National Toxicology Program
U.S. Department of Health and Human Services

Draft Report on Carcinogens Monograph for Cumene

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Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

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FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are *known to be human carcinogens* or are *reasonably anticipated to be human carcinogens* and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of HHS, has delegated responsibility for preparation of the RoC to the NTP, which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions. The most recent RoC, the 12th Edition (2011), is available at http://ntp.niehs.nih.gov/go/roc12.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are evaluated in a scientific review process (http://ntp.niehs.nih.gov/go/rocprocess) with multiple opportunities for scientific and public input and using established listing criteria (http://ntp.niehs.nih.gov/go/15209). A list of candidate substances under consideration for listing in (or delisting from) the RoC can be obtained by accessing http://ntp.niehs.nih.gov/go/37893.

INTRODUCTION

Cumene (isopropylbenzene, CASRN 98-82-8) is an alkylated benzene found in fossil fuels, such as blended gasoline and kerosene, and products of incomplete combustion (IARC 2012). 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 for the Report on Carcinogens (RoC) based on widespread current U.S. exposure and an adequate database of cancer studies. 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).

Monograph contents

This RoC draft monograph on cumene consists of the following components: (Part 1) the cancer evaluation component that reviews the relevant scientific information, assesses its quality, applies the RoC listing criteria to the scientific information, and recommends an RoC listing status for cumene, and (Part 2) the draft substance profile containing the NTP's preliminary listing recommendation, a summary of the scientific evidence considered key to reaching that recommendation, and data on properties, use, production, exposure, and Federal regulations and guidelines to reduce exposure to cumene.

The cancer evaluation component for cumene provides information on the following topics: human exposure and chemical properties (Section 1), disposition and toxicokinetics (Section 2), cancer in experimental animals (Section 4), and mechanistic data and other related effects (Section 5), including studies of relevant toxicological effects, genetic toxicology, and potential mechanisms of carcinogenicity. When human cancer studies are reviewed, they are discussed in Section 3; however, no cancer studies in humans with exposure specifically to cumene were identified. The information in Sections 2 through 5 is synthesized in Section 6.

The information reviewed in Sections 2 through 5 (and synthesized in Section 6) must come from publicly available, peer-reviewed sources. Information in Section 1, including chemical and physical properties, analytical methods, production, use, and occurrence, may come from publicly available, published or unpublished sources.

The cancer evaluation for cumene focuses on the evaluation of the cancer studies in experimental animals and mechanistic data, and also whether there is any evidence that the potential modes of action by which cumene might cause cancer are not relevant to humans.

Process for preparation of the cancer evaluation component

The process for preparing the cancer evaluation component of the monograph included approaches for obtaining public and scientific input and using systematic methods (e.g., standardized methods for identifying the literature, inclusion/exclusion criteria, extraction of data and evaluation of study quality using specific guidelines, and assessment of the

level of evidence for carcinogenicity using established criteria). In addition, the NTP conducted some genotoxicity studies in rodents that were peer reviewed and are publicly available on the NTP website (http://ntp.niehs.nih.gov/go/37895).

The Office of the Report on Carcinogens (ORoC) followed the approaches outlined in the concept document, which discusses the scientific issues and questions relevant to the evaluation of cumene carcinogenicity, the scope and focus of the monograph, and the approaches to obtain scientific and public input to address the key scientific questions and issues, for preparing the cancer evaluation component of the draft monograph. The ORoC presented the draft concept document for cumene to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting that provided opportunity for written and oral public comments and is available on the RoC website (http://ntp.niehs.nih.gov/go/37895).

Key Scientific Questions and Issues Relevant for the Cancer Evaluation

The key scientific questions identified in the concept, which concern the results in experimental animals and mechanisms of carcinogenicity are:

- 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 evidence 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?

Approach for obtaining scientific and public input

Additional scientific input was obtained for the possible role of α_{2u}-globulin as a cause of renal tumors in male rats from NTP scientists with expertise in genetic toxicology, toxicology, and pathology. These scientists were assembled to discuss α_{2u}-globulin nephropathy and renal tumors in relation to the guidelines published by IARC (1999) and the sequence of events identified by EPA for this mechanism of renal carcinogenicity and to provide their individual input to the Office of the RoC (ORoC). Their individual comments on the animal cancer data were considered by the ORoC staff in drafting the mechanistic section and the overall synthesis of neoplastic findings in experimental animals. The discussions of the potential mechanisms(s) of actions were reviewed by an external technical advisor, who provided input on the discussions, especially those on the strength of the genotoxicity data for cumene. (Technical advisors are identified on the "CONTRIBUTORS" page.)

Public comments on scientific issues were requested 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 document, which outlined the rationale and approach for conducting the scientific review. In addition, the NTP posted its preliminary literature search strategy and list of references for public input on the ORoC webpage for cumene (http://ntp.niehs.nih.gov/go/37895) several months prior

to the release of the draft monograph. No information or comments on cumene were received from the public as of the date on this document.

Methods for writing the cancer evaluation component of the monograph

The procedures by which relevant literature were identified, data were systematically extracted and summarized, and the draft monograph was written, together with the processes for scientific review, quality assurance, and assessment and synthesis of data, are described below.

The preparation of the RoC monograph for cumene began with development of a literature search strategy to obtain information relevant to the topics listed above for Sections 1 through 5 using search terms developed in collaboration with a reference librarian (see Appendix A for a detailed description of the literature search strategy). The citations (N = 1,450) identified from these searches were uploaded to a web-based systematic review software for evaluation by two separate reviewers using inclusion/exclusion criteria, and 196 references were selected for final inclusion in the draft monograph using these criteria. Studies identified from the literature searches but excluded from the review include publications on chemicals other than cumene (or relevant structurally related compounds such as cumene metabolites and analogues), and studies involving exposure to cumene that reported results for topics not covered in this monograph (see Monograph Contents).

RoC Listing Criteria

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded, OR

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset, OR

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Information for the exposure, relevant cancer, and mechanistic sections was systematically extracted in tabular format and/or summarized in the text, following specific procedures developed by ORoC, from studies selected for inclusion in the monograph. All sections of the monograph underwent scientific review and quality assurance (QA) (i.e., assuring that all the relevant data and factual information extracted from the publications have been reported accurately) by a separate reviewer. Any discrepancies between the writer and the reviewer were resolved by mutual discussion in reference to the original data source.

Strengths, weaknesses, and data quality of the cancer studies for cumene in experimental animals were assessed based on a series of questions related to characterization of the substance tested, the features of animal husbandry, the design of the study, the methods for clinical observations and necropsy, and the manner in which the data were reported (see Appendix C). Relevant genotoxicity and mechanistic studies were also assessed for their strengths and weaknesses.

RoC listing criteria (see text box) were applied to the available database of carcinogenicity data to assess the level of evidence (sufficient or not sufficient) for the carcinogenicity of cumene from studies in experimental animals. The evaluation of the mechanistic data included a complete discussion and assessment of the strength of evidence for potential modes of action of cumene-induced neoplasia, including metabolic activation, cytotoxicity, genetic-related effects, epigenetic effects, and α_{2u}-globulin-associated nephropathy. The RoC listing criteria were then applied to the body of knowledge (animal and mechanistic) for cumene to reach a listing recommendation.

CONTRIBUTORS

Office of the Report on Carcinogens (ORoC), Division of the National Toxicology Program (NTP)

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Part 1

Draft RoC Cancer Evaluation

Properties and Human Exposure

Disposition (ADME) and Toxicokinetics

Human Cancer

Studies in Experimental Animals

Mechanistic Data and Other Relevant Effects

Overall Cancer Evaluation

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1 Properties and Human Exposure

Cumene is a natural component of petroleum (NAC-AEGL 2007) and an industrial chemical used primarily to manufacture phenol and acetone. It is a ubiquitous pollutant that may be released to the environment from (1) emission from petroleum products such as combustion of fossil fuels by land transportation vehicles, evaporative losses from gasoline stations, refueling losses, and oil spills, (2) emissions from its manufacturing, processing, and use, and (3) tobacco smoking.

This section describes the chemical and physical properties of cumene (Section 1.1); its uses and production (Section 1.2); biological indices of exposure (Section 1.3); the potential for environmental exposure including sources of release of cumene to the environment, cumene daily release estimates, fate and occurrence of cumene concentrations reported for air, water, and soil, and estimates of human exposure to cumene from the environment (Section 1.4); the potential for exposure from other sources such as food, cigarette smoking, and consumer products (Section 1.5); exposure in the workplace (Section 1.6); and exposure levels for people (Section 1.7). Section 1.8 summarizes the information in Sections 1.1 to 1.7. Human exposure tables and U.S. regulations and guidelines that potentially limit exposure to cumene are located in Appendix B. (Note: Links are provided in the text to jump directly to each table as it is discussed, and a link is provided at the end of each table to return to the text citing the table.)

1.1 Chemical identification and properties

Cumene (Figure 1-1) is structurally similar to benzene, toluene, ethylbenzene, xylenes, and styrene (Figure 1-2). Table 1-1 contains some chemical identification information for cumene.

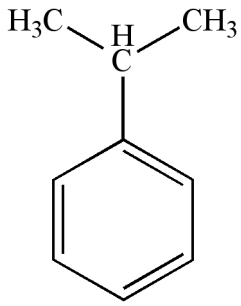


Figure 1-1. Chemical structure of cumene

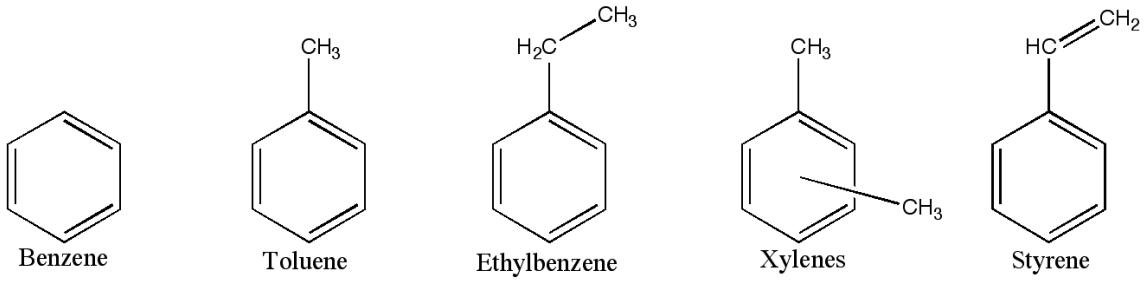


Figure 1-2. Chemical structure of cumene analogues

Table 1-1. Chemical identification of cumene

Characteristic	Information
Chemical Abstracts index name	Cumene
CAS Registry number	98-82-8
Molecular formula	C_9H_{12}
Synonyms	Cumol, isopropylbenzene, isopropylbenzol, (1-methylethyl)benzene, 2-phenylpropane

Sources: NTP 2009, WHO 1999.

Cumene exists as a volatile, colorless liquid with a sharp, penetrating aromatic or gasoline-like odor (NTP 2009). It is a flammable liquid with a flash point of 102°F [32.9°C], a lower flammable limit of 0.9% by volume and an upper flammable limit of 6.5% by volume (HSDB 2005). Cumene is stable under normal conditions but may become unstable at elevated temperatures and pressures. It forms cumene hydroperoxide when exposed to air for long periods and is incompatible with oxidizers, nitric acid, and sulfuric acid. Toxic gases and vapors such as carbon monoxide may be released during decomposition. Some physical and chemical properties for cumene are listed in Table 1-2.

Table 1-2. Physical and chemical properties of cumene

Property	Information
Molecular weight	120.2[a]
Melting point	-96°C[b]
Boiling point	152.4°C[b]
Specific gravity	0.862 at 20°C/4°C[a]
Solubility water (20°C) water (25°C) most organic solvents	 50 mg/L[a] (practically insoluble) 61.3 mg/L[b] soluble[a]
Octanol/water partition coefficient (log K_{ow})	3.66[b]
Vapor pressure (mm Hg)	4.5 at 25°C[b]
Vapor density (air = 1)	4.1[a]
Critical temperature	358°C[a]

Property	Information
Henry's law constant	0.0115 atm-m^3/mol at 25°C[b]
Conversion factors (cumene in air) parts per million (ppm) to µg/m^3 µg/m^3 to parts per million (ppm)	 µg/m^3 = 4,916.18 × (ppm)[c] ppm = 2.034×10^{-4} × (µg/m^3)[c]

Source: [a]HSDB 2005, [b]ChemIDplus 2012, [c]SMARTe.org 2012.

1.2 Uses and production

Cumene is used primarily to manufacture phenol and acetone (98%); but it is also used to manufacture acetophenone, alpha-methylstyrene, diisopropylbenzene, and dicumylperoxide (HSDB 2005). Cumene is also used as a constituent of some petroleum-based solvents such as naphtha, as a catalyst for acrylic and polyester resins, and as a raw material for peroxides and oxidation catalysts (NTP 2009). Other, direct uses include its use as a thinner for paints, enamels, and lacquers and as a solvent for fats and resins; as such, cumene has been suggested as a replacement for benzene. Cumene and phenol are reported to be starting materials used to make aspirin and penicillin (ICIStraining 2012).

Cumene is a naturally occurring component of refined fuels and it has been reported to be used in gasoline blending, diesel fuel, and high-octane motor fuels, particularly as an aviation fuel (Advameg 2012, HSDB 2005, NTP 2009). The proportion of cumene used as a blending component in fuels for internal combustion engines is difficult to estimate because manufacturers customarily do not disclose this information (NRC 1981).

The demand for cumene is largely driven by the demand for products derived from phenol and acetone (BusinessWire 2011), and demand for cumene is strongly tied to the phenol derivatives market. A major use for the cumene-derived molecules is in the production of polycarbonates via bisphenol-A (which is synthesized from two molecules of phenol and one molecule of acetone). Phenolic plastics uses (other than bisphenol-A) in the automobile industry include phenolic disc brake caliper pistons (Malviya 2006), carburetor spacers (AutoZone 2012), and ashtrays (Rebling 2012). Other applications for phenol include phenolic resins to bond construction materials (e.g., plywood and composition board), caprolactam to produce nylon-6 (e.g., carpet fibers and tire cord fabric), and alkylphenols (e.g., surfactant in detergents) (Chameides 2012, Hwang and Chen 2010, NPG6 2006a, 2006b, 2006c).

Demand for cumene ranged from 3.7 billion to 8.0 billion pounds per year from 1986 to 2003 (HSDB 2005); however, U.S. demand for cumene has decreased in recent years as increasing cumene and phenol production capacity at integrated cumene/phenol production plants in Asia decreasing cumene exports from the United States (ICIS 2005). The uses of polycarbonates derived from bisphenol-A (and ultimately from cumene production of phenol and acetone) have increased in downstream industries such as electrical industries and the automobile and construction industries (NTP 1996); both the automobile and construction industries have rebounded in recent years (PRWeb 2011). In an April 2012 report, cumene demand was stable and was predicted to remain consistent for the coming months (ICIS 2012c).

Cumene is synthesized from propylene and benzene using an acidic catalyst, e.g., solid phosphoric acid, or a zeolite catalyst (ICIS 1999a, 1999b, NTP 2009). The cumene product is separated from the propylene and benzene reactants by distillation while non-reacted benzene is recycled (EC 2001). Production data for cumene are shown in Table 1-3. Production data are based on Internet searches of sources dated as noted.

Table 1-3. Production data for cumene

Category	Years covered	Quantity in pounds[a]
Chemical Data Reporting Rule[b]	2006	1 billion and greater
U.S. imports (recent)	2011	2.29 billion (reported as 1.04 billion kg)
U.S. imports (historical)	1989	325 million (reported as 147 million kg)
U.S. exports (recent)	2011	127 million (reported as 57.6 million kg)
U.S. exports (historical)	1989	124 million (reported as 56 million kg)
Producers (U.S.)	2011	At least 8
Producers (worldwide)	2011	At least 50

Sources: EPA 2010, SRI 2011, USITC 2013.
[a]From 1/2013 Internet search; data subject to change.
[b]Formerly called the Inventory Update Rule.

1.3 Biological indices of exposure

Biological indices of exposure to cumene have not been widely used to assess exposure, but potential biological indices include measurement of cumene in blood (see Section 1.8) and measurement of the cumene metabolite dimethylphenylcarbinol (see Section 2 for a discussion of cumene metabolism) in urine. Senczuk and Litewka (1976) showed a directly proportional dependence between the amount of dimethylphenylcarbinol excreted in urine and the amount of cumene absorbed; however, no publication has been identified in which this metabolite was used as a biological index of exposure to cumene.

1.4 Potential for environmental exposure

This section describes sources of release of cumene to the environment (Section 1.4.1), cumene daily release estimates (Section 1.4.2), fate and occurrence of cumene in air, water, and soil (Section 1.4.3), and estimates of human exposure to cumene from the environment (Section 1.4.4).

1.4.1 Release of cumene to the environment

Sources of release of cumene to the environment can be classified as being related to cumene manufacturing, processing, and use, or emission of petroleum products. Cumene release from these sources was estimated to be 21 million pounds annually in the United States (HSDB 2005). See Section 1.5 for a discussion of consumer exposures (e.g., cigarette tobacco during consumption, office equipment, etc.).

Other, unquantified anthropogenic sources of cumene release include operations involving the vulcanization of rubber, building materials, jet engine exhaust, outboard motor operation, solvent uses, paint manufacture, pharmaceutical production, and textile plants. Cumene is also released to the environment from leather tanning, iron and steel

manufacturing, paving and roofing, paint and ink formulation, printing and publishing, ore mining, coal mining, organics and plastics manufacturing, pesticide manufacturing, electroplating, and pulp and paper production (HSDB 2005).

1.4.2 Releases from production, processing, and use

The loss of cumene to air during production has been reported to range between 0.08 kg cumene/tonne for emissions-controlled production and 0.27 kg cumene/tonne for uncontrolled production (EC 2001, Peterson 1980). The reported release factor to air for use of cumene in synthesis is 1.03 kg cumene/tonne phenol. These data indicate that the release of cumene from cumene use in synthesis of phenol is higher than the release of cumene from the production of cumene. Similarly, a release factor for combined release to air (including release to air from wastewater) of 1.31 kg cumene/tonne, a release factor for release to wastewater of 1.5 kg/tonne, and a release factor for release to soil of 0.02 kg/tonne from cumene production and use have been reported.

According to the U.S. Environmental Protection Agency (EPA) Toxics Release Inventory (TRI), total reported on- and off-site release of cumene was slightly over 1 million pounds from more than 300 facilities in 2010 (TRI 2012). Releases to air accounted for 94.1% of total releases, releases to land for 4.4%, off-site disposal for 1.3%, disposal by underground injection for 0.2%, and releases to water for 0.1%. (See Section 1.4.4 for estimates of the numbers of individuals living near facilities reporting release of cumene to the air.)

TOXMAP is a Geographic Information System (GIS) from the National Library of Medicine (NLM) that uses maps of the United States to help users visually explore data from EPA's TRI and Superfund programs. Figure 1-3 shows a color-coded map of reported TRI on-site cumene releases into the air, water, and ground for 2010 (TOXMAP 2012). The color of each circle indicates the amount of total on-site release for calendar year 2010. Figure 1-4 shows a map of Superfund sites on the National Priorities List (NPL) at which cumene was listed as a site contaminant (TOXMAP 2012). The NPL is the list of national priorities among the known releases or threatened releases of hazardous substances, pollutants, or contaminants throughout the United States and its territories. Based on the visual depiction of cumene releases in Figure 1-3, cumene has been released at industrial facilities throughout the United States, largely in the central and northeast regions. Based on Figure 1-4, Superfund sites at which cumene was listed as a site contaminant appear to be located in the northeast and Alaska.

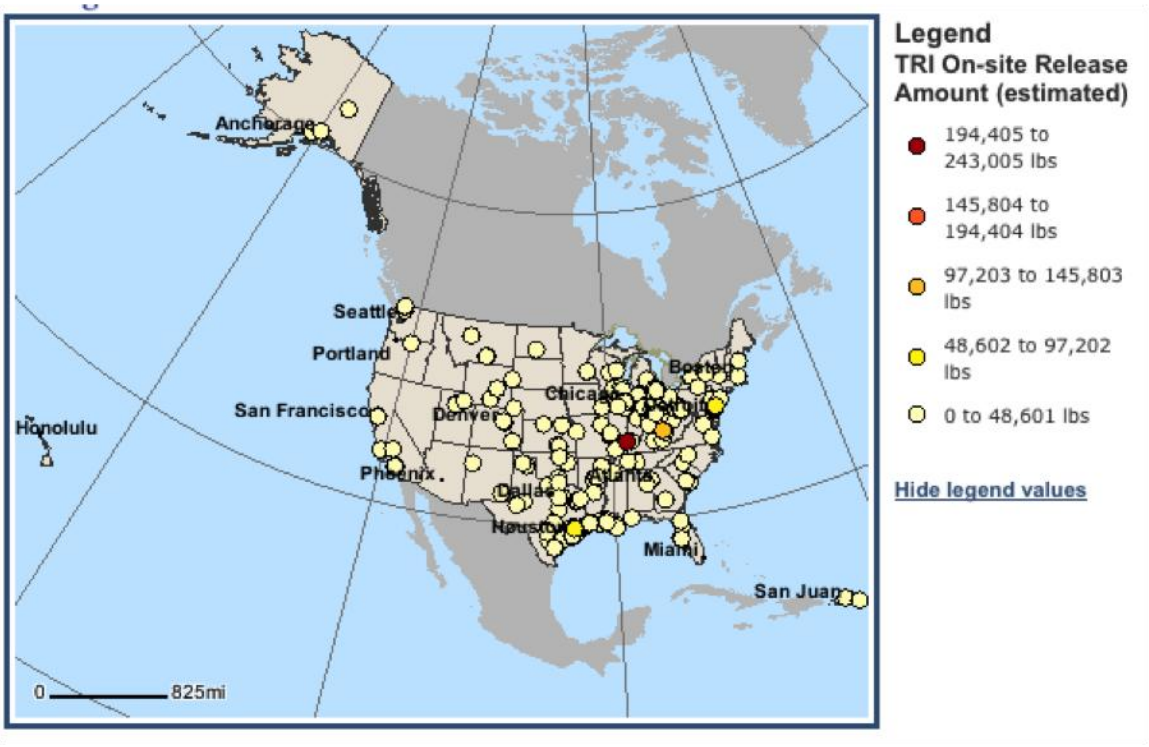


Figure 1-3. Map of reported TRI on-site cumene releases for 2010

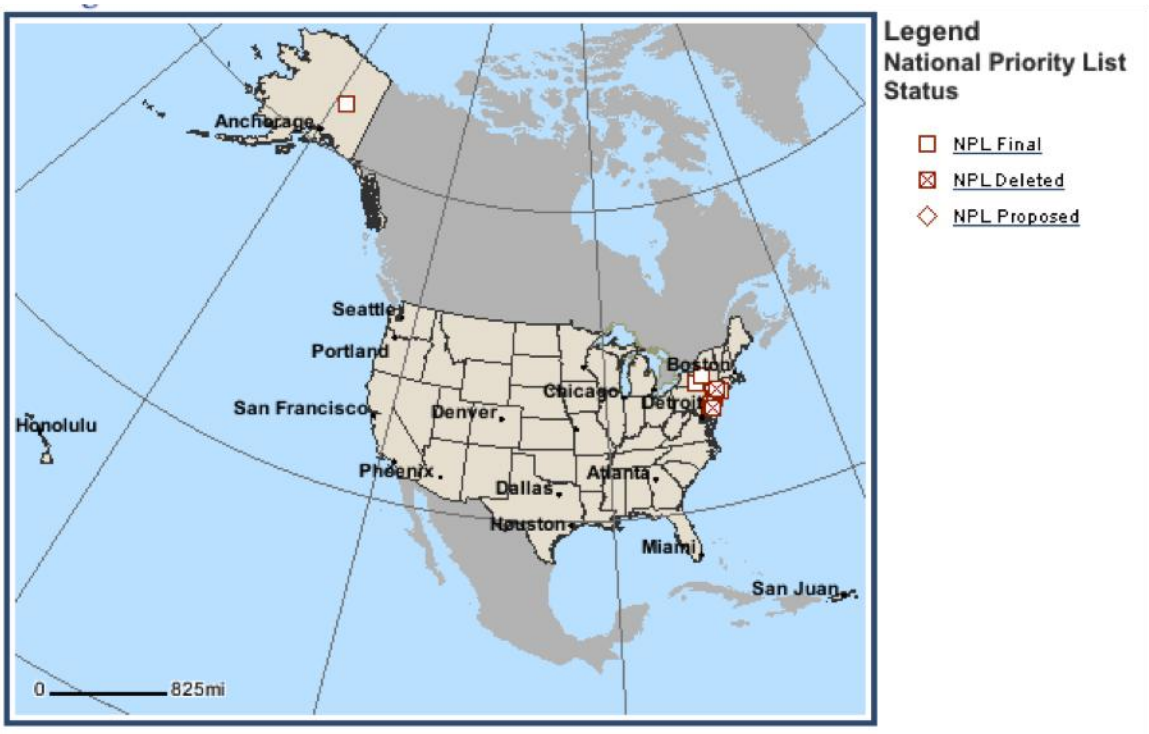


Figure 1-4. Map of the Superfund sites at which cumene was listed as a site contaminant

In 1988, the U.S. EPA estimated that approximately 3 million pounds of cumene were released annually to the environment from cumene manufacturing and processing facilities (EPA 1988). This estimate was derived from emission rate data for vents, flanges, drains, valves, and pumps suspected of leaking cumene in the average cumene manufacturing and/or processing unit. The lower release estimates in the 2010 TRI data may result in part because of manufacturing process improvement involving retrofitting to zeolite catalyst technology from solid phosphoric acid (SPA) catalysts.

