OR cytotoxic* OR "comet assay"	"DNA Damage"[Mesh] OR "DNA Repair"[Mesh] OR "Mutagens"[Mesh] OR "Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Oncogenes"[Mesh] OR "Mutagenicity Tests"[Mesh]
Toxicity	toxic* OR toxin*OR cytotoxic* OR (nephrotoxic* OR hepatotoxic* OR pneumotoxic* OR thyrotoxic*	"Toxic Actions"[Mesh]) OR "Toxicity Tests"[Mesh]) OR "adverse effects" [Subheading]
Mechanisms of Carcinogenicity	(mode* AND "of action") OR (mechanism* AND "of action") OR genetic OR epigenetic OR inhibit* OR promot* OR interact* OR activate* OR detoxific* OR "oxidative damage" OR cytotoxicity OR "alpha 2u globulin" OR ("cyp2f2 protein" AND mouse)	("Alpha 2u globulin"[Supplementary Concept] OR "Cyp2f2 protein, mouse"[Supplementary Concept])

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