Part of the manufacturing, processing, and use chain also includes transportation of cumene product. Based on a review of spill report data from the National Response Center covering the time period of January 1, 1990 to the present, approximately 180 spill incidents involving cumene were reported (NRC 2012). One such incident involved the release of up to an estimated 10,300 gallons of cumene into the Ohio River between Illinois and Kentucky after a barge carrying 960,000 gallons of cumene collided with a lock wall (Platts 2007).

1.4.3 Releases from emission of petroleum products

Releases of cumene related to emission of petroleum products include releases during the transportation, distribution, and use of motor fuels (e.g., emissions from combustion of fossil fuels by land transportation vehicles, evaporative losses from gasoline stations, refueling losses, etc.) and accidental spills of petroleum products such as oil spills. These types of sources are more numerous than sources related to manufacturing, processing, and use; therefore, releases related to emission of petroleum products may be a larger concern to the general population.

Cumene is a naturally occurring component of crude oil, coal tars, and some plants (NTP 2009). Crude oils typically contain 0.1 weight percent (wt%) cumene but may contain up to 1.0 wt% cumene (WHO 1999). Various grades of gasoline have cumene concentrations ranging from 0.14 to 0.51 volume percent (vol%) with an average cumene concentration of 0.3 vol%. The cumene concentration in premium diesel fuel is 0.86 wt% and that in furnace oil (no. 2) is 0.6 wt%.

Emission rates from motor vehicles were studied for vapor-phase, semi-volatile, and particle-phase organics inside and outside a Los Angeles roadway tunnel in 1993; cumene was emitted at a rate of 11 mg/L of gasoline consumed (HSDB 2005). In a study to determine concentrations and emissions of gasoline and other vapors from residential vehicle garages, the average concentration of cumene was reported to be 1.64 $\mu g/m^3$ (Batterman *et al.* 2006). In a study to evaluate the benefits of various vehicles with and without catalytic converters, cumene emissions were reported as 0.0002 and 0.0009 g/km for two vehicles with catalytic converters and as 0.002 g/km for a vehicle without a catalytic converter (HSDB 2005).

Though many data are available regarding environmental monitoring and sampling related to the April 4, 2010 Deepwater Horizon oil spill in the Gulf of Mexico, little information related specifically to exposure to cumene from the spill could be identified. NIOSH Health Hazard Evaluation (HHE) exposure monitoring data for Deepwater Horizon response workers include only 17 cumene concentration data points for

dispersant operations and *in situ* burning operations ranging from 0.13 to 0.79 ppb [0.64 to 3.9 μg/m^3] (NIOSH 2011). Based on an estimated total of 4.9 million barrels [approximately 1.5 billion pounds] of oil discharged from the Deepwater Horizon wellhead from April 20 to July 14, 2010 (FISG 2010) and the WHO estimate of crude oil typically containing 0.1 to 1.0 wt% cumene, approximately 1.5 million to 15 million pounds of cumene might have been released during the Deepwater Horizon oil spill. An Operational Science Advisory Team (OSAT) petroleum residue data analysis indicates that cumene is sufficiently volatile that it was not present in any residual petroleum hydrocarbons that might have existed on Gulf beaches after months of weathering (OSAT 2011), and results of controlled oil spills at sea confirmed that cumene disappeared with 90 minutes (Harrison 1975). No data regarding how cumene in oil is transported from deep water to the surface were identified.

1.4.4 Daily release estimates

Based on data for cumene daily release rate estimates for manufacturing, processing, and use, as well as for gasoline marketing, distribution, and use and other sources of release (see Appendix B, Table B-1.), most of the cumene released into the environment from manufacturing, processing, and use is released to the air (94.1% of total reported on- and off-site releases based on the most recent TRI data). The amount of cumene released to air from cumene use in synthesis of phenol is higher than the release of cumene from the production of cumene (see Section 1.4.1). The estimated amount of cumene released to air from gasoline distribution (3,211 kg/day), and use (20,298 kg/day) (total = 23,509 kg/day) is slightly higher than the release of cumene to air from cumene production and use (17,903 kg/day) (see Appendix B, Table B-1).

1.4.5 Fate and occurrence

This section describes fate and occurrence data for cumene in air (e.g., cumene air concentrations in industrial areas, urban areas, rural areas, etc.), water (e.g., cumene concentrations in drinking water, groundwater, surface water, etc.), and soil.

Air

If released to air, a vapor pressure of 4.5 mm Hg at 25°C indicates cumene will exist solely as a vapor in the ambient atmosphere (HSDB 2005, WHO 1999).

Review of available cumene atmospheric concentration level data for the United States and other countries shows that concentration ranges are mostly similar (see Appendix B, Table B-2) for cumene atmospheric concentration measurement data for industrial, urban, and rural areas within the United States, other countries, and other unspecified areas), but several reported levels from outside the United States exceeded the highest value identified for U.S. data of 144 μg/m^3 measured in Los Angeles, CA in 1966 (HSDB 2005). For both U.S. and non-U.S. data, reported concentrations in industrial settings ranged from 1.6 to 2,700 μg/m^3, the highest value was associated with an electronics fire. For urban settings, concentrations ranged from 0.1 to 900 μg/m^3. Reported concentrations in rural settings ranged from 0 to 34.79 μg/m^3.

Data for cumene in residential indoor air were identified from only two studies, one in the United States in rural western Montana (Ward *et al.* 2009) and the other in Quebec City, Canada (Hèroux *et al.* 2008) (see Appendix B, Table B-3). In Ward *et al.* (2009), maximum indoor cumene concentration levels were greater than maximum ambient cumene concentration levels (see Appendix B, Table B-3) in both the 2004 to 2005 and 2005 to 2006 sampling events. No significant correlation was found between indoor and ambient concentrations of cumene.

Based on these data, cumene has been measured in the atmosphere at significant levels at many geographical locations throughout the United States. Most likely due to the association of cumene with the combustion of petroleum, atmospheric cumene levels are several-fold higher in industrial and urban settings than in rural areas. Thus, measurable exposure of the general population to atmospheric cumene is likely in industrial and urban areas in the United States.

Water

Data for cumene concentrations in drinking water in the United States appear to indicate that drinking water is not a major source of exposure. Appendix B, Table B-4 presents cumene water and sediment concentration measurement data for the United States, other countries, and other unspecified areas. From the large number of samples in these studies with no detectable cumene and others with levels at or below the limit of detection, it is reasonable to conclude that U.S. drinking waters only rarely contain cumene contamination above 0.5 μg/L (EPA 1987, WHO 1999).

Cumene levels in groundwater appear to be highest near industrial sources. Elevated levels were reported in 1984 for groundwater near underground solvent storage tanks in Italy (1,581 μg/L) (EC 2001). Likewise, a level of 360 μg/L was measured near a chemical plant in an unspecified location by researchers in Czechoslovakia (Teply and Dressler 1980). Cumene levels in groundwater are lower in areas not identified as industrial areas, with values ranging from detected but not quantified to less than 0.5 μg/L (HSDB 2005).

Levels of cumene in surface water for the United States and other countries are mostly low and similar. Levels for the United States range from detected but not quantified to 0.017 μg/L (EC 2001, HSDB 2005).

Review of the limited available cumene sediment and biota concentration level data for the United States and other countries shows elevated levels in the United States relative to other countries. Levels for sediments and biota in the United States ranging from 20 to 19,000 μg/kg were measured in Puget Sound, WA in 1979 (WHO 1999).

Cumene concentration levels in wastewater and other industrial effluents appear to vary widely. Cumene levels in unspecified wastewater ranged from 0.1 to 5 μg/L (EC 2001). Elevated cumene levels were reported around outboard motor operations (700 μg/L) and near offshore drilling platforms (140 μg/L) (WHO 1999).

No occurrences of cumene in rainwater have been reported and its removal from atmosphere in rainfall is unlikely. However, a few data have been reported for cumene in snow (see Appendix B, Table B-4).

A European Union risk assessment concluded that the weight of evidence on degradation data and the information available for other related chemicals indicate that cumene should be classified as inherently biodegradable (EC 2001). Measured and estimated bioconcentration factor (BCF) values for cumene suggest a slight potential for cumene to bioconcentrate in fish species (Ogata *et al.* 1984). Cumene was detected at levels of 0.5 to 1.4 ng/g wet weight in 12 of 138 sampled fish of various species from locations near a potential emission source as reported by the Japan Environment Agency in 1987 (WHO 1999).

In summary, cumene has been measured in water in many geographical locations throughout the United States. The highest cumene concentrations appear to be associated with groundwater near industrial sources and with industrial effluents. Elevated cumene levels also have been measured for sediments and biota. Surface water and drinking water concentrations are several-fold lower than concentrations associated with groundwater near industrial sources, industrial effluents, and sediments and biota. People living in the United States are not likely to be exposed to cumene from water intake.

Soil

The main source of soil contamination by cumene is from point emissions caused by garage spills or from locations near gasoline stations (EC 2001). (See Appendix B, Table B-5) for cumene soil concentration measurement data that have been identified.)

Cumene is expected to have low mobility in soil. Volatilization from moist soil surfaces is expected to be an important fate process. Cumene may volatilize from dry soil surfaces based on its vapor pressure; however, adsorption to soil is expected to attenuate volatilization (WHO 1999). Biodegradation is also expected to be fairly rapid. Based on these data, people living in the United States are not likely to be exposed to cumene from soil.

1.4.6 Estimates of human exposure to cumene from the environment

This section describes estimates of the numbers of people living near cumene-emitting facilities based on TRI and U.S. Census data and estimates of daily cumene intake from exposure to cumene from the environment.

Estimated numbers of people living near cumene-emitting facilities

Based on 2010 TRI data, the top 10 cumene-emitting facilities released approximately 742,000 pounds of cumene to the air, accounting for 78% of total cumene air emissions in 2010 (TRI 2012). Table 1-4 presents demographic data from EPA's EJView website based on U.S. Census data for 2000 for areas within 0.5 mile and 1 mile of the top 10 cumene-emitting facilities in 2010. Based on these data, approximately 7,900 people lived within 0.5 mile of these facilities, and 43,400 people lived within 1 mile of these facilities.

Table 1-4. Demographic data for areas within 0.5 mile and 1 mile of the top 10 cumene-emitting facilities in 2010

City	State	Cumene air emissions (pounds)	Total persons within 0.5 Mile	Total persons within 1 Mile
Mount Vernon	IN	243,000	16	62
Franklin Furnace	OH	109,002	104	401
Deer Park	TX	84,531	0	83
Philadelphia	PA	63,370	7,153	26,670
Philadelphia	PA	51,690	261	14,616
Pasadena	TX	44,284	24	134
Plaquemine	LA	40,400	131	520
Freeport	TX	39,730	30	400
Ottawa	IL	33,585	24	122
Theodore	AL	32,666	108	409
Total		**742,258**	**7,851**	**43,417**

Sources: EPA 2012, TRI 2012.

Estimated daily intake from exposure to cumene in the environment

The European Union System for the Evaluation of Substances (EUSES) model has been used to estimate daily human intake of cumene for local and regional exposure levels. These estimates suggest that the greater amount of human exposure to cumene via the environment will be from the air (> 97% of estimated total exposure). The local environment is considered in the European Union document to be a distance of 100 meters from a point source of release, and the regional environment is considered to be a highly industrialized area accounting for 10% of European production or use (EC 2001). Figure 1-5 depicts this information graphically for the local and regional exposure scenarios.

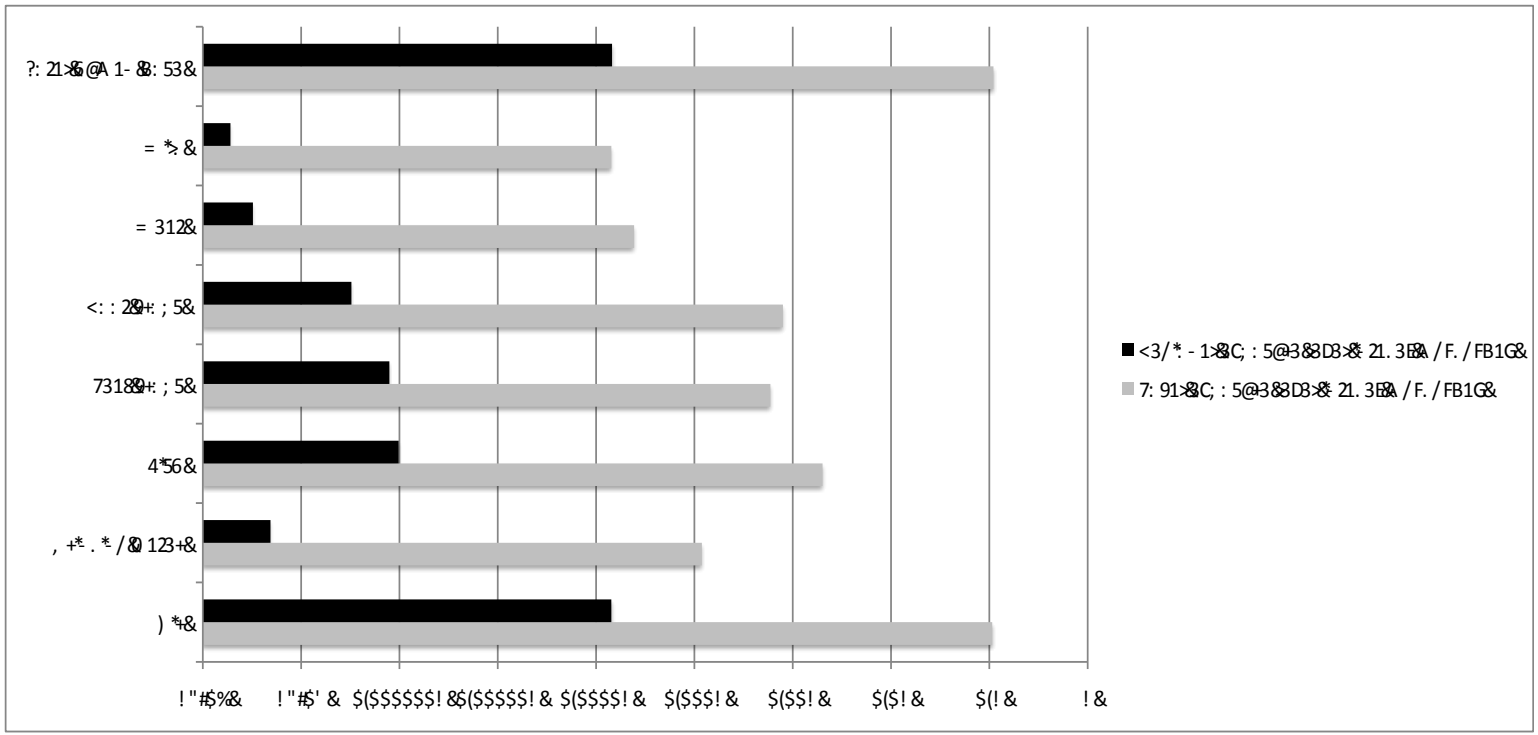


Figure 1-5. Estimated human daily intake of cumene for local exposure level
Source: EC 2001

1.5 Potential for exposure from other sources: food, cigarette smoking, and consumer products

1.5.1 Food

The occurrence of cumene in food may be from environmental or processing sources, or it may occur naturally (EPA 1987). Trace quantities of cumene have been detected in papaya, sapodilla fruit, and Australian honey. Cumene has been detected but not quantified in fried chicken, tomatoes, Concord grapes, cooked rice, oat groats, baked potatoes, Beaufort cheese, fried bacon, dried legumes (beans, split peas, and lentils), southern pea seeds, and Zinfandel wine (HSDB 2005). It also has been detected in chicken and pork.

Cumene has been an analyte in the U.S. Food and Drug Administration's Total Diet Study (TDS). Based on analytical results for TDS market baskets 1991-3 through 2003-4 collected between September 1991 and October 2003, cumene was found at levels ranging from 0.002 to 0.063 ppm in 18 different foods including fruit-flavored popsicles and sherbet, cake doughnuts (any flavor), sweet rolls and Danish pastries, and raw navel and Valencia oranges. Cumene was found at trace levels (defined by FDA as greater than or equal to the limit of detection but less than the limit of quantitation) in 18 additional foods including eggs scrambled with oil, enriched white bread, presweetened fruit-flavored cereal, regular salted margarine and butter, and catfish pan-cooked with oil (FDA 2006).

1.5.2 Cigarette smoking

Cumene levels ranging from 7 to 14 μg/cigarette in condensates of cigarette smoke have been reported (WHO 1999).

1.5.3 Consumer products

Cumene is present at concentrations ranging from 1% to 5% in several consumer products including automobile products (e.g., fuel injector system cleaners), home maintenance products (e.g., roof adhesives, concrete cleaners, and degreasers), and some agricultural herbicides (e.g., weed control for wheat) (HPDB 2012). More than a dozen additional products were reported to contain cumene at less than 1% or with unspecified concentrations of cumene.

Cumene has also been determined to be a volatile organic compound released by photocopying machines during operation at an emission rate ranging from 140 to 220 μg/hour (HSDB 2005).

Cumene has been identified but not quantified in emissions from antistatic fabric softener pads and crib mattresses (Anderson and Anderson 2000a, 2000b). Cumene has also been reported to be a perfume component (NAC-AEGL 2007), but no information was identified on specific products containing cumene or possible exposure.

In summary, cumene has been detected in cigarette smoke, at trace levels in food, and in small amounts in consumer products. Cumene may occur in food naturally, or from

environmental or processing sources. However, in comparison with estimated human daily intake of cumene from air, intake of cumene from food is very low (see Figure 1-5).

1.6 Characterization of exposure in the workplace

Occupational exposure to cumene may occur through inhalation and dermal contact at workplaces where cumene is produced or used (HSDB 2005). Based on data from area monitoring samples for cumene in different occupational settings (See Appendix B, Table B-6) the main exposure route for occupational populations is via inhalation, which may be up to ten thousand-fold greater than ambient atmospheric concentrations at the upper end of the range of reported concentrations. For example, overall urban atmospheric cumene levels have been reported to be 14.7 μg/m^3, while air samples for cumene-exposed workers (performing unspecified tasks in manufacturing and processing cumene) have been reported to be as high as 147,485 μg/m^3 (see Appendix B, Tables B-2 and Table B-6). The majority of exposure levels reported, however, were less than 1 ppm (4,916 μg/m^3). High levels of exposure also may occur for users of products containing cumene outside of the manufacturing industry (e.g., painting [up to 16,715 μg/m^3] and car repair [up to 32,938 μg/m^3]). Occupational populations also may be exposed via the dermal route during shutdown activities (e.g., cleaning and maintenance) at cumene manufacturing and processing facilities, but no quantitative exposure levels were identified for this route of exposure.

The National Institute for Occupational Safety and Health (NIOSH) National Occupational Exposure Survey (NOES), conducted between 1981 and 1983, estimated that 14,267 workers, including 2,760 female workers, were potentially exposed to cumene in the workplace. Among the occupational descriptions with the highest numbers of employees (men and women combined) potentially exposed to cumene were miscellaneous machine operators in business services (2,823), vehicle washers and equipment cleaners at automotive dealers and service stations (1,723), janitors and cleaners in health services (1,584), and laundering and dry cleaning machine operators in personal services (1,475) (NIOSH 1990). (Note: The NOES database has not been updated since July 1, 1990, and NIOSH has not conducted any national surveys of occupational exposure since that time.) An industrial hygiene survey submitted to the U.S. EPA by the Chemical Manufacturing Association Cumene Program Panel reported information on 739 U.S. workers at manufacturing and processing facilities having either routine (393) or intermittent (346) exposure to cumene (EPA 1988, WHO 1999). Personal exposure data for these workers are reported in Appendix B, Table B-6.

Cumene is usually produced, stored, and converted in closed systems. One European company has reported that potential contacts with cumene could occur during sampling, loading of tankers, or cleaning and maintenance activities (EC 2001).

In summary, the main exposure route for cumene in occupational settings is via inhalation. Most reported exposure levels were less than 1 ppm (4,916 μg/m^3); however, at the upper end of the report exposure range, occupational exposures may be as much as ten thousand-fold higher than ambient atmospheric concentrations. Further, high exposure levels (i.e., tens of thousands of μg/m^3) also may occur in occupational

populations other than those in the manufacturing industry, such as painting and car repair. Dermal exposure to cumene may occur at manufacturing and processing facilities during shutdown activities such as cleaning and maintenance. However, as accidental contacts with cumene are not expected to occur on most days and gloves may be worn to avoid direct contact with cumene, dermal exposure is expected to be low to negligible.

1.7 Exposure levels for people

Trace levels of cumene were detected in some of the expired air samples collected from 28 nonsmoking, healthy volunteers who lived in an urban setting with no intentional exposure to the chemical (Krotoszynski *et al.* 1977). Brugnone *et al.* (1989) measured cumene in the blood and breath of two groups, a group of individuals belonging to a hospital staff and a group of chemical workers who were exposed to cumene from the environment rather than from their occupational duties (see Table 1-5). Chemical workers were examined in the plant infirmary in the morning before the start of the work shift, and the hospital staff was examined in the hospital infirmaries. One environmental air sample was taken per each individual biological sample. The environmental concentration of cumene was higher, although not statistically significant, in the plant than in the hospital infirmaries. Blood cumene concentration and alveolar concentration were higher in the chemical workers compared with the hospital workers, but the difference was only statistically significant for blood cumene concentration.

Table 1-5. Cumene environmental, alveolar, and blood concentration data from study of chemical workers and hospital staff

Type of worker	Environmental conc., 8-h, ng/L; mean (range), [N]	Alveolar conc., ng/L; mean (range), [N]	Blood conc., ng/L; mean (range), [N]
Chemical workers	38.9 (1 – 279), [27]	12.0 (1 – 81), [27]	762* (43 – 3,352), [27]
Hospital workers	9.6 (2 – 36), [40]	4.7 (1 – 22), [38]	176 (31 – 929), [33]

Source: Brugnone *et al.* 1989.
*$P < 0.002$, Wilcoxon-Mann-Whitney test.

In Perbellini *et al.* (1988), a study to determine 13 industrial solvents in blood, alveolar air, and urine, the concentration of cumene was measured in 49 Italian blood donors. For an environmental air concentration of 6 ± 2 ng cumene/L (geometric mean ± standard deviation) (range 1 to 21 ng/L), specimen analysis results were as follows: alveolar air, 3 ± 2 ng/L (range 1 to 14 ng/L), blood, 199 ± 2 ng/L (range 17 to 963 ng/L), and urine, 202 ± 2 ng/L (range 20 to 1,190 ng/L) (EC 2001).

1.8 Synthesis and summary

Cumene (isopropylbenzene, CASRN 98-82-8) is an alkylated benzene found in fossil fuels, such as blended gasoline and kerosene, and products of incomplete combustion (IARC 2012). It is a high production volume chemical in the United States with the majority of its use in the synthesis of acetone and phenol.

Significant U.S. exposure to cumene results from its presence in fossil fuels, solvents, and cigarette smoke. Exposure also can occur in the workplace through the production

and use of cumene in the chemical industry. Cumene has been detected in blood, alveolar air, expired air, and urine from people without known occupational exposure to cumene, including non-smoking individuals living in an urban environment.

Exposure to cumene for people living in the United States occurs primarily via inhalation. Cumene has been measured in the atmosphere in many geographical locations throughout the United States, and levels are several-fold higher in industrial and urban settings than in rural areas, presumably because of cumene's presence in petroleum emissions. As cumene is a natural component of petroleum, its emissions are ubiquitous in the environment from combustion of fossil fuels by land transportation vehicles or evaporative losses of fuel during distribution. People living in the United States are not likely to be exposed to cumene from water intake or from exposure to contaminated soil resulting from point emissions caused by garage spills or from locations near gasoline stations.

Potential exposure to cumene for occupational populations results from its primary use as a high-production volume chemical to manufacture phenol and acetone, and the exposure can occur via both inhalation and dermal routes. Most reported levels for inhalation exposures were less than 1 ppm, but high levels up to 1,000 to 10,000 times higher have been reported; these higher exposure levels may also occur for users of products containing cumene outside of the manufacturing industry (e.g., painting and car repair).

Cumene is also present in small amounts (concentrations ranging from 1% to 5% or not quantified) in several consumer products including automobile fuel injector system cleaners, roof adhesives, some agricultural herbicides, fabric softener pads, and crib mattresses. Only trace levels of cumene have been detected in food, which may result from environmental or processing sources, or it may occur naturally. Cumene also has been detected (i.e., tens of μg per cigarette) in cigarette smoke.

2 Disposition and Toxicokinetics

Disposition and toxicokinetics refer to how a chemical can enter and leave the body, what happens to it once it is in the body, and the rates of these processes. Disposition includes absorption, distribution, metabolism, and excretion while toxicokinetics refers to the mathematical description (toxicokinetic models) of the time course of disposition of a chemical in the body. These data are important because they help identify the various factors that affect the toxicity of a chemical. These factors include routes and rates of absorption, tissue concentrations and their temporal changes, reactive metabolites, intoxication and detoxication reactions, routes of elimination, and species differences in these factors. Section 2.1 discusses the absorption, distribution, and excretion of cumene. Although no extensive toxicokinetic models for cumene have been identified, a two-compartment pharmacokinetic model is summarized briefly in Section 2.1.2, below. Metabolism is discussed in Section 2.2 and Section 2.3 provides a summary of Sections 2.1 and 2.2. The mechanistic implications of these data are discussed in Section 5.

2.1 Absorption, distribution, and excretion

Cumene is readily absorbed following inhalation exposure in humans and after inhalation, oral, or dermal exposure in laboratory animals (Chen *et al*. 2011, EC 2001, Seńczuk and Litewka 1976, WHO 1999). These studies also indicate that cumene is widely distributed, extensively metabolized, and rapidly excreted, primarily in the urine. Only one absorption and excretion study in humans was identified. This study was conducted in 10 healthy volunteers while other data were available from non-occupational exposure studies (see Section 1). Several cumene disposition and metabolism studies have been conducted in rats, mice, or rabbits.

2.1.1 Studies in humans

Absorption data in humans is limited to inhalation studies. Respiratory retention of cumene vapor in humans ranged from about 45% to 80% and declined with exposure duration (Brugnone *et al.* 1989, Seńczuk and Litewka 1976). Cumene absorption was directly proportional to the concentration of dimethylphenylcarbinol (2-phenyl-2-propanol), the primary urinary metabolite. No distribution data were available; however, one study did measure cumene in blood (Brugnone *et al.* 1989). Blood concentrations were correlated with cumene concentrations in air for one study population but not in another. Concentrations in blood were about 40 times higher than in alveolar air, which was consistent with a reported blood/air partition coefficient of 37. Urinary excretion of 2-phenyl-2-propanol was biphasic with an initial excretion half-life of 2 hours and a subsequent (post-exposure) half-life of 10 hours (Seńczuk and Litewka 1976). Maximum urinary excretion occurred after 6 to 8 hours of exposure, declined rapidly after exposure ceased, and approached zero after 48 hours. Other studies indicated that some cumene is eliminated in expired air. Trace levels of cumene were detected in some of the expired air samples collected from 28 nonsmoking, healthy volunteers who were selected to represent an urban population (Krotoszynski *et al.* 1977) and from 8 healthy male volunteers from the U.S. Air Force School of Aerospace Medicine (Conkle *et al.* 1975).

2.1.2 Studies in animals

Disposition studies in rats and mice exposed by inhalation, gavage, or intravenous (i.v.) injection show interspecies similarities and differences (Chen *et al.* 2011, EC 2001, WHO 1999). Cumene was absorbed rapidly from the stomach and the lungs and was detected in the blood of rats within 5 minutes after inhalation exposure (EC 2001, WHO 1999). In gavage studies in rats, maximum blood levels were reached within 4 hours after a dose of 33 mg/kg and 8 to 16 hours after a dose of 1,350 mg/kg. Dermal absorption was demonstrated in rats and rabbits but no details of these studies were provided (WHO 1999).

Tissue retention in rats and mice 24 hours after receiving single oral doses was less than 3% in rats and less than 1% in mice (Chen *et al.* 2011). Tissue concentrations were similar for male and female mice administered the low dose (10 mg/kg), but were higher in females exposed to the highest dose (1,000 mg/kg). At comparable single doses, tissue concentrations were significantly higher in rats than in mice, particularly in the kidneys. This suggests that mice are more efficient in metabolizing and excreting cumene than the rat. In rats, the tissue and blood concentrations were proportional to dose with the highest concentrations occurring in the kidneys after single or repeat doses. In mice, the tissue concentrations were more variable across the range of doses but were highest in the liver, kidney, and lung. After seven consecutive daily doses, the highest tissue concentrations occurred in the lungs. Higher tissue concentrations in rat kidneys and mouse lung correlate with the higher incidence of tumors in these tissues (see Section 4). Inhalation studies in rats have reported half-lives of cumene disappearance from blood as 3.9 to 6.6 hours (WHO 1999). Longer half-lives in blood (9 to 16 hours) were reported in gavage studies with rats. There was no evidence of cumene accumulation in tissues following high- or repeated-oral doses in rats or mice.

Excretion data show that the majority of the administered dose is excreted in the urine (70% to 90%) in rats and mice regardless of the route of administration (Chen *et al.* 2011, EC 2001, WHO 1999). Excretion in feces ranged from about 1% to 5.3%, and excretion as radiolabeled volatile organic compounds (VOCs) in expired air ranged from < 1% to about 22%. Cumene accounted for more than 95% of the VOCs excreted in expired air with α-methylstyrene accounting for 3% to 4% in mice and only a trace amount in rats. Increased excretion in the expired air with dose indicates possible saturation of metabolic pathways at high doses, and higher excretion in expired air in female mice than male mice indicates more efficient metabolism in males. Enterohepatic circulation of cumene and/or its metabolites was implied because about 37% of the total dose was detected in the bile in bile-duct cannulated rats, but very little was excreted in the feces in any treatment group. There was little difference in the excretion pattern following single or repeated daily oral doses. The distribution and elimination of cumene in rats following an i.v. bolus dose was described by a two-compartment pharmacokinetic model. The distribution half-lives were calculated to be 0.21 hours for males and 0.27 hours for females while elimination half-lives were 8.6 hours for males and 7.3 hours for females.

2.2 Metabolism

Cumene is extensively metabolized by cytochrome P-450 enzymes (specific subtypes were not identified) within hepatic and extrahepatic tissues, including the lung (WHO 1999). From studies in rabbits, mice, and rats, and evidence in humans, the primary metabolites of cumene are from oxidation of the side chain. Metabolism studies in mice and rats have shown several reactive metabolites may be produced through ring oxidation as well as side-chain oxidation of cumene.These oxidized metabolites are primarily excreted as sulfide or glucuronide conjugates.

2.2.1 Studies in humans

2-Phenyl-2-propanol was identified in urine samples from human volunteers exposed to cumene vapor for 8 hours (Seńczuk and Litewka 1976). This metabolite was not detected in urine samples collected before exposure but accounted for about 35% of the absorbed dose 48 hours after exposure. No other metabolites were reported. 2-Phenyl-2-propanol also has been identified as a primary cumene metabolite in rabbits, mice, and rats (discussed below) and indicates some similarity in cumene metabolism between humans and experimental animals.

2.2.2 Studies in animals

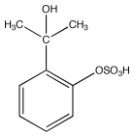
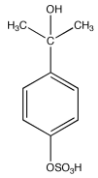
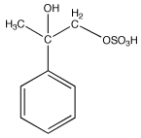
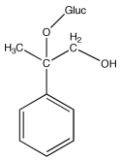
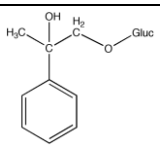
Four cumene metabolites were identified in rabbits following oral exposure: 2-phenyl-2-propanol, 2-phenyl-1-propanol, 2-phenylpropionic acid, and 2-hydroxy-2-phenylpropionic acid (Ishida and Matsumoto 1992, Robinson *et al.* 1955); however, no phenolic metabolites were reported in rabbits or in rats exposed to cumene (Bakke and Scheline 1970). Urinary metabolites detected in this study included 2-phenyl-1-propanol and 2-phenyl-2-propanol. Thus, side-chain oxidation rather than ring oxidation is the primary metabolic pathway in rats and rabbits.

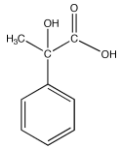
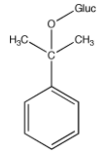
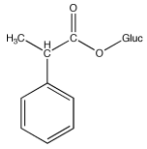
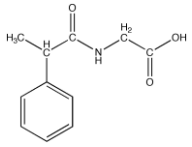
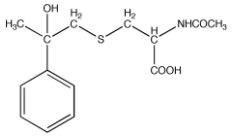
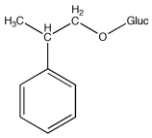
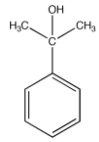
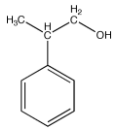
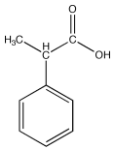
In a study of the metabolism and disposition of cumene in male rats or male and female mice exposed by oral or i.v. routes, Chen *et al.* (2011) identified sixteen metabolites (designated M1 to M16). In addition, *in vitro* metabolism of cumene was investigated using female rat and mouse liver and lung microsomes. Cumene was the primary compound detected in expired air but, in mice, up to 4% was α-methylstyrene. The 16 metabolites and their relative proportions in urine are shown in Table 2-1. Five of these metabolites (M6, M7, M9, M13, and M16) also were detected in bile from male rats, and three metabolites (α-methylstyrene, M14, and M15) were detected in the microsomal incubations. 2-Phenyl-2-propanol glucuronide was the most abundant metabolite in rat and mouse urine and rat bile. Mouse lung microsomes metabolized more cumene than microsomes from mouse liver, rat lung, or rat liver. These data indicate that metabolism primarily proceeds through side-chain oxidation (Figure 2-1a); however, this study was the first to demonstrate that ring oxidation also occurs *in vivo* (Figure 2-1b). Several reactive metabolites may be produced through ring oxidation of cumene and side-chain oxidation to 2-phenyl-2-propanol (M14). These include arene oxide intermediates, a quinone or semi-quinone radical derived from a catechol intermediate (not shown), and quinonemethide. Another potential reactive metabolite is α-methylstyrene. This metabolite can form by dehydration of M14 and could be further oxidized by P-450 to α-methylstyrene oxide. Although α-methylstyrene oxide was not detected, all metabolites

from the α-methylstyrene pathway (M5, M6, M7, M8, and M12) are derived from the oxide (Figure 2-1a).

Only one study of types of cytochromes P450 metabolizing cumene was identified, and it was limited to two mammalian cytochromes and one bacterial one. Henne *et al.* (2001) investigated the active site topography of rabbit CYP4B1 relative to rat CYP2B1 and bacterial CYP102 *in vitro* using cumene and several other aromatic substrates. CYP4B1 is primarily an extrahepatic monooxygenase and does not have a clearly defined endogenous substrate. Each of these cytochromes metabolized cumene to hydroxylated products. CYP2B1 and CYP102 preferentially formed 2-phenyl-2-propanol; however, reaction with CYP4B1 preferentially formed 2-phenyl-1-propanol along with a relatively small amount of 2-phenyl-2-propanol. CYP102 was the only enzyme that formed significant amounts of isopropylphenol, a ring-hydroxylated metabolite. α-Methylstyrene was not a significant metabolite for any of the enzyme preparations.

Table 2-1. Cumene metabolites in rat and mouse urine (oral exposure)

Metabolite	Structure	% of Radiolabeled peaks		
			Mouse	
		Male Rat	Male	Female
M1: (dihydrodiol?)	Not determined	N.D.	N.D. – trace	1.8 – 3.0
M2: 2-(2-hydroxy-2-propyl)phenylsulfate		trace	N.D. – trace	N.D. – 4.4
M3: 4-(2-hydroxy-2-propyl)phenylsulfate		7 – 11.4	N.D.	N.D. – trace
M4: (unknown)	Not determined	5.2 – 5.6	N.D.	N.D. – trace
M5: 2-hydroxy-2-phenylpropylsulfate		2.2 – 2.6	3 – 8.4	5.8 – 19.1
M6: 2-phenyl-1,2-propandiol 2-glucuronide		N.D. – 1.6	2.9 – 4.4	2.5 – 4.2
M7: 2-phenyl-1,2-propandiol 1-glucuronide		17.8 – 20.1	8.6 – 16.9	6.1 – 16.5

Metabolite	Structure	% of Radiolabeled peaks		
		Male Rat	Mouse	
			Male	Female
M8: 2-hydroxy-2-phenylpropionic acid		12.1 – 16.4	12.8 – 15.7	11.4 – 20.4
M9: 2-phenyl-2-propanol glucuronide		38.1 – 48.4[a]	33.5 – 42.8	29.8 – 36.8
M10: 2-phenylpropionyl glucuronide		–[b]	N.D.	N.D.
M11: 2-phenylpropionyl glycine		N.D.	5.1 – 11	2.8 – 3.7
M12: *S*-(2-hydroxy-2-phenylpropyl)-*N*-acetylcysteine		4 – 4.9[c]	trace	trace
M13: 2-phenyl-1-propanol glucuronide		4 – 4.9[c]	1.6 – 5.8[c]	1.5 – 2.3[c]
M14: 2-phenyl-2-propanol		trace – 1.8	N.D. – 1.5	N.D.
M15: 2-phenyl-1-propanol		N.D.	N.D. – 1.6	N.D.
M16: 2-phenylpropionic acid		trace – 2.1	N.D. – trace	N.D. – trace

Source: Chen *et al.* 2011.
N.D. = not detected.
[a] Total of M9 and M10.
[b] M10 reported as a minor metabolite that coeluted with M9.
[c] Total of M12 and M13.

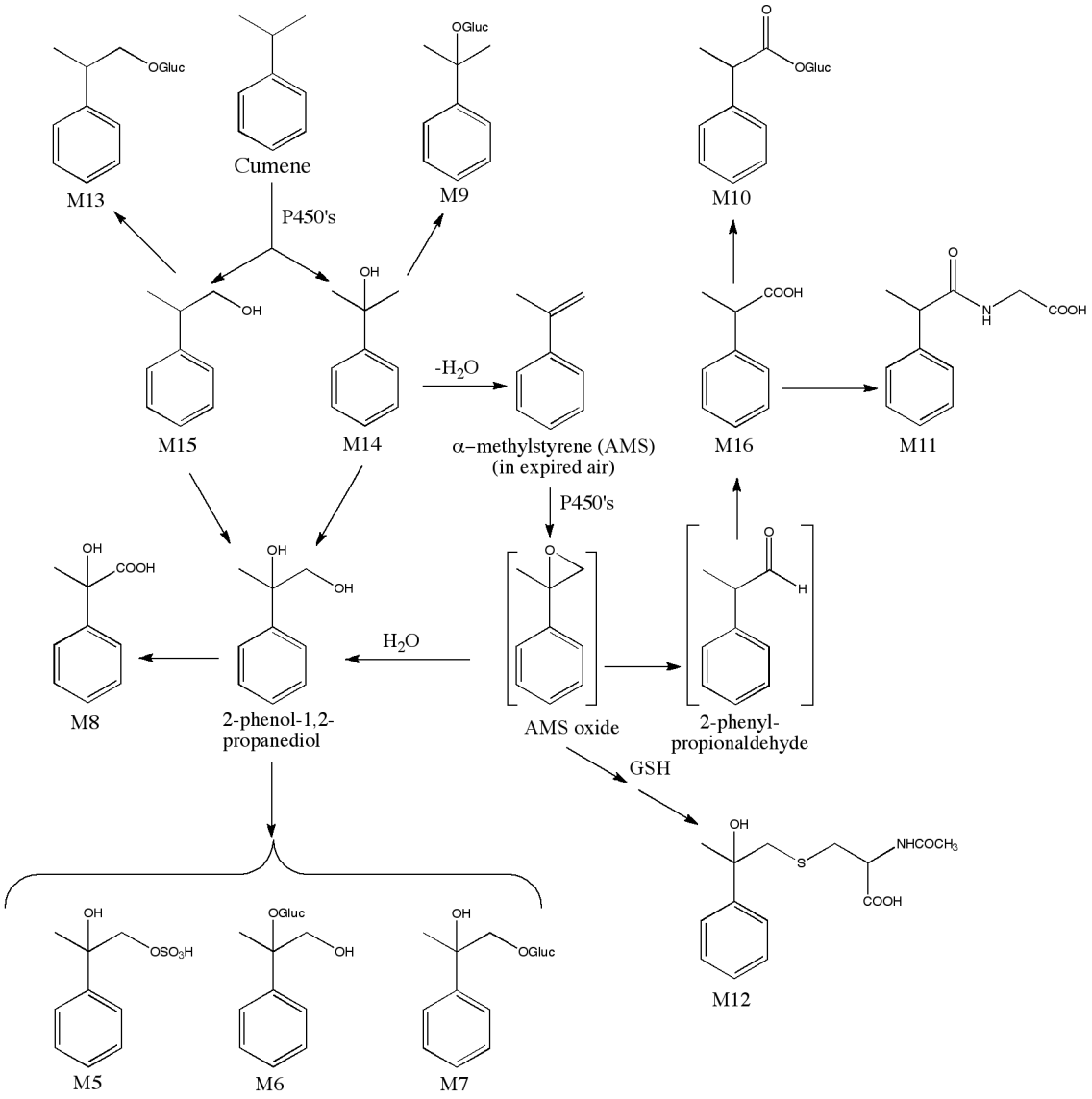


Figure 2-1a. Cumene metabolism: side-chain oxidation
Source: Chen *et al.* 2011

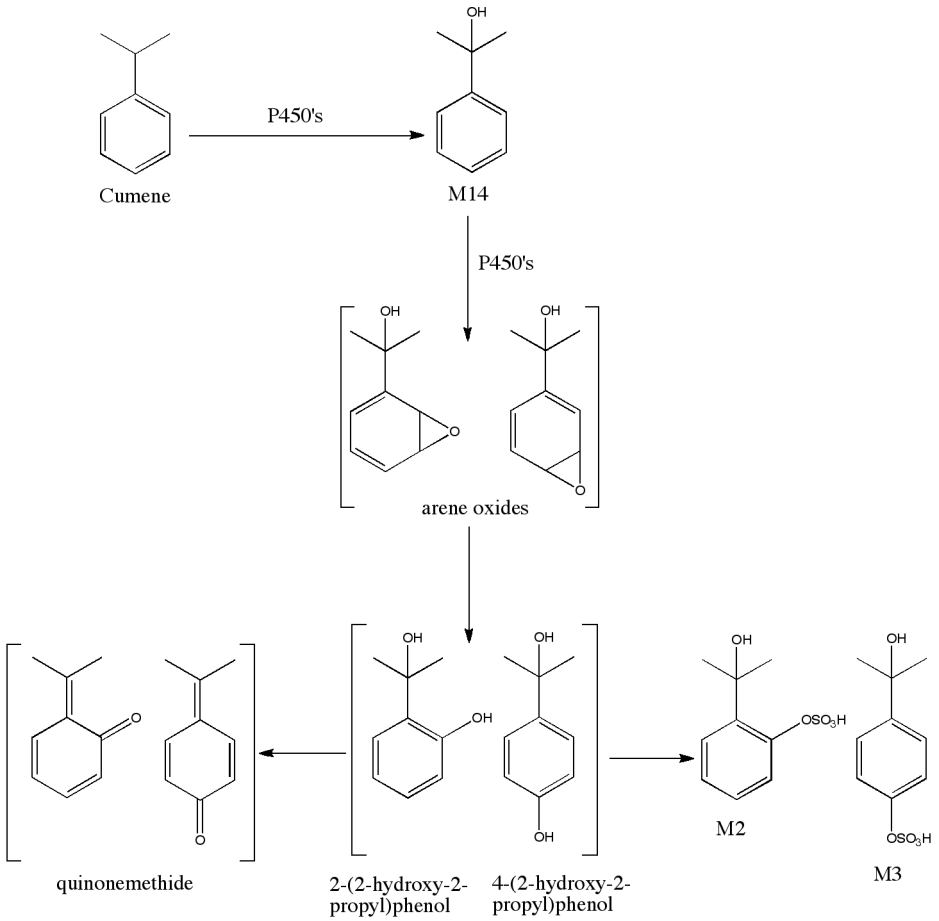


Figure 2-1b. Cumene metabolism: ring oxidation
Source: Chen *et al.* 2011

2.3 Synthesis and Summary

Few studies have investigated the absorption, distribution, metabolism, and excretion of cumene in humans. The available human data show that cumene or its metabolites are excreted in expired air and the urine. In a study of experimentally exposed volunteers, retention of cumene in the pulmonary tract ranged from 64% down to 45% with decreased retention with increasing exposure time. Urinary excretion of the primary cumene metabolite dimethylphenylcarbinol (2-phenyl-2-propanol) was monitored and the excretion half-life was biphasic with a half-life of 2 hours for phase I and 10 hours for phase II.

From studies in rodents and rabbits, it is known that cumene is readily absorbed following inhalation or oral exposure, and it is also absorbed through the skin and cumene is rapidly excreted in the urine. Disposition and excretion studies in rodents report that at 24 hours post-exposure, tissues contained less than 3% of the total dose cumene, with 70% to 90% of cumene excreted in the urine. Excretion of radioactivity in feces ranged from about 1% to 5.3%, and that in volatile organic compounds (VOCs) in expired air ranged from < 1% to about 22%. Cumene accounted for more than 95% of the radioactivity recovered in VOCs excreted in expired air with the cumene metabolite, α-methylstyrene, accounting for 3% to 4% in mice and a trace amount in rats. Enterohepatic circulation of cumene and/or its metabolites was implied because about 37% of the total dose was detected in the bile in bile-duct cannulated rats, but very little was excreted in the feces in any treatment group.

Cumene is extensively metabolized by cytochrome P-450 (specific subtypes were not identified) within hepatic and extrahepatic tissues, including the lung. Sixteen metabolites were identified in male rat urine, and five of these metabolites (2-phenylpropionic acid and four glucuronidated metabolites) also were detected in bile from male rats. These data indicate that metabolism primarily proceeds through side-chain oxidation, but ring oxidation also occurs *in vivo*. Proposed reactive metabolites that may be produced through ring oxidation of 2-phenyl-2-propanol include arene oxide intermediates, a catechol, and quinonemethide. Three metabolites (α-methylstyrene, 2-phenyl-2-propanol, and 2-phenyl-1-propanol) were detected in microsomal incubations; female mouse lung microsomes metabolized more cumene than female mouse liver, female rat lung, or female rat liver microsomes. 2-Phenyl-2-propanol glucuronide was the most abundant metabolite in rat and mouse urine and rat bile.

3 Human Cancer Studies

No epidemiological studies or case reports were identified the evaluated the relationship between human cancer and exposure specifically to cumene.

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4 Studies of Cancer in Experimental Animals

This section reviews and assesses carcinogenicity studies in experimental animals exposed to cumene. These studies were identified by searching databases, comprehensive reviews, and citations from studies retrieved from the literature searches as described in Appendix A. Identified citations were reviewed using exclusion and inclusion criteria that limited selection of the studies to those examining neoplastic lesions, non-neoplastic or preneoplastic lesions relevant to carcinogenicity, and subchronic studies that provide information on dose selection. Chronic inhalation studies (2-year) conducted by NTP and the associated subchronic studies (90-day) in mice and rats were the only studies identified that examined tissues for neoplastic or preneoplastic endpoints. Independent acute and subchronic inhalation studies in rats, guinea pigs, rabbits, dogs, and monkeys and a gavage study in rats were identified (Cushman *et al.* 1995, Fabre *et al.* 1955a, Jenkins *et al.* 1970, Wolf *et al.* 1956), but these studies did not examine tissues for neoplastic or preneoplastic endpoints or report any neoplastic lesions. The duration of these subchronic studies was not long enough to ensure the detection of cumene-induced carcinogenesis in the experimental animal models used at the doses tested and are not reviewed.

The characteristics, methodology, and relevant non-neoplastic findings from the chronic studies by NTP and the associated subchronic studies are reported in Sections 4.1. An assessment of the evidence for carcinogenicity is discussed in Section 4.2 and the recommendation for the level of evidence is provided in Section 4.3.

4.1 Studies in experimental animals: characteristics, methodology, and relevant non-neoplastic findings

Both the subchronic and chronic study in rats were conducted under FDA Good Laboratory Practice regulations in the same facility and using the same supplier and lot for the test chemical and husbandry and testing procedures as in the chronic study (NTP 2009). The subchronic studies in rats and mice were used to determine the test exposure groups in the chronic study. $B6C3F_1$ mice or F344/N rats were exposed to cumene (99.9% pure) in inhalation chambers for 6 hours and 10 minutes per day, 5 days a week, for either 14 weeks (subchronic studies, 10 males and 10 females per exposure group) or 105 weeks (chronic studies, 50 males and 50 females per exposure group), with controls exposed to filtered air only. (Note: The additional 10 minutes of exposure were based on experimental data for the time required to achieve 90% of the target concentration (T_{90}) after the beginning of vapor generation.) Complete necropsies and histopathology were performed on all animals. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were processed and stained for histopathologic examination.

4.1.1 Rats

Subchronic study

The subchronic study did not identify any neoplastic lesions at the exposure levels tested (0, 62.5, 125, 250, 500, and 1,000 ppm). Kidney and liver weights of males at exposures of 250 ppm or greater and liver weights of females at 1,000 ppm were significantly

increased. Clinical chemistry results indicated hepatocyte injury. Alanine aminotransferase, sorbitol dehydrogenase, and alkaline phosphatase activities decreased with increasing exposure. However, no exposure-related gross or microscopic lesions were observed in the liver. To assess nephropathy in rats, kidneys from male rats were evaluated for α_{2u}-globulin, soluble protein, and proliferating cell nuclear antigen. Kidneys of male and female rats were evaluated for histopathology and hyaline droplets (results relating to α_{2u}-globulin nephropathy are discussed in Section 5.2.4). Exposure selection for the chronic study was based on the low degree of toxicity found in the subchronic study demonstrated by minimal organ weight increases; survival and body weight gain were not decreased.

Chronic study

The exposure concentrations tested in the chronic study were 0, 250, 500, and 1,000 ppm. During the chronic study, survival of exposed groups was similar to that of controls and body weights were also similar.

No malignant neoplasms of the nasal mucosa were observed in this study. A significantly increased incidence of olfactory basal-cell and respiratory epithelial-cell hyperplasia in all exposure groups and goblet-cell hyperplasia at 250 ppm also occurred in males (Table 4-1). Goblet-cell hyperplasia was not increased in female rats. In females, there were significant incidences of olfactory basal-cell hyperplasia in all exposure groups and respiratory epithelial-cell hyperplasia in the high-exposure group. Hyperplasia of the respiratory epithelium of the nose was not observed in the subchronic study in rats or in the subchronic or chronic studies in mice. Neoplastic findings are discussed in Section 4.3.

Table 4-1. Incidence of preneoplastic and neoplastic nasal lesions observed in Fischer 344/N rats exposed to cumene by inhalation for 2 years

Sex	Conc (ppm)	Rats (#) at termination[#]	Olfactory basal-cell hyperplasia	Respiratory epithelial-cell hyperplasia	Goblet-cell hyperplasia	Adenoma (% incidence)[bc]
Male	0	26	0/50	0/50	3/50 (1.7)	0/50 (0.0)[d]
	250	23	19/50** (1.1)[a]	15/50** (2.0)	11/50* (2.3)	7/50**(17.6)
	500	27	27/49** (1.0)	16/49** (2.9)	7/49 (2.3)	18/49*** (43.2)
	1,000	24	26/50** (1.0)	23/50** (2.7)	5/50 (2.0)	10/50*** (23.3)
	trend[+]	—	NR	NR	NR	P = 0.004
Female	0	21	0/50	0/50	4/50	0/50 (0.0)[e]
	250	27	14/48** (1.0)	0/48	6/48	5/48* (12.2) [f]
	500	31	25/50** (1.0)	4/50 (3.0)	1/50	4/50 (9.3)
	1,000	32	31/50** (1.1)	6/50 * (2.3)	5/50	3/50 (6.9)
	trend[+]	—	NR	NR	NR	P = 0.320

Source: NTP 2009.
NR = not reported, Conc = concentration, # = number
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (compared with chamber controls by Poly-3 test).
[+]Determined by Poly-3 trend test.

[#]All 50 animals per exposure group were necropsied and included in tumor incidence calculations, except when examination was prevented by cannibalism or autolysis as noted by the denominator.
[a]Incidence (severity), average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[b]Number of animals with tumors; (Poly-3 estimated tumor percent incidence after adjustment for intercurrent mortality).
[c]Respiratory epithelium of the nose.
[d]Historical control range: 0%–2% for inhalation studies and studies by all routes.
[e]Historical control range: 0%–0% for inhalation studies and studies by all routes.
[f]Incidence includes multiple adenomas detected in male rats at 0 (0 ppm), 1 (250 ppm), 2 (500 ppm), 6 (1,000 ppm, $*P \leq 0.05$).

Renal tubule hyperplasia and hyperplasia of the transitional epithelium of the renal pelvis, considered to be preneoplastic lesions, were found to be significantly increased in males at the 500- and 1,000-ppm exposures; no significant increases were seen in females. Kidneys of males had mineralization of the renal papilla that significantly increased in incidence compared with the chamber control group, and severity values were higher in all exposed groups. Females had incidences of mineralization similar to or less than the chamber control group. See Section 5.2.4 ("Mechanisms and Other Related Effects") for a discussion of α_{2u}-globulin nephropathy as a potential mechanism for cancer induction.

4.1.2 Mice

Subchronic study

Exposure concentrations tested were 0, 62.5, 125, 250, 500, and 1,000 ppm. Eight out of 10 females died in the high-exposure group; all males and females in the other exposure groups survived to the end of the study. There were no changes in hematology or clinical chemistry variables for the surviving animals. Upon necropsy, liver inflammation was noted in both sexes of mice. Exposure concentrations for the chronic study were based on toxicity found in the subchronic study of a slight decrease in body weight gain in males along with minimal increases in organ weights and a significant increase in the incidence of liver necrosis. In females, selection of exposure groups was based on a decrease in survival at 1,000 ppm and significant increases in thymic necrosis as well as focal chronic inflammation of the liver and non-significant increases in forestomach lesions (squamous hyperplasia, acute inflammation, and chronic inflammation).

Chronic study

Exposures for the chronic study were 0, 250, 500, and 1,000 ppm in males and 0, 125, 250, and 500 ppm in females. During the chronic study, survival was significantly decreased in males, but not females and body weight gains for the male high-exposure group were less than for the control group, but were similar to the control group in females.

Lesions of the nose in mice consisted of hyperplasia or atypia of the olfactory epithelium and hyperplasia of Bowman's glands (olfactory epithelial glands) (Table 4-2). There was a significant increase in hyperplasia of the olfactory epithelium and Bowman's glands in exposed groups of male mice and in the 500-ppm exposure group of female mice. In particular, olfactory atypical basal-cell hyperplasia in four male mice in the high-dose

group had features of preneoplastic change. However, no nasal olfactory epithelial neoplasms in mice were found in this study.

Table 4-2. Incidences of hyperplastic lesions of the nose in B6C3F$_1$ mice exposed to cumene by inhalation for 2 years

Sex	Conc (ppm)	Rats (#) at termination[b]	Olfactory epithelial hyperplasia (severity)[a]		
			Basal-cell	Atypical basal-cell	Bowman's glands
Male	0	38	0/50	0/50	3/50 (1.0)
	250	34	0/50	0/50	11/50* (1.0)
	500	30	15/49** (1.0)	5/49* (1.6)	9/49* (1.1)
	1,000	23	33/48** (1.1)	11/48** (1.7)	23/48** (1.0)
	trend[+]		NR	NR	NR
Female	0	37	0/50	0/50	1/50 (1.0)
	125	36	1/50 (1.0)	0/50	4/50 (1.0)
	250	39	11/50**(1.0)	2/50 (1.0)	4/50 (1.0)
	500	35	25/50** (1.1)	10/50** (1.2)	11/50** (1.0)
	trend[+]		NR	NR	NR

Source: NTP 2009.
Conc = concentration, # = number, NR = not reported
[+]Determined by Poly-3 trend test.
*$P \leq 0.05$, ** $P \leq 0.01$ (compared with chamber controls by Poly-3 test)
[a]Average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

4.2 Assessment of neoplastic findings

The chronic inhalation study in B6C3F$_1$ mice and Fischer 344/N rats conducted by NTP was of sufficient duration to adequately assess the carcinogenic potential of cumene. Factors considered in study design were the number of animals per exposure group, exposure period, dose selection, monitoring of animal health, and complete necropsies of all animals and histopathologic examination of all major tissues. This study is considered a high quality study and provides strong evidence to support the cancer assessment. Details of study quality criteria and assessment are reported in Appendix C.

In the NTP 2-year bioassay, cumene exposure significantly increased the incidences of adenoma of the respiratory epithelium of the nose in all exposed groups of males with a positive trend and in the 250-ppm exposed female rats. Incidences in all exposed groups of rats exceeded the historical control ranges for inhalation studies and studies by all routes. Multiple adenomas were detected in male rats, but not female rats, at significant levels in the high-exposure group. Hyperplasia of the respiratory epithelium (see Table 4-1) and adenoma form a morphologic continuum. Adenomas of the respiratory epithelium of the nose in males are considered to be treatment related due to significant pairwise and trend exposure data and significant pairwise incidences of respiratory epithelial hyperplasia. Although it is possible that nasal respiratory epithelial adenoma of the nose can progress to adenocarcinoma, the tumor typically does not progress (Brown *et al.* 1991) and no evidence was reported of tumor progression to malignancy in this study.

The combined incidences of renal-tubule adenoma and carcinoma were significantly increased in male rats exposed to 500 ppm (mid-exposure) (Table 4-3). The incidences of adenoma, carcinoma, and adenoma and carcinoma (combined) in males exceeded the historical control ranges from inhalation studies and studies by all routes at all exposure levels except for carcinoma in the 250-ppm (low-exposure) group. Hyperplasia of renal tubules and renal pelvis in male rats was observed in 500- and 1,000-ppm (high-exposure) exposure groups, and increased mineralization of renal papilla was observed in all exposed groups (see Table 5-3, Section 5.2.4). Renal-tubule hyperplasia, adenoma, and carcinoma are part of a morphologic continuum. These results are considered to be treatment related based on evidence of neoplastic progression from hyperplasia of the renal pelvis and tubules, and tumor incidences outside of historical control values for adenoma, carcinoma, and adenoma and carcinoma (combined). No renal tumors were reported in females for any of the dose groups. The potential relevance to humans of these renal tumors in male rats and α_{2u}-globulin nephropathy, which is a mechanism of renal tumor formation specific to male rats, is addressed in Section 5.2.4.

Table 4-3. Incidences of kidney neoplasms observed in Fischer 344/N rats exposed to cumene by inhalation for 2 years

Sex	Conc. (ppm)	Rats (#) at termination	Renal Neoplasia (% incidence)[a]			Comments
			Tubule adenoma	Tubule carcinoma	Combined	
Males	0	26	1/50 (2.4)[b]	1/50 (2.4)[b]	2/50 (4.8)[c]	Hyperplasia of renal tubules and renal pelvis in 500 and 1,000 ppm dose groups and increased mineralization of renal papilla in all exposed groups (see Table 5.3 in "Mechanisms and Other Related Effects").
	250	23	4/50 (10.0)	1/50 (2.5)	5/50 (12.5)	
	500	27	5/50 (12.1)	3/50 (7.3)	8/50 (19.2)*	
	1,000	24	4/50 (9.3)	3/50 (7.0)	7/50 (16.2)	
	trend[+]	—	*P* = 0.219	*P* = 0.180	*P* = 0.087	
Females	0	21	0/50 [d]	0/50 [d]	0/50 [d]	
	250	27	0/50	0/50	0/50	
	500	31	0/50	0/50	0/50	
	1,000	32	0/50	0/50	0/50	

Source: NTP 2009. Conc = concentration, , # = number

*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (compared with chamber controls by Poly-3 test)

[+]Determined by Poly-3 trend test.

[a] Number of animals with tumors (Poly-3 estimated tumor percent incidence after adjustment for intercurrent mortality).

[b]Historical control range: 0%–2% for inhalation studies and studies by all routes.

[c]Historical control range: 0%–4% for inhalation studies and studies by all routes.

[d]Historical control range: not reported for inhalation studies and studies by all routes.

The incidence of interstitial-cell adenoma (including bilateral) of the testis was significantly increased at 1,000 ppm with a positive trend and exceeded the historical control range from inhalation studies (Table 4-4). Interstitial cell adenomas do not progress to malignancy. The severity grade of interstitial-cell hyperplasia increased across all dose groups (data not shown). Therefore, the results for interstitial-cell adenoma at the high-exposure concentration may have been exposure related.

Table 4-4. Incidences of testicular tumors observed in male Fischer 344/N rats exposed to cumene by inhalation for 2 years

Sex	Conc. (ppm)	Rats (#) at termination	Interstitial-cell adenoma (% incidence)[a]
Male	0	26	36/50 (80.0)[b,c]
	250	23	38/50 (84.6)
	500	27	40/50 (85.7)
	1,000	24	46/50** (96.1)
	trend[+]	—	*P* =0.006

Source: NTP 2009.
Conc = concentration, # = number
*$P \leq 0.05$, ** $P \leq 0.01$ (compared with chamber controls by Poly-3 test)
[+]Determined by Poly-3 trend test.
[a]Number of animals with tumors; (Poly-3 estimated tumor percent incidence after adjustment for intercurrent mortality).
[b]Historical control range: 66%–84% for inhalation studies.
[c]Historical control range: 66%–98% for studies by all routes.

Statistically significant incidences of malignant and benign lung tumors (alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and combined) in both sexes of exposed mice were detected for all treatment groups with significant trends, and incidences exceeded the ranges for historical controls by inhalation and by all routes (Table 4-5). Further, significant increases in bronchiolar hyperplasia and alveolar metaplasia were found in both sexes of all exposed mice. Alveolar/bronchiolar epithelial hyperplasia is considered a preneoplastic change and may progress to adenoma and carcinoma and is supportive of the cancer assessment. Based on positive pairwise comparisons, highly significant trend data, and historical control values, these results are considered to be treatment related.

Table 4-5. Incidences of pre-neoplastic and neoplastic lung lesions in B6C3F$_1$ mice exposed to cumene by inhalation for 2 years

Sex	Conc (ppm)	Mice (#) termination[c]	Pre-neoplastic lung lesions incidence (severity)[a]		Alveolar/bronchiolar tumors (% incidence)[b]		
			Alveolar epithelium bronchiolar metaplasia	Bronchiolar hyperplasia	Adenoma	Carcinoma	Combined
Male	0	38	5/50 (1.4)	0/50	13/50 (27.5)[d]	9/50 (19.1)[e]	19/50 (39.8)[f]
	250	34	43/50** (2.9)	11/50** (2.1)	31/50 (66.7)***	19/50 (41.5)*	38/50 (81.4)***
	500	30	42/50** (3.1)	17/50** (3.2)	31/50 (66.9)***	32/50 (70.5)***	42/50 (89.5)***
	1,000	23	39/50** (3.0)	18/50** (2.8)	29/50 (67.9)***	33/50 (71.3)***	43/50 (92.1)***
	trend[+]	—	NR	NR	$P \leq 0.001$	$P \leq 0.001$	$P \leq 0.001$
Female	0	37	0/50	0/50	1/50 (2.3)[g]	3/50 (6.7)[h]	4/50 (8.9)[i]
	125	36	42/50** (2.6)	17/50** (2.7)	26/50 (56.3)***	16/50 (35.3)***	31/50 (66.8)***
	250	39	49/50** (2.9)	10/50** (2.8)	36/50 (74.5)***	20/50 (41.9)***	42/50 (86.0)***
	500	35	47/50** (3.3)	14/50** (2.8)	38/50 (77.9)***	34/50 (69.5)***	46/50 (92.4)***
	trend[+]	—	NR	NR	$P \leq 0.001$	$P \leq 0.001$	$P \leq 0.001$

Source: NTP 2009.
NR = not reported. Conc = Concentration, # = number
*$P \leq 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$ (compared with chamber controls).
[+]Determined by Poly-3 trend test.
[a]Average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[b]Number of animals with tumors; (Poly-3 estimated tumor percent incidence after adjustment for intercurrent mortality).
[c]All 50 animals per exposure group were necropsied and included in tumor incidence calculations, except when examination was prevented by cannibalism or autolysis as noted by the denominator.
[d]Historical control range: 12%–26% for inhalation studies and 6%–28% for studies by all routes.
[e]Historical control range: 10%–24% for inhalation studies and 2%–24% for studies by all routes.
[f]Historical control range: 26%–44% for inhalation studies and 12%–44% for studies by all routes.
[g]Historical control range: 2%–8% for inhalation studies and 0%–12% for studies by all routes.
[h]Historical control range: 0%–12% for inhalation studies and 0%–12% for studies by all routes.
[i]Historical control range: 2%–14% for inhalation studies and 0%–18% for studies by all routes.

Female mice had statistically significant increased incidences of hepatocellular adenoma and adenoma and carcinoma (combined) at the high exposure, with significant positive trends (Table 4-6). These significantly increased incidences exceeded the historical control ranges for inhalation studies for hepatocellular adenoma and adenoma and carcinoma (combined) and the historical control range for all routes for combined tumors. Based on positive pairwise comparisons, significant trend data, and historical control values, these results are considered to be treatment related. Male mice had significantly increased incidences of eosinophilic foci in the liver at 500 and 1,000 ppm, while females had apparent increased incidences at 125 and 500 ppm, but not to a significant extent. Eosinophilic foci, hepatocellular adenoma, and hepatocellular carcinoma are thought to represent a morphologic continuum. However, male mice did not develop liver tumors at significantly increased incidences or with significant positive trends.

Table 4-6. Incidence of pre-neoplastic and neoplastic liver lesions in B6C3F$_1$ mice exposed to cumene by inhalation for 2 years

Sex	Conc (ppm)	Mice (#) at termination[b]	Eosinophilic foci	Hepatocellular tumors (% incidence)[a]		
				Adenoma	Carcinoma	Combined
Males	0	38	6/50	34/50 (70.6)[c]	13/50 (27.1)[d]	40/50 (81.0)[e]
	250	34	5/50	33/50 (69.9)	18/50 (38.1)	42/50 (85.8)
	500	30	16/50**	37/50 (77.9)	21/50 (43.3)	43/50 (87.2)
	1,000	23	14/50*	35/50 (79.5)	17/50 (37.8)	41/50 (87.1)
	trend[+]	—	NR	$P = 0.135$	$P = 0.184$	$P = 0.250$
Females	0	37	8/50	18/50 (40.5)[f]	10/50 (22.2)[g]	25/50 (55.6)[h]
	125	36	11/50	23/50 (50.0)	7/50 (15.5)	26/50 (56.5)
	250	39	7/50	27/50 (56.4)	6/50 (12.7)	29/50 (60.4)
	500	35	14/50	29/50 (59.8)*	12/50 (25.4)	36/50 (74.1)*
	trend[+]	—	NR	$P = 0.040$	$P = 0.311$	$P = 0.024$

Source: NTP 2009.
Conc = concentration, # = number, NR = not reported
*$P \leq 0.05$, **$P \leq 0.01$ (compared with chamber controls).
[+]Determined by poly-3 trend test
[a] Number of animals with tumors (Poly-3 estimated tumor incidence percent after adjustment for intercurrent mortality).
[b]All 50 animals per exposure group were necropsied and included in tumor incidence calculations, except when examination was prevented by cannibalism or autolysis as noted by the denominator.
[c]Historical control range: 30%–60% for inhalation studies and 14%–70% for studies by all routes.
[d]Historical control range: 18%–32% for inhalation studies and 8%–48% for studies by all routes.
[e]Historical control range: 50%–80% for inhalation studies and 20%–85% for studies by all routes.
[f]Historical control range: 12%–36% for inhalation studies and 2%–62% for studies by all routes.
[g]Historical control range: 6%–20% for inhalation studies and 0%–28% for studies by all routes.
[h]Historical control range: 22%–50% for inhalation studies and 8%–64% for studies by all routes.

In male mice, tumors in the blood vessels of the spleen (hemangiosarcoma) and in the thyroid gland (follicular-cell adenoma) may have been treatment related based on marginal increases over historical control values (Table 4-7). Male mice had a significant increase in hemangiosarcoma at the high-exposure treatment for the spleen and all organs; the incidence in the spleen exceeded the historical control ranges for inhalation studies and for all routes. However, these blood vessel tumors occur in multiple tissue types and are not specific to the spleen, and the incidence in all organs was within the historical control ranges for inhalation studies and for all routes. Male mice also had a significant increase in the incidence of adenoma of the thyroid gland at the high exposure, but the unadjusted overall tumor rate (6%) at the high exposure was within the historical control range (0%–6%) for inhalation studies and for all routes.

Table 4-7. Incidence of vascular and thyroid gland tumors in B6C3F$_1$ mice exposed to cumene by inhalation for 2 years

Sex	Concentration (ppm)	Mice (#) at termination	Hemangiosarcoma (% incidence)[a]		Thyroid gland: follicular-cell adenoma (% incidence)[a]
			All organs	Spleen	
Male	0	38	0/50 (0.0)[b]	0/50 (0.0)[c]	0/50 (0.0)[f]
	250	34	1/50 (2.2)	0/50 (0.0)	0/50 (0.0)
	500	30	2/49 (4.5)	0/49 (0.0)	0/49 (0.0)
	1,000	23	4/50*(9.9)	4/50* (9.9)	3/50** (7.5)[g]
	trend[+]	—	P = 0.015	P = 0.002	P = 0.010
Female	0	37	1/49[d] (2.3)	0/49 (0.0)[e]	1/50 (2.3)
	125	36	3/50 (6.6)	0/50 (0.0)	4/50 (8.9)
	250	39	6/50 (12.8)	3/50 (6.4)	0/50 (0.0)
	500	35	1/50 (2.1)	1/50 (2.1)	3/50 (6.4)
	trend[+]	—	P = 0.518N	P = 0.271	P = 0.432

Source: NTP 2009.
Conc = concentration, # = number
*$P \leq 0.05$, ** $P \leq 0.01$ (compared with chamber controls by Poly-3 test)
[+]Determined by Poly-3 trend test, a negative trend is indicated by N.
[a] Number of animals with tumors; (Poly-3 estimated tumor incidence percent after adjustment for intercurrent mortality).
[b]Historical control range: 0%–12% for inhalation studies and studies by all routes.
[c]Historical control range: 0%–4% for inhalation studies and studies by all routes.
[d]Historical control range: 2%–8% for inhalation studies and 2%–16% for studies by all routes.
[e]Historical control range: 0%–4% for inhalation studies and 0%–8% for studies by all routes.

[f]Historical control range is 0%-6% for inhalation studies and studies by all routes.
[g]The unadjusted incidence is 6%.

4.3 Preliminary recommendation on the level of evidence

These data meet the RoC criteria for sufficient evidence of carcinogenicity in experimental animals with an increased incidence of malignant and/or a combination of malignant and benign tumors in rats and mice or at multiple tissue sites. This conclusion is based on treatment-related malignant and/or a combination of malignant and benign

tumors in the kidneys of male rats, the lungs of male and female mice, and livers of female mice.

Benign tumors of the respiratory epithelium of the nose were identified in the nasal cavities of male and female rats, but no malignant tumors were described. Since these tumors do not typically progress to malignancy, the finding of benign tumors without the presence of malignancy does not meet the RoC criteria of increases in the incidence of malignant or combined malignant and benign tumors.

5 Mechanistic Data and Other Relevant Effects

This section reviews data related to identifying and evaluating putative mechanisms for the potential carcinogenicity of cumene including (1) genetic and related effects, (2) mechanistic considerations, and (3) mutagenic and/or carcinogenic effects of metabolites and analogues. The primary purpose is to identify potential mechanisms of action of carcinogenicity, review the strength of evidence for potential mechanisms, and discuss any key issues that address the relevance of carcinogenic effects observed in experimental animals to effects in humans.

5.1 Genetic and related effects

Cumene has been evaluated in mutagenicity and genotoxicity assays in several laboratories. Much of the information available is from several authoritative, peer-reviewed reports (EC 2001, EPA 1997, NTP 2009, WHO 1999), based on a series of unpublished genotoxicity studies submitted to the EPA in partial fulfillment of the Toxic Substances and Recovery Act (TSCA). The descriptions of the primary studies in these reviews are limited and do not allow for comprehensive evaluation. The database of genotoxicity studies of cumene consists of *in vitro* studies in bacteria and yeast (Section 5.1.1), and mammalian cells (Section 5.1.2), *in vivo* studies in rodents (Section 5.1.3) and mutation studies in mice (Section 5.1.4). Genotoxicity studies are also available on cumene metabolites (Section 5.1.5).

5.1.1 *In* vitro studies in bacteria and yeast

Cumene was tested in six studies using *Salmonella typhimurium* tester strains to measure mutagenic potential in a histidine reversion assay, in one study with *Escherichia coli* in a tryptophan reversion assay, and in one study in the yeast *Saccharomyces cerevisiae* D3 to measure mitotic recombination; the findings are reported in Appendix D, Table D-1. The *S. typhimurium* (Ames) assay can detect two types of DNA damage: base-pair substitution, producing a missense mutation (tester strains TA100 and TA1535), or frameshift mutation (tester strains TA97, TA98, TA1537 and TA1538).

Cumene was not mutagenic in any of the *S. typhimurium* strains tested using the spot test or standard plate incorporation Ames assay, with or without the addition of metabolic activation (EC 2001, Florin *et al.* 1980, NTP 2009, Simmon *et al.* 1977). One study (Tardiff *et al.* 1976) reported a positive mutagenic response in TA100; however, a subsequent study by the same researchers was negative (Simmon *et al.* 1977). Cumene was also negative in all tested strains using modifications of the standard Ames assay, including preincubation of the culture with cumene, treating cultures in a closed chamber or sealed tubes, and using hamster liver S9 instead of rat liver S9 for metabolic activation (EC 2001, NTP 2009, Simmon *et al.* 1977). An additional study reported that addition of cumene (10% by volume) to diesel fuel did not increase mutagenicity in *S. typhimurium* (strains not specified) (Jensen *et al.* 1988).

Although all of the *S. typhimurium* quantitative studies reported negative results for mutation induction by cumene, only three studies utilized the preincubation method, which is generally more sensitive than plate incorporation. One study (Simmon *et al.*

1977) performed the assay (plate incorporation) in a closed chamber – preferable for a volatile, water-insoluble substance, such as cumene – and results were negative when tested to treatment levels that were toxic to the cells. In the NTP (2012) study, special efforts were made to prevent a reduced exposure due to the volatility of cumene, by preparing dosing samples in capped (with septa) vials flushed with N_2 and carrying out the preincubation treatment in capped tubes. Using this modified technique, cumene was tested in *E. coli*, as well as *S. typhimurium* strains TA98 and TA100, and showed no mutagenic activity in these bacteria. Since all the NTP (2012) testing was performed to toxic levels, exposure of the cells to cumene was demonstrated to be adequate, under these conditions. Limitations are noted for some of these studies, including presenting averaged rather than raw data, not testing in a closed chamber, not testing to toxic doses, etc.; however, based on a review of all the available data, cumene is not mutagenic in the *S. typhimurium* or *E. coli* reversion assays.

Cumene was not mutagenic in the yeast *S. cerevisiae* D3 assay measuring mitotic recombination (*ade*$^-$ homozygosity), tested both with and without rat S9 (Simmon *et al.* 1977).

5.1.2 *In vitro* studies in mammalian cells

Cumene was tested in several mammalian *in vitro* studies to measure genotoxic effects including mutation, chromosomal aberration, cell transformation, and unscheduled DNA synthesis. Findings from these studies are reported in Appendix D, Table D-2.

Cumene was not mutagenic in mammalian cells, tested with and without rat liver S9, in the Chinese hamster ovary (CHO)/HGPRT assay (GLSC 1985a, Yang 1987, as described in EC 2001, NTP 2009). In addition, cumene did not induce chromosomal aberrations in CHO cells when tested to toxic doses without S9 added (EC 2001). A small but statistically significant increase in structural chromosomal aberrations per cell was observed for 156 µg/mL cumene treatment in the presence of S9 compared with the vehicle control; however, this increase was not significant relative to the untreated control. There was no statistically significant increase in the percentage of cells with aberrations due to cumene treatment.

Cell transformation in BALB/3T3 mouse embryo cells was initially reported as positive at 60 µg/mL but, when a data review called the result equivocal, the assay was repeated and gave negative results when tested to toxicity (EC 2001, NTP 2009). An initial study of unscheduled DNA synthesis (UDS) in F344 rat hepatocytes was positive at 16 µg/mL; however, a review of this study considered it invalid because of inconsistent responses in replicate cultures and the high incidence of repair-positive cells in negative controls. A subsequent study failed to find evidence of unscheduled DNA synthesis in rat hepatocytes at doses up to 24 µg/mL (higher doses were toxic) (EC 2001).

The available database of *in vitro* studies on cumene includes some peer-reviewed publications, but most of the available information is from reviews (EC 2001, EPA 1997, NTP 2009, WHO 1999) of several unpublished studies, which often did not have adequate information on study methodology and results. Overall, an evaluation of the *in vitro* test results indicates that cumene is not mutagenic in bacteria or mammalian cells. However, *in vitro* testing with small molecular weight volatile compounds such as cumene poses a number of challenges. For one, the chemical tends to volatilize from the medium and therefore may not be sufficiently available to the test cell or organism. This issue has been addressed in some studies by using a closed chamber or sealed tubes. Findings for chromosomal aberrations were inconclusive. Although positive results were initially reported for both cell transformation and UDS, repeat studies by different laboratories reported negative results. The repeat testing used somewhat varied methods (e.g., a different Pluronic surfactant was used, but the reason for and significance of this are not known) and the reported toxicity levels varied between original and retest for both assays. Toxicity levels should be similar in repeat testing; differences in toxic dose levels suggest that test parameters were changed that affected toxicity and potentially could also affect mutagenicity. A limitation of the cell transformation study in BALB/3T3 cells was that metabolic activation was not used. There are other problems with *in vitro* testing that are often overlooked (Eastmond 2012). These chemicals are often preferentially metabolized by CYP2E1, which is generally found at low levels in Aroclor 1254-induced rat liver S9. Common diluents used in *in vitro* studies such as DMSO, ethanol and methanol are also metabolized by CYP2E1 so the diluents can act as competitive inhibitors of the enzyme in the test system. Whether the same would occur with the CYP2F isoforms is unknown. As a result, some caution should be exercised in interpreting the negative results for these types of chemicals in *in vitro* studies.

5.1.3 *In vivo* studies of chromosomal and DNA damage by cumene in rodents

Cumene was tested in rodents *in vivo* for micronucleus induction in erythrocytes, from bone marrow or peripheral blood, by various treatment routes including gavage, inhalation, and intraperitoneal injection. DNA damage was assessed using the comet assay in several tissues from rats and mice treated with cumene by gavage. In an additional study, rats were treated with cumene by inhalation to assess oxidative damage using the fragment length analysis with repair enzyme (FLARE) assay in conjunction with the comet assay. Findings from these studies are reported in Appendix D, Table D-3.

Cumene was tested *in vivo* for micronucleus induction in erythrocytes of both bone marrow and peripheral blood in studies in male rats, and in both males and females of two strains of mice. These studies reported results for mature erythrocytes (normochromatic erythrocytes or NCEs), immature erythrocytes (polychromatic erythrocytes or PCEs), or both NCEs and PCEs.

In the mouse, cumene did not induce micronuclei in peripheral blood erythrocytes, in either males or females, when treatment was by inhalation (NTP 2009) or by gavage (NTP 2012); results were also negative for micronucleus induction in bone marrow erythrocytes when the mice (both sexes) were exposed to cumene by gavage (EC 2001).

Findings in rats were mixed. Exposure to cumene in male F344/N rats by intraperitoneal (i.p.) injection, in two independent trials, resulted in statistically significant increases in the induction of micronuclei in polychromatic erythrocytes in bone marrow as well as a statistically significant trend test (NTP 2009). The results for the two trials in this study were consistent, which argues against it being a false positive. However, in a second NTP study, male F344/DuCrl rats were treated by gavage and no increased micronucleus formation in peripheral blood erythrocytes was observed at any treatment dose (NTP 2012). Both of these studies were short term (3 to 4 days), but there were several differences between the protocols. Micronuclei in PCEs were measured in different tissues; bone marrow PCEs were assessed using microscope slide scoring, whereas, peripheral blood PCEs were scored by flow cytometry. In addition, the studies were done using different substrains of rats exposed by different routes of administration. It is unlikely that the results are explained by differences in the sensitivity of the micronucleus protocol assays because the study measuring micronuclei in peripheral blood restricted its analysis to the youngest reticulocytes (subpopulation of erythrocytes with the highest CD71 expression) that were least altered by the efficient action of the rat spleen in sequestering and destroying micronucleated red blood cells. In addition, the study evaluated 20,000 PCE and the methodology is considered to have similar sensitivity as the bone marrow assay. One plausible explanation for the inconsistent results may be the treatment doses and differences in the routes of administration used in these studies. The micronucleus-inducing dose in the i.p. study was 1250 mg/kg while the highest dose administered in the gavage study was 800 mg/kg. There were also differences in toxicity between the studies; no bone marrow toxicity was observed in the i.p. study but there was toxicity (as shown by decreased % PCE) when rats were treated by gavage. How the animal absorbs and metabolizes the chemical from these routes (i.p. and gavage) may differ, resulting in a higher or lower effective dose.

A study by Kim *et al.* (2008) used the formamidopyrimidine (Fpg)/endonuclease III (Endo III) FLARE assay to investigate cumene-induced oxidative DNA damage in hepatocytes and lymphocytes. The study was limited by high background values and inadequate reporting of methods and results and was determined to be inadequate for evaluation (see Appendix D, Table D-3).

The comet assay was used to detect DNA damage in the blood (leukocytes), liver, lung, and kidney of male rats and female and male mice administered cumene by gavage for four days (NTP 2012). Male F344 rats were treated with 200, 400, or 800 mg/kg cumene, female mice with 250, 500, or 1000 mg/kg, and male mice with 312, 625, or 1250 mg/kg. Results of the assay in the male rat showed a statistically significant increase in DNA damage in the liver at the high dose ($P = 0.004$, $P < 0.025$ is significant for pairwise comparisons) and a positive trend across doses of cumene ($P_{trend} = 0.002$, $P < 0.025$ is significant for trend test). No significant treatment effects were observed in the blood, lung, or kidney of the rat. In the female mouse, there was a statistically significant increase in DNA damage in the lung at the high dose ($P = 0.016$) and a positive trend ($P_{trend} = 0.008$). No significant treatment effects were observed in the blood, liver, or kidney of male or female mice and in the lung of male mice (see Appendix D, Table D-3). Recent evaluations have found that the comet assay detected nearly 90% of carcinogens that were negative or equivocal in the micronucleus assay and thus several

investigators have recommended a combined micronucleus/comet assay to broadly assess *in vivo* genotoxic potential (Kirkland and Speit 2008, Pfuhler *et al.* 2007).

5.1.4 Mutations in cumene-induced lung tumors in mice

Hong *et al.* (2008) evaluated spontaneous and cumene-induced lung tumors (alveolar/bronchiolar adenoma and carcinoma) in male and female $B6C3F_1$ mice for K-*ras* mutations in exons 1 and 2 (codons 12, 13, and 61) and *p53* mutations in exons 5 to 8. This study included data from 52 cumene-induced lung tumors (6 adenomas and 46 carcinomas), 7 spontaneously occurring carcinomas from concurrent controls, and 6 samples of normal lung tissue. Findings were also compared with *ras* mutation data in spontaneous lung tumors from 117 historical controls. Lung tumors also were examined for *p53* protein expression and loss of heterozygosity (LOH) at the *p16* locus on chromosome 4 and near the K-*ras* gene on chromosome 6. The data showed differences in the incidence of K-*ras* mutations between cumene-induced (87%) and spontaneous lung tumors (14%) and historical controls (28%) (Appendix D, Table D- 4). K-*ras* mutations (all dose groups combined) were more prevalent in males (41/45, 91%) than in females (4/7, 57%). The predominant K-*ras* mutations in lung tumors from cumene-exposed mice were codon 12 G to T transversion (36% vs. 18% in historical controls) and codon 61 A to G transition (29% vs. 6% in historical controls). Codon 12 G to A transition (42%) was the most common mutation in spontaneous lung tumors. There were no significant differences in *ras* mutations at codon 13 between spontaneous and cumene-induced lung tumors. Mutation spectra at codons 12 and 61 for cumene-induced and spontaneous lung tumors (historical controls) are compared in Figure 5-1.

Mutations in the *p53* tumor suppressor gene were not observed in seven spontaneous lung tumors in concurrent controls but occurred in 52% of cumene-induced lung tumors (Appendix D, Table D- 5). Data from historical controls were not provided. These *p53* mutations were identified in exon 5 (24/27, 89%) and exon 7 (3/27, 11%). As with K-*ras* mutations, *p53* mutations were more prevalent in males (26/45, 58%) than in females (1/7, 14%); however, relatively few tumors were available from female mice. Increased *p53* protein expression occurred in 56% of cumene-induced tumors but in only 1 of 7 spontaneous tumors. Both K-*ras* and *p53* mutations showed a dose-dependent increase (total of all exposed groups), and similar mutation rates were reported for adenomas and carcinomas.

LOH also occurred in cumene-induced mouse-lung tumors (mainly carcinomas) but not in spontaneous tumors. The prevalence of LOH on chromosome 4 near the *p16* tumor suppressor gene was 13% and that on chromosome 6 near the K-*ras* gene was 12%. Allele loss of *p16* has been detected in human non-small cell lung tumors. These data are similar to those reported for other chemically induced lung tumors from $B6C3F_1$ mice (Devereux *et al.* 2002, Sills *et al.* 1999b, Zhang *et al.* 2001). These studies showed a high correlation between LOH near K-*ras* and K-*ras* mutations in lung tumors induced by vanadium pentoxide or chloroprene. These studies further demonstrated that wild-type K-*ras* can be a mouse lung tumor suppressor gene and that loss of the wild-type allele may be necessary for mutant K-*ras* to drive mitogen-activated protein kinase (MAPK) activation and mouse lung tumorigenesis.

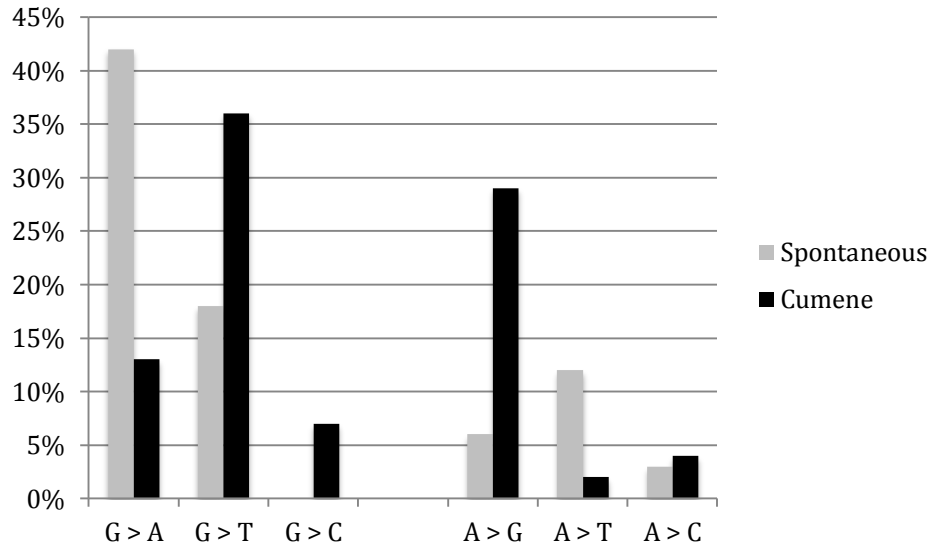


Figure 5-1. K-*ras* mutation spectra (codons 12 and 61) for spontaneous and cumene-induced lung tumors in B6C3F$_1$ mice
Source: Hong *et al.* 2008.

5.1.5 Genotoxic effects of cumene metabolites

Results from several genetic toxicology studies of α-methylstyrene, a metabolite of cumene, were reported by NTP (2007); the available information is summarized in Appendix D, Table D-6a and Table D-6b.

When tested *in vitro* in the *S. typhimurium* preincubation assay, α-methylstyrene was not mutagenic in any strains (TA97, TA98, TA100, and TA1535) tested with and without rat or hamster S9 metabolic activation (NTP 2007, Zeiger *et al.* 1992). α-Methylstyrene (50 to 150 μg/mL) significantly increased the frequency of SCEs in CHO cells in the presence of S9. Another study reported weakly positive results for SCE in human whole blood lymphocytes exposed to α-methylstyrene (Norppa and Vainio 1983). However, it did not induce mutations or chromosomal aberrations in CHO cells with and without S9. In an NTP (2007) study, exposure by inhalation to 0 to 1,000 ppm α-methylstyrene in male and female mice for three months caused dose-related increases in the females (but not males) for micronuclei in normochromatic erythrocytes, with statistical significance ($P = 0.0006$) at the highest dose as well as for the trend test ($P \leq 0.001$). However, micronuclei were not induced in the polychromatic immature erythrocytes, indicating that the observed micronucleus induction results reflected long-term accumulation of damage. The gender difference in micronucleus induction in mice is consistent with the gender difference in tumorigenicity of α-methylstyrene; the NTP concluded there was clear evidence of carcinogenic activity of α-methylstyrene in female mice based on increased incidence of hepatocellular adenoma and carcinoma and equivocal evidence in male mice based on marginal increases of hepatocellular adenoma or carcinoma (combined).

α-Methylstyrene oxide, a putative metabolite of cumene via P450 oxidation of α-methylstyrene, was mutagenic when tested *in vitro* with *S. typhimurium* strain TA100 in the preincubation assay (Rosman *et al.* 1986).

In conclusion, there is some evidence that the cumene metabolite, α-methylstyrene, is genotoxic: it induced SCEs *in vitro* in CHO cells and human lymphocytes and micronuclei in mice *in vivo*. α-Methylstyrene was not mutagenic in the *S. typhimurium* assay and did not induce chromosomal aberrations in CHO cells. α-Methylstyrene oxide, the oxidation product of α-methylstyrene, was mutagenic in the *S. typhimurium* assay.

5.2 Mechanistic considerations

The mechanism(s) by which cumene might cause carcinogenic effects are not understood. However, potential modes of action or molecular alterations have been identified. Cumene was associated with neoplasms in several tissue types in rats and mice and the tumor profiles showed some distinct species and gender differences. Renal tumors were observed in male rats only, while lung tumors were observed in mice but not in rats Proposed modes of action include species-specific metabolism leading to cytotoxic metabolites, and species and/or sex differences such as α_{2u}-globulin nephropathy in male rats. Epigenetic and genetic effects can result from these modes of action or occur through other means leading to carcinogenicity. Proposed mechanistic considerations are not mutually exclusive and more than one mechanism might operate in a particular tissue and are discussed below.

5.2.1 Mutational spectra and evidence for genotoxicity - lung tumors

Genetic alterations (see Section 5.1.4), gene expression and histone modifications (see Section 5.2.2) have been reported in the lung tumors from cumene-exposed mice in the 2-year bioassay and are different from those observed in spontaneous tumors.

Mutational data for cancer-related genes in target organs can provide important information for determining whether or not an agent acts through a mutagenic mechanism (e.g., direct interaction of a carcinogen with DNA and DNA repair processes); however, this evaluation must be done cautiously. Mutations may also reflect the selection of cumene-induced or spontaneous mutations that provide a growth advantage to preneoplastic and neoplastic cells (Sills *et al.* 1999a). Tumors that arise spontaneously or through non-genotoxic or indirect genotoxic mechanisms (indirect DNA damage) may also contain increased frequencies of proto-oncogene mutations (Eastmond 2012, Hong *et al.* 2008) and many of these molecular changes may be an effect rather than a cause of cell transformation (Stanley 1995).

The difference in the specific mutations (mutation spectra) in K-*ras* and *p53* genes between cumene-exposed mice and spontaneous lung tumors suggest that the lung tumors developed through different pathways of carcinogenicity and that the lung tumors in cumene-exposed mice were related to chemical exposure (Hong *et al.* 2008). The high frequency of K-*ras* mutations in adenomas (4 of 6) suggest that K-*ras* activation was a relatively early event and occurred either prior to or during this benign stage of carcinogenesis; however, the sample size was small (only 6/191 adenomas were

examined for *ras* mutations) and K-*ras* mutations were not examined in pre-neoplastic lesions, tumors less than 1 mm in size, or in normal tissue adjacent to neoplastic or pre-neoplastic lesions. Thus, the observed differences in mutation spectra between spontaneous and cumene-exposed tumors are required but not sufficient to determine whether or not cumene is genotoxic in mouse lung at the K-*ras* and *p53* genes.

Ras oncogene activation is common in both spontaneous and chemically induced lung tumors in mice. Mutational hot spots include codon 12 G > A transitions and G > T transversions and codon 61 A > T transversions and A > G transitions (Jackson *et al.* 2006, Stanley 1995). The incidence of GC > TA transversions, AT > GC transitions, and other prominent mutations for agent-induced and spontaneous mouse lung tumors reported in the NIEHS Genetic Alterations in Cancer (GAC) database and from Hong *et al.* (2008) are shown in Appendix D, Table D-8. Most of these chemicals are considered genotoxic or mutagenic and many caused a shift in the mutational spectrum (similar to cumene) compared with spontaneous tumors consistent with adduct formation. Although cumene forms reactive metabolites (see Section 2.2); no data on DNA adducts for cumene or its metabolites were identified and cumene is not mutagenic in *vitro.* No examples of a non-genotoxic chemical causing a shift in the mutational spectra (increased incidences of specific mutations compared with spontaneous tumors) similar to cumene were identified.

It is also possible that indirect (e.g., oxidative damage to DNA or genomic instability) DNA damage contributed to the mutation profile and development of lung tumors in mice exposed to cumene. G to T transversions in K-*ras* reported by Hong *et al.* (2008) are often associated with reactive oxygen species and are known to be caused by 8-oxo-deoxyguanosine adducts (Kino and Sugiyama 2005). No adequate studies were identified that evaluated 8-oxo-deoxyguanosine adducts or oxidative DNA damage with cumene exposure. However, the findings of DNA damage in female mouse lung tissue (as measured by the comet assay) provides some support that the G to T K-*ras* mutations may have been caused by cumene via DNA damage.

5.2.2 Gene expression and epigenetic effects – lung tumors

Global gene expression analysis was conducted to compare gene regulation patterns between normal lung tissue and cumene-induced tumor tissue from the NTP (2009) two-year bioassay with and without K-*ras* mutations (Wakamatsu *et al.* 2008). Cluster analysis identified significant expression changes between normal tissue from untreated animals and tumor tissue from exposed mice in genes associated with the extracellular signal-regulated kinase mitogen activated pathway (Erk MAPK). Differences also were observed for some of these genes between tumors with and without K-*ras* mutations. Although some genes were altered regardless of K-*ras* mutation status, many were significantly altered only in tumors with K-*ras* mutations (Appendix D, Table D-7). These data indicate that mouse lung carcinomas with K-*ras* mutations form differently from tumors without these mutations. Specifically, cumene-induced lung tumors with K-*ras* mutations were associated with increased expression of genes involved in the Erk MAPK signaling pathway, invasion and metastasis, inhibition of apoptosis, increased angiogenesis, and increased metastatic potential. The difference in gene expression suggests that cumene-induced carcinomas with K-*ras* mutations have a higher degree of malignancy than tumors without K-*ras* mutations. These authors noted that many of the genes with altered expression in the mouse tumor model represent major genes that may play a role in lung and other cancers in humans. This work was supported by findings that the cumene mouse model recapitulates molecular alterations (K-*ras* and *p53* mutations) found in human lung cancer (Hoenerhoff *et al.* 2009). Activation of the K-*ras* proto-oncogene and inactivation of the *p53* tumor suppressor gene are among the major genetic alterations detected in human pulmonary adenocarcinoma. Taken together, the results of the gene expression and mutational spectra studies suggest that, in cumene–induced lung tumors in mice, DNA damage and genomic instability can result in K-*ras* and *p53* dysregulation and upregulation and selection for pathways associated with a greater degree of malignancy and the development of lung cancer. Many of the genes with altered expression in the mouse tumor model represent major genes that may play a role in lung and other cancers in humans.

The potential involvement of epigenetic mechanisms in cumene-induced lung cancer using significance analysis of function and expression (SAFE) was investigated (Wakamatsu *et al.* 2008). SAFE is used to test functional categories in gene expression experiments and has the ability to detect changes in a set of genes that otherwise might have been missed when considering expression patterns of individual genes in isolation. Genes associated with the histone deacetylase (HDAC) complex were significantly altered ($P = 0.046$) in mouse lung carcinomas. Posttranslational modification (acetylation or deacetylation) of histone tails is a common epigenetic mechanism for regulating gene transcription. There was a stronger association between altered genes putatively associated with HDACs and tumors with K-*ras* mutations than with tumors without K-*ras* mutations; thus, K-*ras* activation may affect histone modification or vice versa. The potential role of methylation also was investigated using microarray analysis. There was no evidence that the methylation status of genes known to be methylated and downregulated (*Akap12*, *Gata2*, and *Timp3*) had changed in any of the cumene-induced lung tumors. Taken together, the genetic and epigenetic data suggest that mechanisms involved in causing alveolar/bronchiolar carcinomas observed in cumene-exposed mice

involve K-*ras* mutations resulting in increased Erk MAPK signaling and histone modification.

5.2.3 Disposition and species-specific metabolism leading to cytotoxic metabolites

Chen *et al.* (2011) compared the disposition and metabolism of cumene in male F344 rats and $B6C3F_1$ mice of both sexes following oral or intravenous administration (see Section 2). Several differences were noted that might partially explain the carcinogenic effects observed in these species. They reported that cumene-derived ^{14}C concentrations in the kidneys of male rats were significantly higher ($P < 0.0001$) than concentrations in the kidneys of male or female mice following exposure to similar oral doses (see Section 5.2.4). In female mice, the lungs had the highest ^{14}C concentration after seven consecutive daily doses, which is consistent with the higher incidence of alveolar/bronchiolar adenoma or carcinoma reported in mice in the NTP (2009) study. This increase in bioavailability may also explain the positive trend with dose of female mouse lung for DNA damage (as measured by the comet assay), but not in the male rat. In contrast, ^{14}C-cumene did not accumulate in rat lung (see Table 3-1) and did not induce lung tumors in rats. The *in vitro* study with female mouse and female rat lung and liver microsomes demonstrated that mouse lung microsomes were the most efficient in metabolizing cumene to 2-phenyl-2-propanol, 2-phenyl-1-propanol, and α-methylstyrene (Chen *et al.* 2011). 2-Phenyl-2-propanol, which has also been detected in human urine, can dehydrate to form α-methylstyrene or undergo further oxidation to form other metabolites, including ring-oxidized metabolites. These data are consistent with accumulation of [^{14}C]cumene in mouse lung after multiple doses and may help explain the carcinogenic effect of cumene observed in the mouse, but not rat, lung.

Alveolar/bronchiolar adenoma and carcinoma were increased in male and female mice exposed to cumene, while lung neoplasms were not increased in rats but nasal tumors were (NTP 2009). This tissue-response pattern for tumors in mice and rats has been observed for other chemicals containing aromatic rings. Cruzan *et al.* (2009, 2012) have proposed a mechanism by which the CYP2F2 isoform of cytochrome P450 in mice generates ring-hydroxylated metabolites that are cytotoxic to the lung. Cytotoxicity and associated inflammation can lead to generation of ROS, subsequent indirect DNA damage, and result in lung tumors. Cruzan *et al.* based this proposed mode of action on collective data from studies with styrene, ethylbenzene, coumarin, naphthalene, divinylbenzene, benzofuran, cumene and its metabolite α-methylstyrene. Although α-methylstyrene is included in this list, the conclusion of the NTP for the 2-year bioassay of that molecule in rats or mice was that no exposure-related neoplasms of the lung were observed (NTP 2007) (see Section 5.3.5).

While a role for CYP2F2-mediated metabolism of cumene to lung-cytotoxic metabolites has been postulated by Cruzan and coworkers, no direct evidence of involvement of this isoform in cumene metabolism was reported by Cruzan *et al.* or found in a search of the published, peer-reviewed literature. Very little information on specific cytochrome P450 isoforms responsible for metabolizing cumene was identified. Similarities with other alkylbenzenes indicate that CYP2E1 and CYP2F2 are likely candidates for mammalian enzymes that metabolize cumene (NTP 2009). Henne *et al.* (2001) reported that bacterial CYP102, but not rabbit CYP4B1 or rat CYP2B1, metabolized cumene *in vitro* to

isopropylphenol, a ring-oxidized metabolite. NTP (2009) proposed a metabolic activation pathway for cumene that included ring hydroxylation to isopropylphenol; although isopropylphenol has not been confirmed as a cumene metabolite in mammals, conjugates formed from hydroxyl-isopropylphenol (M2 and M3 in Table 2-3) have been detected.

Chen *et al.* was the first to identify three ring-oxidized metabolites of cumene *in vivo* (Figure 2-1b); however, it is unclear whether these explain the findings of lung tumors in mice and not in rats. One of the ring metabolites, 4-(2-hydroxy-2-propyl)phenylsulfate (designated as M3) was detected in rats but not mice (or only in trace amounts), and a second, 2-(2-hydroxy-2-propyl)phenylsulfate, designated as M2) was detected in female mice but was detected only at trace levels in male mice or rats. The third metabolite (thought to be a dihyrodrodiol) was detected in mice but not rats, consistent with the tumor profile; however, the structure was not confirmed (see Section 2.2 for more details). As mentioned in Section 4.2, bronchiolar hyperplasia and alveolar epithelial bronchiolar metaplasia also were significantly increased in both sexes of mice in the 2-year study, but no evidence of lung cytotoxicity (e.g., necrosis or inflammation) was observed in the subchronic or chronic studies.

5.2.4 α_{2u}-Globulin-nephropathy

One of the few mechanisms of action currently recognized by the EPA and IARC as unlikely to be relevant to humans is α_{2u}-globulin-associated nephropathy in male rats (EPA 1991a, IARC 1999). α_{2u}-Globulin is a low-molecular-weight protein that is synthesized in the liver of male rats and is regulated by complex hormonal interactions. Androgens stimulate synthesis, whereas estrogens suppress synthesis. Although humans and other species synthesize proteins that are similar to α_{2u}-globulin, there is no evidence that these proteins are involved in a similar nephropathy.

α_{2u}-Globulin nephropathy is characterized by the rapid accumulation of α_{2u}-globulin (observed as hyaline droplets) in lysosomes in the P2 segment of the proximal tubule. With continued exposure, hyaline droplet accumulation is followed sequentially by tubule epithelial single-cell degeneration and necrosis, granular cast formation at the cortico-medullary junction, sustained compensatory cell proliferation in the renal cortex, linear papillary mineralization, accelerated onset of cortical changes typical of chronic progressive nephropathy commonly seen in older rats, formation of sporadic foci of atypical hyperplasia within the proximal tubules, and progression to renal-tubule tumors (EPA 1991a, IARC 1999, Swenberg and Lehman-McKeeman 1999). There is a quantitative relationship between sustained renal-cell proliferation and the promotion of preneoplastic and neoplastic lesions in the male rat. These changes do not occur in similarly treated female rats. Furthermore, renal tumors associated with α_{2u}-globulin nephropathy typically have a longer latency period (requiring at least 18 months of continuous exposure) and a lower tumor rate (25% or less) than those associated with classical renal carcinogens (Swenberg and Lehman-McKeeman 1999).

Hyaline droplet accumulation in the proximal convoluted tubules is one of the most common histological findings in toxicity studies in rats (Hard 2008). However, many chemicals that induce hyaline droplets do not necessarily meet all the criteria of an α_{2u}-

globulin-associated response. Therefore, IARC (1999) developed a specific list of criteria, all of which must be met, for identifying agents that cause this syndrome (Table 5-1).

Table 5-1. Criteria for α_{2u}-globulin-associated nephropathy

1.	Lack of genotoxic activity (agent and/or metabolites) based on an overall evaluation of *in vitro* and *in vivo* data
2.	Male rat specificity for nephropathy and renal tumorigenicity
3.	Induction of the characteristic sequence of histopathological changes in shorter-term studies, of which protein droplet accumulation is obligatory
4.	Identification of the protein accumulating in the tubule cells as α_{2u}-globulin
5.	Reversible binding of the chemical or metabolite to α_{2u}-globulin
6.	Induction of sustained increased cell proliferation in the renal cortex
7.	Similarities in dose-response relationship of the tumor outcome with the histopathological end-points (protein droplets, α_{2u}-globulin accumulation, cell proliferation).

Source: IARC 1999.

It is important to note that renal tumors induced by α_{2u}-globulin accumulation in male rats must be assessed independently of evaluations regarding tumors at other sites or other exposed animals and, as mentioned above, some chemicals that induce hyaline droplets will not necessarily meet all the criteria associated with an α_{2u}-globulin response. The EPA (1991a) identified three possible categories for chemicals inducing renal tumors in male rats. These are: (1) the α_{2u}-globulin sequence of events accounts solely for the renal tumors, (2) other potential mechanisms account for the renal tumors, and (3) both α_{2u}-globulin-associated events and other potential carcinogenic mechanisms account for the renal tumors. Thus, the first question is whether or not α_{2u}-globulin is involved. If it is, then a substantial database for each specific chemical will be required to determine the extent to which the α_{2u}-globulin process is involved. Evidence of genotoxicity in short-term tests, nephrotoxicity and/or kidney tumors in female rats or either sex of other species, or data from specialized tests or biochemical studies may indicate that other carcinogenic mechanisms are involved.

The data from subchronic and chronic cumene toxicity studies and disposition studies in rats are consistent with α_{2u}-globulin nephropathy (Chen *et al.* 2011, Cushman *et al.* 1995, NTP 2009). Chen *et al.* (2011) reported that cumene-derived ^{14}C concentrations in the kidneys of male rats were significantly higher ($P < 0.0001$) than concentrations in the kidneys of male or female mice 24 hours after exposure to similar oral doses (see Sections 2.1 and 2.2). These data are consistent with binding of cumene and/or a metabolite with α_{2u}-globulin in the kidneys of male rats. Cushman *et al.* (1995) exposed male and female F344 rats to cumene vapor at 0, 100, 500, or 1,200 ppm for 6 hours/day, 5 days/week, for 13 weeks. Cumene exposure-related findings in this study were increased liver, kidney, and adrenal gland weights in both sexes for treatments at the higher doses. Interstitial nephritis, renal proximal tubular-cell hypertrophy and hyperplasia, and hyaline droplet formation were also observed in male rats exposed to 500 or 1,200 ppm. Although α_{2u}-globulin was not specifically identified in this study, the kidney lesions are consistent with those reported for male rats exposed to other chemicals

known to induce α_{2u}-globulin nephropathy. In the 2-week toxicity study by NTP (2009), groups of 5 male and female rats were exposed to cumene vapor concentrations of 250, 500, 1,000, 2,000, or 4,000 ppm for 6.2 hours/day, 5 days/week for 16 days. All animals in the high-dose group died on the first day. Kidney weights were increased in all exposed groups compared with controls. Male rats exposed to cumene vapor concentrations of 250 to 2,000 ppm had minimal to mild hyaline droplet accumulation in the renal tubular cortex. No evidence of other renal tubule epithelium damage was observed. In the 3-month study, groups of 10 male or female rats were exposed to cumene vapors at 62.5, 125, 250, 500, or 1,000 ppm for 6.2 hours/day, 5 days/week for 14 weeks. All animals survived to the end of the study. Relative kidney weights, but not absolute kidney weights, were increased in female rats exposed to 250 ppm or greater. Male rats had significantly increased kidney weights, increased amounts of α_{2u}-globulin in the kidneys, and increased incidences of medullary granular casts (Table 5-2). The severity of hyaline droplet accumulation and the incidence and severity of renal cortical tubule regeneration were slightly increased with increasing exposure concentrations. The presence of granular casts, combined with an exposure-related increase in the severity of renal cortical tubule hyaline droplet accumulation and regeneration, demonstrated that cumene exposure caused damage to the renal tubule epithelium. Cell proliferation indices were determined in male rats by staining a section of the left kidney with proliferating cell nuclear antigen (PCNA) complexed with avidin and biotin. PCNA analyses indicated that the mean numbers of proximal tubule cells in *S*-phase were significantly increased in the two highest dose groups; however, the number of cells labeled and the labeling index were not significantly different from the control group.

Table 5-2. Renal toxicity data for male rats exposed to cumene vapor for 3 months

Conc. (ppm)	Kidney weight (g)		α_{2u}-Globulin (nmol/g kidney)	Cortical renal tubules		Medullary granular casts
	Absolute	Relative		Hyaline droplet accumulation	Regeneration	
0	0.92	2.96	172.2 ± 22.3	10[a] (1.1)[b]	8 (1.0)	0
62.5	0.98	3.13**	328.1 ± 69.6	10 (1.4)	6 (1.2)	0
125	1.01*	3.13**	383.4 ± 46.3**	10 (1.9)	8 (1.5)	2 (1.0)
250	1.06**	3.19**	420.7 ± 50.1**	10 (2.4)	10 (1.8)	8** (1.5)
500	1.07**	3.41**	363.2 ± 41.4**	10 (3.0)	10 (2.1)	10** (2.5)
1,000	1.15**	3.56**	575.2 ± 74.8**	10 (2.9)	10 (2.1)	9** (2.2)

Source: NTP 2009.
* $P \leq 0.05$ (compared with chamber controls).
** $P \leq 0.01$.
[a]Number of animals with lesion (10 animals examined per group).
[b]Average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

In NTP's 2-year study, incidences of renal tubule hyperplasia, mineralization of the renal papilla, and hyperplasia of the transitional epithelium of the renal pelvis were significantly increased in male rats (Table 5-3). Renal tubule hyperplasia was distinguished from regenerative epithelial changes commonly seen as part of nephropathy and was considered a preneoplastic lesion. Renal tubule hyperplasia, adenoma, and carcinoma are recognized as part of a morphologic continuum. Incidences of hyperplasia

of the transitional epithelium of the renal pelvis were significantly increased in the two highest dose groups, and the hyperplasia also increased in severity. This lesion is common in rats and frequently increases with the severity of nephropathy. Incidences of nephropathy in exposed groups of rats were not significantly different from chamber controls; however, the incidence and severity of nephropathy in both males and females showed a slight increase with dose.

Table 5-3. Renal toxicity data for rats exposed to cumene vapor for 2 years

Sex	Conc. (ppm)	Renal tubule hyperplasia	Renal papilla mineralization	Renal pelvis transitional epithelium hyperplasia	Nephropathy
Male	0	0	5 (1.0)	3 (1.7)	47 (2.3)
	250	3[a] (3.3)[b]	35** (1.7)	5 (1.8)	47 (2.6)
	500	8** (2.6)	44** (2.1)	14** (2.4)	47 (2.9)
	1,000	6* (2.2)	41** (2.1)	15** (2.0)	50 (2.7)
Female	0	NR	6 (NR)	1 (NR)	38 (1.4)
	250		3	1	37 (1.5)
	500		4	6	41 (1.9)
	1,000		6	1	44 (1.9)

Source: NTP 2009.
NR = Not reported.
*$P \leq 0.05$ (compared with chamber controls).
**$P \leq 0.01$.
[a]Number of animals with lesion (50 animals examined per group).
[b]Average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

The NTP (2009) concluded that the nonneoplastic lesions of the kidney observed in male rats were characteristic of α_{2u}-globulin accumulation. Renal tubule tumors occurred only in male rats and at doses that also resulted in increased histopathological end-points associated with α_{2u}-globulin nephropathy. However, the available data do not clearly show that all of the IARC (1999) criteria (see Table 5-1) were met. Criteria that are questionable include the following: lack of genotoxicity, male rat specificity for nephropathy, and evidence of sustained cell proliferation. Reversible binding to α_{2u}-globulin was not assessed.

Overall, the available evidence for the genotoxicity of cumene is equivocal, therefore, we cannot rule out a genotoxic mechanism as contributing to carcinogenesis (see Section 5.1 for an assessment of the genotoxicity studies).

Kidney tumors occurred only in male rats but there was some evidence of nephrotoxicity in female rats. The incidence and severity of nephropathy increased slightly with dose in both male and female rats in the 2-year study. Kidney weights also were increased in exposed male and female rats in the 2-week and 3-month studies.

Although α_{2u}-globulin accumulation was identified in the male rat kidney in the subchronic study, no binding data with cumene were available for either the subchronic or chronic studies. Data were inadequate to determine if there was a sustained increase in

cell proliferation in the renal cortex. Cell proliferation data were available only for the 2-week study. Although there was an increase in the number of cells in *S*-phase, the number of labeled cells and the labeling index were not increased. This is in contrast with data reported for *d*-limonene, a classic α_{2u}-globulin nephropathy-inducing chemical. Dietrich and Swenberg (1991b) reported that male rats exposed to *d*-limonene had a 4- to 5-fold increase in the labeling index of proximal tubule cells after 5 and 30 weeks of exposure. In that study, cell proliferation was determined by incorporation of 5-bromo-2'-deoxyuridine delivered via osmotic mini pumps and by immunohistochemistry rather than by PCNA staining.

Taken together, the available data indicate that cumene exposure induces α_{2u}-globulin-associated nephropathy in male rats; however, other mechanisms could not be unequivocally ruled out. Although limited, some data suggest weak genotoxic activity for cumene metabolites and nephropathy in female rats exposed to cumene.

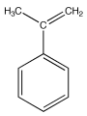
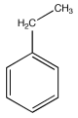
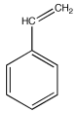
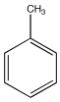
5.2.5 Carcinogenicity of metabolites and analogues

Cumene is structurally similar to several alkylbenzenes including α-methylstyrene, ethylbenzene, styrene, and toluene (Table 5-4). These compounds have been tested for carcinogenicity by the NTP (1979, 1990, 1999, 2007). No other well-conducted carcinogenicity studies were identified for any of these compounds other than styrene. α-Methylstyrene, which is a metabolite of cumene, had clear evidence of carcinogenic activity in female mice (hepatocellular adenoma and carcinoma), equivocal evidence in male mice (marginal increase in combined incidences of hepatocellular adenoma and carcinoma), some evidence in male rats (renal-tubule adenoma and carcinoma combined), and no evidence in female rats (NTP 2007). The NTP concluded that both the toxicity and carcinogenicity of cumene are more widespread that those of its metabolite, α-methylstyrene (NTP 2009). α-Methylstyrene has not yet been reviewed for possible listing in the Report on Carcinogens (RoC) but is listed by IARC as possibly carcinogenic to humans (Group 2B) (IARC 2012).

There was clear evidence of carcinogenic activity of ethylbenzene in male rats (renal tubule neoplasms) and some evidence of carcinogenic activity in female rats (renal tubule adenomas) and mice of both sexes (lung or liver neoplasms) (NTP 1999). Ethylbenzene has not been reviewed for possible listing in the RoC.

Styrene was recently reviewed and listed in the RoC as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals based on lung tumors in three strains of mice by two routes of administration (NTP 2011). There was equivocal evidence that styrene caused mammary tumors in female rats. There was no evidence of carcinogenic activity in rats or mice exposed to toluene (NTP 1990).

Table 5-4. Cumene analogues tested for carcinogenicity.

Chemical	Molecular weight	Structure	Tumor site(s)[a]			
			Mice		Rats	
			Male	Female	Male	Female
α-Methylstyrene	118.2		–[b]	Liver	Kidney	None
Ethylbenzene	106.2		Liver, lung	Liver, lung	Kidney	Kidney
Styrene	104.2		Lung	None	None	–[c]
Toluene	92.1		None	None	None	None

Sources: Cruzan *et al.* 2001, NTP 1979, 1990, 1999, 2007, 2011.
[a]Tumor sites listed only if NTP concluded there was some or clear evidence of carcinogenicity or other studies found treatment-related increases in tumor incidence.
[b]Equivocal evidence of liver tumors.
[c]Equivocal evidence of mammary tumors.

2-Hydroxy-2-phenylpropionic acid (M8) was the second most abundant cumene metabolite in mice and the third most abundant in rats as reported by Chen *et al.* (2011) (see Table 2-1). This compound also is known as phenyllactic acid. Phenyllactic acid may be formed endogenously through degradation of phenylalanine. Rauschenbach *et al.* (1975) investigated the carcinogenic effects of phenyllactic acid and *p*-hydroxyphenyllactic acid in mice. *p*-Hydroxyphenyllactic acid is an endogenous metabolite of tyrosine that is excreted in high concentrations in the urine of leukemia patients but is rarely detected in healthy individuals. C57BL/6 and CC57BR mice were exposed to phenyllactic acid and *p*-hydroxyphenyllactic acid administered by subcutaneous injections twice a week for 16 to 20 weeks. The total dose per mouse was 42 mg for *p*-hydroxyphenyllactic acid and 50 mg for phenyllactic acid (CC57BR mice only). The study was terminated after 22 months. Mice treated with *p*-hydroxyphenyllactic acid had an increased incidence of several neoplasms (leukemia, lung adenoma, vascular tumors, hepatomas, and benign and malignant bladder tumors). Tumors (primarily leukemia, lung adenoma, and hemangioma) also occurred in CC57BR mice treated with phenyllactic acid, but these results were not considered significant because the tumor profile was similar to the spontaneous tumors observed in the control group. Total tumor incidences were 4/29 (14%) in C57BL/6 controls, 10/26 (38%) in CC57BR controls, 19/42 (45%) in CC57BR mice exposed to phenyllactic acid, 54/84 (64%) in C57BL/6 mice exposed to *p*-hydroxyphenyllactic acid, and 61/74 (82%) in CC57BR mice exposed to *p*-hydroxyphenyllactic acid.

2-Phenylpropionic acid was one of the minor cumene metabolites identified in rat and mouse urine by Chen *et al.* (2011) (see Table 2-1). Ahmad and Caldwell (1994) demonstrated that 2-phenylpropionic acid is a peroxisome proliferator in rats. The (*R*)- and (*S*)-enantiomers showed similar potency. Peroxisome proliferation in rodents is characterized by hepatomegaly, proliferation of peroxisomes with associated enzyme changes, increased mitochondrial number and enzyme levels, proliferation of the smooth endoplasmic reticulum, enhanced synthesis of cytochrome P450 isoenzymes of the 4A family, and hepatocarcinogenesis (Ahmad and Caldwell 1994). Incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in female mice in the high-dose group in the cumene carcinogenicity study (NTP 2009); however, peroxisome proliferation was not reported.

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6 Overall Cancer Evaluation – Synthesis of Animal, Human, and Mechanistic Data

Cumene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. Although some cancer tissue sites are candidates for species-specific mechanisms, there were no compelling data to indicate that cumene causes cancer by mechanisms that would not occur in humans. No epidemiological studies were identified that evaluated the relationship between human cancers and exposures specifically to cumene.

6.1 Cancer studies in experimental animals

Sufficient evidence for carcinogenesis by inhalation of cumene was found in mice and rats. This conclusion is based on treatment-related malignant and/or a combination of malignant and benign tumors in the kidneys of male rats, the lungs of male and female mice, and livers of female mice (NTP 2009). Malignant and benign lung tumors (alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma combined) in both sexes of mice and malignant and benign liver tumors (hepatocellular adenoma and adenoma or carcinoma combined) in female mice were detected with a significant trend with increasing exposure concentrations. Benign or malignant kidney tumors (tubule adenoma or carcinoma combined) and benign nasal tumors (respiratory epithelium of the nose adenoma) in male rats had significant increases over control data with a significant positive trend for nasal tumors. Less robust evidence for carcinogenesis was reported for a significant increase in benign tumors of the nose (respiratory epithelium adenoma of the nose) in female rats.

Benign tumors of the respiratory epithelium were identified in the nasal cavities of male and female rats, but no malignant tumors were identified. Since these tumors do not typically progress to malignancy, the finding of benign tumors without the presence of malignancy does not meet the RoC criteria of increases in the incidence of malignant or combined malignant and benign tumors.

Tumors that may have been related to cumene exposure were found in the blood vessels (hemangiosarcoma primarily of the spleen) and thyroid gland (follicular-cell adenoma) of male mice and testes (interstitial-cell adenoma) of male rats.

6.2 Mechanistic and other relevant data

The mechanisms by which cumene causes cancer in experimental animals are not understood; however, several possible modes of action have been identified. These include genetic and epigenetic effects, metabolic activation leading to cytotoxic metabolites, and α_{2u}-globulin nephropathy.

Chemical agents that induce cancer in multiple tissues in more than one species are frequently genotoxic carcinogens. Although cumene was not mutagenic or genotoxic in most of the standard *in vitro* and *in vivo* assays, there was evidence from the comet assay that cumene causes DNA damage in the male rat liver and female mouse lung. It has been shown that cumene metabolism primarily proceeds through side-chain oxidation, but ring

oxidation also occurs *in vivo* (Chen *et al.* 2011). Metabolism of cumene to proposed electrophilic intermediates by side-chain oxidation of α-methylstyrene to α-methylstyrene oxide or by ring oxidation to arene oxides could potentially cause DNA damage. Although α-methylstyrene was not mutagenic in bacteria, there is some evidence that it may cause chromosomal damage in rodents and cultured cells, and α-methylstyrene oxide is mutagenic in bacteria. Thus, a genotoxic mechanism of action for cumene (presumably via its metabolism to α-methylstyrene or other chemicals) could not be ruled out.

The mutation spectra of K-*ras* and *p53* in lung tumors from mice exposed to cumene are different from the mutation spectra observed in spontaneous lung tumors and suggest that DNA damage (either direct damage from adduct formation or indirect damage through reactive oxygen species) and genomic instability were involved (Hong *et al.* 2008). The K-*ras* and *p53* mutations observed in cumene-induced lung tumors, and many of the genes with altered expression (e.g., Erk MAPK signaling, invasion and metastasis, inhibition of apoptosis, increases in angiogenesis, and increased metastatic potential) recapitulate molecular alterations found in human lung and other cancers.

Alveolar/bronchiolar neoplasms observed in mice but not in rats may be partially explained by differences in disposition and metabolism. Chen *et al.* (2011) reported that cumene-derived ^{14}C concentrations were highest in the lungs of female mice after seven consecutive daily doses. In rats, ^{14}C concentrations in lungs did not increase after multiple doses. Metabolism studies using mouse and rat lung and liver microsomes demonstrated that mouse lung microsomes were the most efficient in metabolizing cumene, which was consistent with accumulation of cumene metabolites in mouse lung after multiple doses. Based on a comparison with ethylbenzene, styrene, and other compounds that also induced lung tumors in mice but not in rats, Cruzan *et al.* (2009, 2012) proposed that species-specific metabolism in the Clara cells of mouse lung by CYP2F2 results in the production of cytotoxic metabolites that produce tumors. However, there are very few data on the specific P450 isoforms responsible for metabolizing cumene. CYP2E1 and CYP2F2 are likely candidates based on similarities with other alkylbenzenes, but metabolism of cumene by CYP2F2 in mouse lung has not been demonstrated to date. The orthologous isozyme, CYP2F1, is found in human lung. Therefore, these data are insufficient to conclude that mouse lung tumors are not relevant to humans based on species-specific metabolism to cytotoxic metabolites. In the NTP chronic study, bronchiolar hyperplasia and alveolar epithelial bronchiolar metaplasia were significantly increased in both sexes of mice; however, there was no evidence of cytotoxicity in the lung (e.g., necrosis or inflammation) in this study or in the 3-month subchronic study. As mentioned above, the gene expression data provide some evidence of similar molecular targets in mouse and human lung. Thus, no experimental evidence is available that argues against the relevance of the mouse lung tumors to humans.

The relevance of male rat kidney tumors based on α_{2u}-globulin nephropathy as a possible mechanism of action was also reviewed. α_{2u}-Globulin nephropathy is a recognized mechanism associated with kidney tumors in male rats and is not considered relevant to humans. Both IARC (1999) and the USEPA (1991a) have identified specific criteria and

a sequence of events for evaluating this possible mechanism of action. Although the available data are consistent with an α_{2u}-globulin nephropathy mode of action in renal tumor formation, all of the criteria were not met. Criteria that are questionable include the following: lack of genotoxicity, male rat specificity for nephropathy, and evidence of sustained cell proliferation in the renal cortex. Therefore, other modes of action could not be unequivocally ruled out and the human relevance of the kidney tumors in male rats was not dismissed.

At least one metabolite (α-methylstyrene) of cumene is carcinogenic in experimental animals and increased hyaline droplet formation in male rats consistent with α_{2u}-globulin nephropathy (Morgan *et al.* 1999). Under similar exposure conditions as cumene, α-methylstyrene caused renal tumors in male rats and liver tumors in male and female mice, but did not cause lung tumors or benign nasal tumors (NTP 2007). NTP (2009) concluded that both the toxicity and carcinogenicity of cumene was more widespread than that of α-methylstyrene; therefore, this metabolite cannot be the sole active contributor to the carcinogenicity of cumene.

There is little information on metabolism of cumene in humans, but it is known that the primary urinary metabolite is the same one found in rodents, 2-phenyl-2-propanol, suggesting similar metabolism between these species. Overall, there is no compelling data indicating that cumene acts through mechanisms that do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

6.3 Preliminary listing recommendation

Cumene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. Cumene exposure resulted in tumors (benign and malignant) in two species of rodent at multiple tissue sites: lung tumors in male and female mice, liver tumors in female mice and renal tumors in male rats. No convincing evidence was identified to rule out the relevance of these tumors to humans. There is some evidence to suggest that cumene may cause DNA damage, and lung tumor genotypes (mutation spectra and gene expression profiles) observed in mice with cumene exposure are similar to molecular alterations found in human lung and other cancers.

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Abbreviations

^{1}H NMR:	proton nuclear magnetic resonance
8-OH-dG:	8-hydroxydeoxyguanosine
AAF:	2-acetylaminofluorene
ACGIH:	American Conference of Governmental Industrial Hygienists
ADBAQ:	1-amino-2,4-dibromoanthraquinone
AEGL:	Acute Exposure Guideline Level
CHO:	Chinese hamster ovary
dA:	deoxyadenosine
DEN:	diethylnitrosamine
dG:	deoxyguanosine
DNA:	deoxyribonucleic acid
EASE:	Estimation and Assessment of Substance Exposure
EG:	ethylguanine
Endo III:	endonuclease III
ENU:	*N*-Ethyl-*N*-nitrosourea
EPA:	Environmental Protection Agency
Erk MAPK:	extracellular signal-regulated kinase mitogen activated pathway
ET:	ethylthymine
EUSES:	European Union System for the Evaluation of Substances
FDA:	Food and Drug Administration
FLARE:	fragment length analysis with repair enzyme
Fpg:	formamidopyrimidine
FRTG:	Flow Rate Technical Group
G:	guanine

GAC: Genetic Alterations in Cancer

GI: gastrointestinal

GIS: Geographic Information System

HDAC: histone deacetylase

HEG: (2-hydroxyethyl) guanine

HGPRT: hypoxanthine-guanine phosphoribosyl transferase

HHE: Health Hazard Evaluation

HIC: highest ineffective concentration

HID: highest ineffective dose

HPLC: high-performance liquid chromatography

hr: hour

I: inconclusive

i.p.: intraperitoneal

i.v.: intravenous

kg: kilogram

L: liter

LEC: lowest effective concentration

LED: lowest effective dose

LOH: loss of heterozygosity

m^3: cubic meter

MG: methylguanine

mg: milligram

mL: milliliter

MS: mass spectrometry

N.D.: not detected; not determined

NA:	not applicable
NCE:	normochromatic erythrocyte
NDMA:	*N*-nitrosodimethylamine
NIOSH:	National Institute for Occupational Safety and Health
NLM:	National Library of Medicine
NNK:	4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone
NOES:	National Occupational Exposure Survey
NPL:	National Priorities List
NR:	not reported; none reported
NS:	not significant
NT:	not tested
OEG:	(2-oxoethyl)guanosine
OGG1:	8-oxoguanine glycosylase 1
OSAT:	Operational Science Advisory Team
OSHA:	Occupational Safety and Health Administration
OTM:	olive tail moment
PCE:	polychromatic erythrocyte
PCNA:	proliferating cell nuclear antigen
ppm:	parts per million
ROS:	reactive oxygen species
RQ:	reportable quantity
SAFE:	significance analysis of function and expression
SCE:	sister-chromatid exchange
SOCMI:	synthetic organic chemical manufacturing industry
SPA:	solid phosphoric acid

TDS: Total Diet Study

TL: tail length

TRI: Toxics Release Inventory

TSCA: Toxic Substances and Recovery Act

UDS: unscheduled DNA synthesis

UK: United Kingdom

VOC: volatile organic compound

wt%: weight percent

µg: microgram

Glossary

Alpha α_{2u}-globulin: α_{2u}-Globulin is a low molecular weight protein that is synthesized in the liver of male rats and is regulated by complex hormonal interactions. Androgens stimulate synthesis, whereas estrogens repress synthesis.

Ames assay: The Ames *Salmonella*/microsome mutagenicity assay is a short-term bacterial reverse mutation assay specifically designed to detect a wide range of chemical substances that can produce genetic damage that leads to gene mutations.

Biexponential process: A process of drug (or xenobiotic) clearance with two phases with different rates. The first phase often involves rapid distribution of a drug to peripheral tissues, while the second phase represents clearance mechanisms that eliminate the drug from the body. (See "Two-compartment pharmacokinetic model.")

Biodegradation: Biotransformation; the conversion within an organism of molecules from one form to another. A change often associated with change in pharmacologic activity.

Boiling point: The boiling point of the anhydrous substance at atmospheric pressure (101.3 kPa) unless a different pressure is stated. If the substance decomposes below or at the boiling point, this is noted (dec). The temperature is rounded off to the nearest °C.

Comet assay: single cell gel electrophoresis for assessment of DNA damage in presumptive target tissues.

Critical temperature: The temperature at and above which a gas cannot be liquefied, no matter how much pressure is applied.

Differential selection: Selective pressure for self renewal. Gene mutations that confer a growth or survival advantage on the cells that express them will be selectively enriched in the genome of tumors.

Disposition: The description of absorption, distribution, metabolism, and excretion of a chemical in the body.

Epigenetic mechanisms: Changes in gene function that do not involve a change in DNA sequence but are nevertheless mitotically and/or meiotically heritable. Examples include DNA methylation, alternative splicing of gene transcripts, and assembly of immunoglobulin genes in cells of the immune system.

Genomic instability: An increased propensity for genomic alterations that often occurs in cancer cells. During the process of cell division (mitosis) the inaccurate duplication of the genome in parent cells or the improper distribution of genomic material between daughter cells can result from genomic instability.

Henry's Law constant: The ratio of the aqueous-phase concentration of a chemical to its equilibrium partial pressure in the gas phase. The larger the Henry's law constant the less

soluble it is (i.e., greater tendency for vapor phase). The relationship is defined for a constant temperature, e.g., 25°C.

Loss of heterozygosity: If there is one normal and one abnormal allele at a particular locus, as might be seen in an inherited autosomal dominant cancer susceptibility disorder, loss of the normal allele produces a locus with no normal function. When the loss of heterozygosity involves the normal allele, it creates a cell that is more likely to show malignant growth if the altered gene is a tumor suppressor gene.

Melting point: The melting point of the substance at atmospheric pressure (101.3 kPa). When there is a significant difference between the melting point and the freezing point, a range is given. In case of hydrated substances (i.e., those with crystal water), the apparent melting point is given. If the substance decomposes at or below its melting point, this is noted (dec). The temperature is rounded off to the nearest °C.

Metabolic activation: The chemical alteration of an exogenous substance by or in a biological system. The alteration may inactivate the compound or it may result in the production of an active metabolite of an inactive parent compound.

Micronuclei: Small nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

Miscible: A physical characteristic of a liquid that forms one liquid phase with another liquid (e.g., water) when they are mixed in any proportion.

Molecular weight: The molecular weight of a substance is the weight in atomic mass units of all the atoms in a given formula. The value is rounded to the nearest tenth.

Mutations: A change in the structure of a gene, resulting from the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes. The genetic variant can be transmitted to subsequent generations.

Normochromatic erythrocyte: A mature erythrocyte that lacks ribosomes and can be distinguished from immature, polychromatic erythrocytes by stains selective for RNA.

Osmotic mini pump: A miniature implantable infusion pump that is used to continuously infuse laboratory animals with a drug or other material. Absorption of water from surrounding tissues by osmosis through an outer rigid shell provides the means by which the material is forced out of a collapsible internal chamber at a constant rate.

Plate incorporation: A commonly used procedure for performing a bacterial reverse mutation test. Suspensions of bacterial cells are exposed to the test substance in the presence and in the absence of an exogenous metabolic activation system. In the plate-incorporation method, these suspensions are mixed with an overlay agar and plated immediately onto minimal medium. After two or three days of incubation, revertant colonies are counted and compared with the number of spontaneous revertant colonies on

solvent control plates.

Point emission: A release that can be identified with a single discharge source or attributed to a specific physical location.

Polychromatic erythrocyte: A newly formed erythrocyte (reticulocyte) containing RNA.

Poly-3 trend test: A survival-adjusted statistical test that takes survival differences into account by modifying the denominator in the numerical (quantal) estimate of lesion incidence to reflect more closely the total number of animal years at risk.

Sister-chromatid exchange: The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

Solubility: The ability of a substance to dissolve in another substance and form a solution. The Report on Carcinogens uses the following definitions (and concentration ranges) for degrees of solubility: (1) *miscible* (see definition), (2) *freely soluble*- capable of being dissolved in a specified solvent to a high degree (> 1,000 g/L), (3) *soluble*- capable of being dissolved in a specified solvent (10–1,000 g/L), (4) *slightly soluble*- capable of being dissolved in a specified solvent to a limited degree (1-10 g/L), and (5) practically insoluble- incapable of dissolving to any significant extent in a specified solvent (< 1 g/L).

Solvent classes: Classifications of organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients or in the preparation of drug products, as defined by the United States Pharmacopeial Convention. These chemicals, called residual solvents, are not completely removed by practical manufacturing techniques. *Class 1 solvents* (i.e., "solvents to be avoided") are known to cause unacceptable toxicities and should be avoided unless their use can be justified strongly in a risk-benefit assessment (e.g., known or strongly suspected human carcinogens, or environmental hazards). *Class 2 solvents* (i.e., "solvents to be limited") are associated with less severe toxicity and should be limited to protect patients from potential adverse effects (e.g., non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity, or solvents suspected of other significant but reversible toxicities). *Class 3 solvents* (i.e., "solvents with low toxic potential") are less toxic and should be used where practical (e.g., solvents with low toxic potential to humans; no health-based exposure limit needed).

Specific gravity: The ratio of the density of a material to the density of a standard material, such as water at a specific temperature; when two temperatures are specified, the first is the temperature of the material and the second is the temperature of water.

Spot test: Qualitative assay in which a small amount of test chemical is added directly to a selective agar medium plate seeded with the test organism, e.g. Salmonella. As the chemical diffuses into the agar, a concentration gradient is formed. A mutagenic chemical will give rise to a ring of revertant colonies surrounding the area where the chemical was applied; if the chemical is toxic, a zone of growth inhibition will also be observed.

Toxicokinetics: The mathematical description (toxicokinetic models) of the time course of disposition of a chemical in the body.

TOXMAP: A Geographic Information System from the National Library of Medicine that uses maps of the United States to help users visually explore data from EPA's TRI and Superfund programs.

Transitions: DNA nucleotide substitution mutation in which a purine base is substituted for another purine base (adenine → guanine or guanine → adenine) or a pyrimidine base for another pyrimidine base (cytosine → thymine or thymine → cytosine).

Transversions: DNA nucleotide substitution mutation in which a purine base (adenine or guanine) is substituted for a pyrimidine base (cytosine or thymine) or vice versa.

Two-compartment pharmacokinetic model: A two-compartment pharmacokinetic model resolves the body into a central compartment and a peripheral compartment. The central compartment generally comprises tissues that are highly perfused such as heart, lungs, kidneys, liver and brain. The peripheral compartment comprises less well-perfused tissues such as muscle, fat and skin. A two-compartment model assumes that, following drug administration into the central compartment, the drug distributes between that compartment and the peripheral compartment. However, the drug does not achieve instantaneous distribution (i.e., equilibrium), between the two compartments. After a time interval (t), distribution equilibrium is achieved between the central and peripheral compartments, and elimination of the drug is assumed to occur from the central compartment.

Vapor density, relative: A value that indicates how many times a gas (or vapor) is heavier than air at the same temperature. If the substance is a liquid or solid, the value applies only to the vapor formed from the boiling liquid.

Vapor pressure: The pressure of the vapor over a liquid (and some solids) at equilibrium, usually expressed as mm Hg at a specific temperature (°C).

Appendix A: Literature Search Strategy

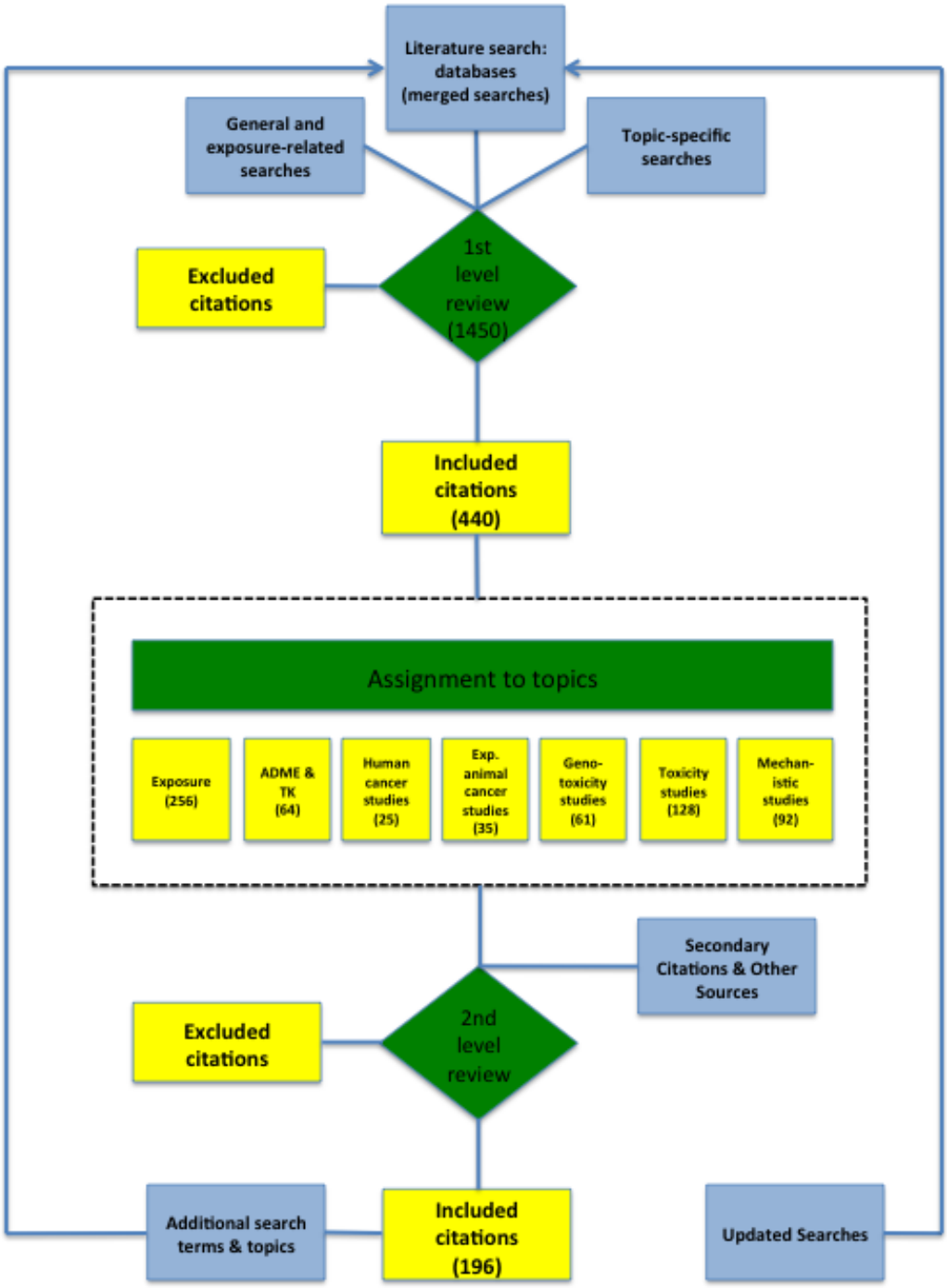
This document identifies the data sources, search terms, and search strategies that were used to identify literature for the draft monograph on cumene (CASRN 98-82-8). The literature search strategy used for cumene involved several approaches designed to identify potentially useful information for the 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)
- Studies of Cancer in Experimental Animals
- Mechanisms and Other Relevant Effects
  - 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 illustrated in Figure 1 and discussed below.

Click here to return to text citing Appendix A

Figure A-1. Literature search strategy and review



Search strategies

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

1. **General data search:** This search covers a broad range of general data sources (see Table A-1) for information relevant to many or all of the wide range of monograph topics pertaining to cumene.
2. **Exposure-related data search:** This search covers a broad range of potential sources (see Table A-2) for exposure-related information and physical-chemical properties.
3. **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 A-3 and the search terms are listed in Table A-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 A-4 for each of the monograph topics listed above to create the specific literature searches in Table A-5. See Table A-4 for details on this approach and Table A-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
4. **QUOSA library of occupational case-control studies** 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).
5. **Special topic-focused searches:** The two specific topics for which additional searches were conducted for cumene are listed below and described in Table A-3.
   - α_{2u}-Globulin-associated renal nephropathy
   - Role of genotoxic mechanisms in K-*ras* mutations in mouse lung tumors
6. **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.

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.

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.
The questions based on inclusion/exclusion criteria for Levels 1 and 2 are listed below.

Inclusion/exclusion questions for literature

Level 1:

Is this paper relevant or possibly relevant for any section(s) of the monograph? Check all that apply.

- ☐ Properties and Human Exposure
- ☐ Toxicokinetics (also includes ADME, i.e., absorption, distribution, metabolism, and excretion)
- ☐ Human Cancer Studies
- ☐ Studies of Cancer in Experimental Animals
- ☐ Mechanisms- Genetic Toxicology
- ☐ Mechanisms- Toxicity
- ☐ Mechanisms of Carcinogenicity

If this paper contains potentially relevant information, what type of paper is it?

- ☐ Primary research report
- ☐ Review article
- ☐ Meta-analysis
- ☐ Other

If this paper is not useful, check all the reasons that apply.

- ☐ It does not contain relevant information on the candidate substance or any related substance (metabolite or structural analogues).
- ☐ It is related to the candidate substance but does not contain information relevant to any topic covered by the monograph.
- ☐ It is an abstract or proceedings report.

☐ It is not peer reviewed.

Note: In the context of the systematic review of literature used for cumene, "relevant information" as it applies to primary screening can include any of the following:

- The article specifically mentions cumene, a metabolite, or structural analogue and reports information on one of the topics included in a cancer evaluation (see Question #1 above for a list of topics)
- The article does not specifically mention the cumene or any related substance, but it does one of the following:
  - It reports information on one of the topics included in a cancer evaluation with potential for exposure to cumene and should be included until full-text review, which would provide more information if the study is specific for exposure to cumene or a related substance.
  - It reports information on an exposure scenario that could include exposure to cumene.
  - It reports information on methodology that is potentially informative for evaluating cancer or mechanistic studies on exposure to cumene.
  - It reports information on a potential mode of action that may be informative for cumene.

Level 2:

Exposure

1. Does this paper contain information that is useful for the Exposure section? If "Yes" we will obtain a pdf if one is not already available.
   ❍ Yes
   ❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the exposure section can include information, from either primary research papers, review articles, databases, or other published sources, on any of the following topics: occupational exposure, environmental occurrence, occurrence in consumer products, food, cigarette smoke, or other sources, biological indices of exposure, and Federal regulations or guidelines to reduce exposure.

Toxicokinetics (including Absorption, Distribution, Metabolism, and Excretion)

1. Does this paper contain information that is useful for the Toxicokinetics section? If "Yes" we will obtain a pdf if one is not already available.
   ❍ Yes
   ❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the toxicokinetics (and ADME) section can include (but is not limited to) information from primary research papers or review articles on any of the following topics: absorption, distribution, metabolism, excretion (ADME), toxicokinetics, and physiologically based pharmacokinetic models (PBPK).

Human Cancer

1. Does this paper contain information that is useful for the human cancer section? If "Yes" we will obtain a pdf if one is not already available.

❍ Yes
❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the human cancer section can include, but is not limited to, epidemiologic studies, descriptive studies, pooled analyses, meta-analyses, case reports, reviews, letters to editors, exposure-assessment studies (for use in epidemiologic studies) and information on co-exposures or potential confounders and other special topics of relevance to the evaluation.

Animal Tumors

1. Does this paper contain information that is useful for the animal tumor section? If "Yes" we will obtain a pdf if one is not already available.

❍ Yes
❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the animal tumors section can include, but is not limited to, information from primary research papers or review articles on (1) chronic studies (ideally for lifetime of the animal) in experimental animals that are assessing neoplastic endpoints, non-cancer data important for cancer assessment, such as preneoplastic lesions that are considered part of a morphologic continuum to neoplasia, or (2) subchronic studies in experimental animals that provide information on preneoplastic lesions, neoplastic lestions, or on dose setting for chronic studies**.**

Genetic Toxicology

1. Does this paper contain information that is useful for the genetic toxicology section? If "Yes" we will obtain a pdf if one is not already available.

❍ Yes
❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the genetic toxicology section can include, information from primary research papers or review articles on studies in experimental systems (both *in vitro* and *in vivo*) and in exposed humans assessing the following endpoints: both direct and indirect DNA or chromosomal damage, events associated with mutagenesis, cellular transformation or other related effects.

Toxicity

1. Does this paper contain information that is useful for the toxicology (toxicity) section? If "Yes" we will obtain a pdf if one is not already available.
   ❍ Yes
   ❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the toxicity section can include any of the following: information from primary research papers or review articles on toxicity of cumene to organs or tissues that were identified as tumor sites from studies in experimental animals.

Mechanism data

1. Does this paper contain information that is useful for the mechanism data section? If "Yes" we will obtain a pdf if one is not already available.
   ❍ Yes
   ❍ No

Note: In the context of the systematic review of literature used for cumene, "useful information" as it applies to screening for the mechanism data section can include information from primary research papers or review articles on data related to molecular alterations associated with carcinogenicity or potential modes of action, such as genotoxicity, epigenetics, gene expression, immune-response modulation, inflammation, cytotoxicity and compensatory cell proliferation, mitogenicity, chronic metabolic or physiologic overload, nutrient deficiency, and interference with intercellular communication, for cumene, its metabolites and analogues.

Table A-1. General sources checklist for: Cumene

Source	Name of document
A) Comprehensive sources or reviews	
1) NTP technical reports	NTP 2009
2) NTP nomination for toxicological evaluation documents	NTP 1996
3) IARC monographs	--
4) ATSDR Toxicological Profiles	--
5) EPA IRIS	EPA 1997
6) NAS Reports and Publications	--
7) WHO (IPCS) INCHEM-related documents (a-k below)	
a) CICADS	WHO 1999
b) EHC	--
c) HSGs	--
d) IPCSs	IPCS 2004
e) JECFA	--
f) JMPR	--
g) KemI-Riskline	--
h) PDs	--
i) PIMS	--
j) SIDS	--
k) UKPID	--
8) California EPA Prop 65 hazard identification documents	CAEPA 2010
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	HSDB 2005
b) CCRIS	CCRIS 2011
c) GENETOX	GeneTox 1991
d) ITER	ITER 2012
e) LactMed	--
f) CPD	--
g) CTD	CTD 2012
2) PubChem	PubChem 2012
3) Kirk-Othmer Encyclopedia	Hwang and Chen 2010
4) USGS (Minerals)	--
C) European Union – sources to search	
1) International Uniform Chemical Information Database (IUCLID)	IUCLID 2000
2) European Chemicals Agency	ECHA 2011 UKCA 2008
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 A-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	ChemIDplus 2012
b) Haz-Map	Haz-Map 2012
c) HPDB	HPDB 2012
d) TOXMAP	TOXMAP 2012
2) Akron database	Akron 2010
3) SRI Directory of Chemical Producers	SRI 2011
4) Chem Sources Suppliers	ChemSources 2011
5) National Health and Nutrition Examination Survey (NHANES) data studies	NHANES 2010
6) National Occupational Exposure Survey (NOES) (1981-1983)	NIOSH 1990
7) National Institute for Occupational Safety and Health (NIOSH) - Health Hazard Evaluations	Burton and McCullough 2002
8) National Response Center (NRC) Database	NRC 2012
9) U.S. International Trade Commission (USITC)- Import/Export data	USITC 2011
10) EPA Toxics Release Inventory (TRI)	TRI 2012
11) EPA AP-42, Compilation of Air Pollutant Emission Factors	--
12) EPA Enforcement and Compliance History Online (ECHO) Database	--
13) EPA EJView Database	EPA 2012
14) EPA HPV Challenge Program Chemical List	--
15) EPA Inventory Update Rule (IUR)	EPA 2011a
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 2005 FDA 2006
21) Medline Plus	--
22) United States Patent Office	USPTO 2012
23) Trademark Electronic Search System (TESS)	TESS 2012
24) Material Safety Data Sheets (MSDS)	Citgo 2005 MSDSXchange 2012
25) Dow Chemical Product Safety Assessments	--

Table A-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 (1991b)
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 A-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 A-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])
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	"DNA Damage"[Mesh] OR "DNA Repair"[Mesh] OR "Mutagens"[Mesh] OR "Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Oncogenes"[Mesh] OR

Monograph Topic	Search terms used in PubMed, Scopus, and Web of Science	MeSH terms used in Pubmed
	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"	"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])

Appendix B: Human Exposure Tables and Regulations and Guidelines

Human exposure tables

The six tables on the following pages contain data discussed in the "Properties and Human Exposure" section (Section 1) for the potential for environmental exposure (Section 1.4) and the characterization of exposure in the workplace (Section 1.6).

Data are reported for cumene for daily release rates (Table B-1), atmospheric concentration levels (Table B-2), residential indoor air concentration levels (Table B-3), water and sediment concentration levels (Table B-4), soil concentration measurement data (Table B-5), and work area monitoring samples in different occupational settings (Table B-6).

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Table B-1. Cumene daily release rate estimates

Location reference	Media	Source	Emission rate (kg/day)
Los Angeles, CA (measured 2 days, 1987) Harley and Cass 1994[a]	Air	All sources	2,300
United States estimated value EPA 1988[b]	Air	All sources	[26,027[c]] (reported as 9,500 tonnes/yr)
European Union estimated value EC 2001[d]	Air[e]	Production and use	17,903
		Gasoline distribution	3,211[f]
		Motor exhaust	20,298[g]
		Total	41,412
	Water[h]	Production and use	20,500
	Soil[i]	Production and use	273
European Union reported value EC 2001[d]	Air 1993 1995	Production	 [342[c]] (reported as 125 tonnes/yr) [205[c]] (reported as 75 tonnes/yr)

Sources: EC 2001, HSDB 2005, IARC 2012, WHO 1999 (Note: IARC 2012 also reported data from the other 3 sources).
[a]As cited by HSDB 2005.
[b]As cited by WHO 1999.
[c]Based on division by 365 days per year; estimated daily rates would be higher if production processes are assumed to occur on fewer (e.g., 300) days per year.
[d]As cited by EC 2001.

[e]Assumes maximum production per site of 500,000 tonnes (4,100,000 tonnes/year for entire European Union) and a release factor of 1.31 kg/tonne (see Section 1.4.1).
[f]Assumes cumene as 0.2% of hydrocarbon loss, VOC emission factor of 5 kg/tonne delivered, and 117,205,000 tonnes/yr of gasoline for the entire European Union.
[g]Assumes 0.2% cumene in motor vehicle exhaust, emission of 617,400 tonnes VOC/yr in the United Kingdom, and a population ratio of 6 to extrapolate to the entire European Union.
[h]Assumes maximum production per site of 500,000 tonnes and a release factor of 1.5 kg/tonne (see Section 1.5.1).
[i]Assumes maximum production per site of 500,000 tonnes and a release factor of 0.02 kg/tonne (see Section 1.5.1).

Click here to return to text citing Table B-1.

Table B-2. Cumene atmospheric concentration levels

Country	Location/ sample	Mean concentration[a], μg/m^3, ppm	Concentration range[a], μg/m^3, ppm	References
Industrial settings				
United States	Deer Park, TX (near Shell Oil Refinery)	–	29.4 (downwind) [0.006] and 53.9 (upwind) [0.01]	Oldham *et al.* 1979[b]
Sweden	Near factory	–	4.5 [0.0009]	Petersson *et al.* 1982[c]
Spain	Field storage area for creosote-treated wood near Sant Martí de Torroella and Sant Joan de Vilatorrada	–	2,440 (day 1 of residence in storage field) – 275 (day 8 of residence in storage field) [0.5 – 0.06]	Gallego *et al.* 2008
United Kingdom	Gatwick airport – ambient air	–	1.6 – 12 [0.0003 – 0.002]	Tsani-Bazaca *et al.* 1982[c]
Not reported	Electronics factory fire	[340] (reported as 0.07 ppm)	[2 – 2,700] (reported as 0.0004 to 0.55 ppm)	Austin *et al.* 2001a
Urban settings				
United States	Urban overall	14.7 [0.003]	–	World Health Organization 1999[d]
	Boston, MA	–	0.1 [0.00002]	US EPA 1986[c]
	Chicago, IL	–	0.59 – 1.1 [0.0001 – 0.0002]	US EPA 1986[c]
	Houston, TX (21 samples, 88% positive)	12.15 [0.002]	None detected – 24.89 [None detected – 0.005]	U.S. EPA 1979[bd]
	Houston, TX (urban and industrial areas)	–	0 – 42.2 [0 – 0.009]	US EPA 1979[c]
	Houston, TX,	–	0.14 – 0.81 [0.00003 –	US EPA 1986[c]

Country	Location/ sample	Mean concentration[a], μg/m^3, ppm	Concentration range[a], μg/m^3, ppm	References
	1973 – 1974		0.0002]	
	Los Angeles, CA (10 samples, 80% positive)	16.7 [0.003]	< 2.45 – 36 [< 0.0005 – 0.007]	US EPA 1987[bd]
	Los Angeles, CA, 1966 (136 samples, 100% positive)	14.7 (144 max) [0.003 (0.03 max)]	–	Lonneman *et al.* 1968[bd]
	Los Angeles, CA, 1981 (17 samples, 94% positive)	–	None detected – 9.8 [None detected – 0.002]	Grosjean and Fung 1984[bd]
	Miami, FL (urban air)	–	1.11 – 2.59 [0.0002 – 0.0005]	Lonneman *et al.* 1978[c]
	St. Petersburg, FL (urban air)	–	0.83 – 1.29 [0.0002 – 0.0003]	Lonneman *et al* 1978[c]
Belgium	Antwerp Belgium Craeybeckx tunnel – normal traffic conditions, 1991	0.003 g/kg carbon[e]	–	DeFre *et al.* 1994[b]
	Antwerp Belgium Craeybeckx tunnel – congested traffic conditions, 1991	0.009 g/kg carbon[e]	–	DeFre *et al.* 1994[b]
Brazil	Porte Alegre, 1996 – 1997	[900] (reported as 0.9 mg/m^3)	–	Grosjean *et al.* 1998[b]
China	Taiwan urban air – away from heavy traffic	–	0.5 [0.0001]	Hung and Liao 1991[c]
	Taiwan urban air – near heavy traffic	–	0.6 – 0.9 [0.0001 – 0.0002]	Hung and Liao 1991[c]
France	Grenoble area, 1987	1.6 [0.0003]	0.9 – 7.45 [0.0002 – 0.002]	Foster *et al.* 1991[cd]
Germany	Hamburg – Major road tunnel	–	3 – 3.8 [0.0006 – 0.0008]	Danneker *et al.* 1990[c]
	Urban air	–	6 – 9 [0.001 – 0.002]	Bouscaren *et al.* 1986[c]

Country	Location/ sample	Mean concentration[a], μg/m^3, ppm	Concentration range[a], μg/m^3, ppm	References
Italy	Milan – urban air	–	1.1 – 1.8 [0.0002 – 0.0004]	European Commission 2001[c]
	Rome – urban air	–	1.1 [0.0002]	European Commission 2001[c]
Netherlands	Delft ambient air	–	< 0.49 – 1.96 [< 0.0001 – 0.0004]	Bos *et al.* 1977[c]
	Rotterdam and Ede – near homes	–	0.3 [0.00006]	Lebret *et al.* 1986[c]
	Urban air	–	0.3 [0.00006]	Bouscaren *et al.* 1986[c]
Sweden	Göteborg	–	0.6 [0.0001]	Petersson 1982[c]
United Kingdom	London – urban air	–	5 [0.001]	Tsani-Bazaca *et al.* 1982[c]
	Southampton estuary – ambient air	–	0.6 – 410 [0.0001 – 0.08]	European Commission 2001[c]
	Urban air	–	1 – 20 [0.0002 – 0.004]	Bouscaren *et al.* 1986[c]
Former USSR	Leningrad – urban air, 1977 – 1979	8.3 [0.002]	0.98 – 11.76 [0.0002 – 0.002]	Isidorov *et al.* 1983[cd]
Rural settings				
United States	Rural overall	2.5 [0.0005]	–	World Health Organization 1999[d]
	Great Smoky Mountains, TN	–	0.28 – 0.65 [0.00006 – 0.0001]	Arnts and Meeks 1981[c]
	Jones State Forest, TX, near Houston (15 samples, 100% positive)	2.45 [0.0005]	0.108 – 9.8 [0.00002 – 0.002]	Seila *et al.* 1979[bd]
	Lake Michigan, 1000 – 3000 feet above (2 samples, 100% positive)	0.49 [0.0001]	–	Miller and Alkezweeny 1980[b]
	Missoula, MT, 2004 – 2005 (35 samples)	< 0.04 (median) [0.000008]	< 0.04 – 0.1 [< 0.000008 – 0.00002]	Ward *et al.* 2009
	Missoula, MT, 2005 – 2006 (51 samples)	< 0.04[f] (median) [0.000008]	< 0.04[f] – 0.3 [< 0.000008 – 0.00006]	Ward *et al.* 2009
	Rio Blanco County, CO	–	1.57 [0.0003]	Arnts and Meeks 1981[c]

Country	Location/ sample	Mean concentration[a], μg/m^3, ppm	Concentration range[a], μg/m^3, ppm	References
	Smoky Mountains National Park, TN, near campfires (9 samples, 44% positive)	0.245 [0.00005]	< 0.049 – 0.392 [< 0.00001 – 0.00008]	Arnts and Meels 1980[b]
Nepal	Mount Everest	–	0.07 [0.00001]	European Commission 2001[c]
Netherlands	Rural air	–	0 – 5 [0 – 0.001]	Bouscaren *et al.* 1986[c]
Sweden	Rural sample	–	0.02 [0.000004]	Petersson 1982[c]
Netherlands	Ambient air	–	0.49 – 34.79 [0.0001 – 0.007]	Guicherit and Schulting 1985[c]

Sources: EC 2001, HSDB 2005, IARC 2012, WHO 1999 (Note: IARC 2012 reported data from the other 3 sources).
[a]Values in brackets were converted to ppm (or μg/m^3) using the conversion factors in Table 1-2.
[b]As cited by HSDB 2005.
[c]As cited by EC 2001.
[d]As cited by WHO 1999.
[e]Cumene concentration in relation to the total amount of carbon-based pollutants.
[f]Reported as ng/m^3; however, the correct units are μg/m^3 (T.J. Ward, personal communication to Sanford Garner, ILS, Inc., June 15, 2012).

Click here to return to text citing Table B-2.

Table B-3. Cumene residential indoor air concentration levels

Country	Location/sample	Report	Mean concentration[a], μg/m^3, ppm	Concentration range[a], μg/m^3, ppm
United States	Missoula, MT, 2004 – 2005 (35 samples)	Ward *et al.* 2009	0.1 (median) [0.00002]	< 0.04 – 1.7 [0.000008 – 0.0004]
	Missoula, MT, 2005 – 2006 (51 samples)	Ward *et al.* 2009	< 0.04[b] (median) [< 0.000008]	< 0.04 – 2.4[b] [0.000008 – 0.0005]
Canada	Quebec City (96 samples, 95 above detection limit[c])	Hèroux *et al.* 2008	0.88 (geometric mean) [0.0002]	0.10 – 45.48 [0.00002 – 0.009]

[a]Values in brackets were converted to ppm using the conversion factor in Table 1-2.
[b]Reported as ng/m^3; however, the correct units are μg/m^3 (T.J. Ward, personal communication to Sanford Garner, ILS, Inc., June 15, 2012).
[c]Detection limit = 0.2 μg/m^3. For concentrations < detection limit, 0.1 μg/m^3 was used for calculations.

Click here to return to text citing Table B-3.

Table B-4. Cumene water and sediment concentration levels

Country or industrial site	Location/ sample	Mean concentration, μg/L (for water), μg/kg (for sediment)	Concentration range, μg/L (for water), μg/kg (for sediment)	References
Drinking water				
United States	Drinking water – Terrebonne-Parish, Louisiana	–	0.01	Keith *et al.* 1976[a]
	Drinking water – 9 other cities	–	Not detected	Keith *et al.* 1976[a]
	Drinking water – Cincinnati, OH	–	0.014	Coleman *et al.* 1984[ab]
	Drinking water – 945 U.S. systems	–	Not detected (detection limit = 0.5)	Westrick *et al.* 1984[a]
	Drinking water – New York State	–	Detected but not quantified	Burmaster 1982[ab]
Japan	Tap water	–	Detected but not quantified	Shiraishi *et al.* 1985[b]
Groundwater				
United States	Groundwater – 50 states and Puerto Rico	–	< 0.5	Westrick *et al.* 1984[b]
	Groundwater – Ames, Iowa	–	Detected but not quantified	Burnham *et al.* 1972[b]
	Groundwater – New York State	–	Detected but not quantified	Burmaster 1982[b]
	Groundwater – Wyoming (underground coal gasification plants)	–	19 – 54	Steurmer *et al.* 1982[c]
	Groundwater – Hoe Creek, WV (underground coal gasification plants) (3 samples)	35	19 – 59	Steurmer *et al.* 1982[b]
Australia	Groundwater – Melbourne (near a dump site)	–	Detected but not quantified	Stepan *et al.* 1981[b]

Country or industrial site	Location/ sample	Mean concentration, μg/L (for water), μg/kg (for sediment)	Concentration range, μg/L (for water), μg/kg (for sediment)	References
Denmark	Fredericia, groundwater contaminated with creosote and/or gasoline (5 samples)	–	None detected – 3	Johansen *et al.* 1997[b]
	Holte, groundwater from shallow sandy aquifer contaminated with creosote and/or gasoline (3 samples)	–	2 – 22	Johansen *et al.* 1997[b]
Italy	Groundwater (underground solvent storage tanks near chemical plants)	–	1,581	Botta *et al.* 1984[ac]
United Kingdom	Groundwater – East Anglia (near an airfield)	–	1 – 30	Tester and Harker 1981[c]
	Groundwater - Great Ouse Basin, near a gasoline storage tank (5 samples)	9.8	0.01 – 30	Tester and Harker 1981[b]
Unspecified country	Groundwater (near chemical plants)	11	–	Pellizzari *et al.* 1979[a]
	Groundwater	360	–	Teply and Dressler 1980[a]
Unspecified country	Groundwater (petroleum plants and refineries)	5	–	Snider and Manning 1982[a]
Surface water				
United States	Surface water – Narraganset Bay, RI	–	Detected but not quantified	Wakeham *et al.* 1983[b]
	Surface water – River Brazos, Texas	–	0.006 – 0.017	McDonald *et al.* 1988[c]
Germany	Surface water – Lake Constance	–	0.006 – 0.028	Jüttner 1988[c]
	Surface water – River Rhine	–	0.028	European Communities 2001[c]

Country or industrial site	Location/ sample	Mean concentration, μg/L (for water), μg/kg (for sediment)	Concentration range, μg/L (for water), μg/kg (for sediment)	References
Japan	Surface water	–	0.09 – 0.44	Japan Environmental Agency 1987[a]
Spain	Surface water – River Gallego	–	[< 0.000001] (reported as < 0.001 ng/l)	European Communities 2001[c]
United Kingdom	Surface water – British North Sea	–	0.001 – 0.069	Hurford *et al.* 1990, 1989[c]
	Surface water – River Lee (2 samples)	–	< 0.1 and > 0.1	Waggot 1981[b]
	Solent estuary	–	0.01 – 47.3	European Communities 2001[c]
Sediment and biota				
United States	Sediments and biota – Puget Sound, WA	[2,300] (reported as 2.3 μg/g)	[20 – 19,000] (reported as 0.02 – 19 μg/g)	Brown *et al.* 1979[a]
	Sediment – Strait of Juan de Fuca, WA[d]	–	[20 – 5,500] (reported as 0.02 – 5.5 μg/g)	Brown *et al.* 1979[bc]
	Sediment – Puget Sound, WA	–	Detected but not quantified	Malins *et al.* 1984[b]
Japan	Sediment – near potential emission source (6 of 11 samples)	–	0.58 – 11 (detection limit = 0.5 ng/g)	Japan Environmental Agency 1987[a]
United Kingdom	Sediment - Southampton	–	0.25 – 43.37	Bianchi *et al.* 1991[c]
Wastewater				
Germany	Wastewater	–	0.5 – 5	European Communities 2001[c]
Sweden	Wastewater – Göteborg	–	0.1 – 0.8	European Communities 2001[c]
Other levels in water				
Around outboard motor operations	–	–	700	Montz *et al.* 1982[a]
Near offshore drilling platform	Sea water – Gulf of Mexico	–	140	Sauer 1981[a]

Country or industrial site	Location/ sample	Mean concentration, μg/L (for water), μg/kg (for sediment)	Concentration range, μg/L (for water), μg/kg (for sediment)	References
Snow				
Antarctica	Snow – 1987/88 expedition (8 surface snow samples)	[0.008] (reported as 8 ng/L)	–	Desideri *et al.* 1994[b]
	Snow – 1988/89 expedition (8 surface snow samples)	[0.016] (reported as 16 ng/L)	–	Desideri *et al.* 1994[b]
	Snow – 1990/91 expedition (8 surface snow and 6 deep snow samples)	Not detected	–	Desideri *et al.* 1994[b]

Sources: EC 2001, HSDB 2005, IARC 2012, WHO 1999 (Note: IARC 2012 reported data from the other 3 sources).
[a]As cited by WHO 1999.
[b]As cited by HSDB 2005.
[c]As cited by EC 2001.
[d]Incorrectly reported as Alaska in EC 2001.

Click here to return to text citing Table B-4.

Table B-5. Cumene soil concentration measurement data

Country or industrial site	Location/sample	Report	Mean concentration, μg/kg	Concentration range, μg/kg
Germany	Soil – beneath a building	Bachhausen 1990[a]	–	[24,000] (reported as 24 mg/kg)
Netherlands	Soil – contaminated sites	European Communities 2001[b]	–	12 – 20
Not reported	Soil – garage spills	Kliest *et al.* 1989[b]	–	[10,000 – 305,000] (reported as 10 to 305 mg/kg)

Sources: EC 2001, HSDB 2005, IARC 2012 (Note: IARC 2012 reported data from the other 2 sources).
[a]As cited by HSDB 2005.
[b]As cited by EC 2001.

Click here to return to text citing Table B-5.

Table B-6. Work area monitoring samples (measured levels) for cumene in different occupational settings

Occupational setting	Number of samples	Mean concentration, ppm [µg/m^3]	Concentration range, ppm [µg/m^3]	References
8-hour Time Weighted Average (TWA)				
Manufacture – all job categories	7 European companies	0.1 – 0.65 (range of means from individual companies) [491.6 – 3,195.52]	0.05 – 4.46 [245.81 – 21,926.16]	European Communities 2001[a]
Cumene production plant – specific jobs: runner, filling station attendant, laboratory co-worker, chemical technology co-worker	Personal air samples	–	< 1 [< 4,916]	European Communities 2001[a]
Manufacture – long-term exposure, 1991	40 to 50 samples (8-h TWA)	–	< 0.1 [< 491.6]	European Communities 2001[a]
Offset printing works	17 person-related measurements	–	0.1 – 1.3 [491.6 – 6,391]	European Communities 2001[a]
Printing of signs using lacquering machines	2 person-related measurements	–	0.2 [983.2]	European Communities 2001[a]
Maintenance painters – 23 different job locations	45 person-related measurements	–	0 – 0.81 [0 – 3,982.11]	Scheffers 1985[a]
Short-term (10 – 20 minute or 20 – 30 minute) exposure data				
Car repair work (manual compressed air-spray guns in spray booths)	8 person-related measurements	–	1.9 – 6.7 [9,340.7 – 32,938.4]	European Communities 2001[a]
Rubber manufacturing processes				Cocheo *et al.* 1983[a]
Shoe sole factory, vulcanization area	13 samples	–	0.012 – 0.05 [58.99 – 245.81]	
Tire retreading factory, vulcanization area	6 samples	–	0.0004 – 0.04 [1.966 – 196.6]	
Tire retreading factory, extrusion area	6 samples	–	0 – 0.002 [0 – 9.83]	
Electrical cable insulation plant, extrusion area	10 samples	–	Not detected	

Occupational setting	Number of samples	Mean concentration, ppm [µg/m^3]	Concentration range, ppm [µg/m^3]	References
1-hour exposure duration – 90% value				
Production of paints	125 samples	–	0.8 [3,932.9]	European Communities 2001[a] (1991 – 1995, Germany)
Surface treatment, manual (painting, paint rolling)	255 samples	–	3.4 [16,715.01]	
Surface treatment, manual (spraying)	300 samples	–	1.01 [4,965.34]	
Surface treatment, mechanical	84 samples	–	0.8 [3,932.9]	
Other monitoring data				
Cumene production and processing				Chemical Manufacturing Association Cumene Program Panel 1985[b]
Distillation	Not reported	0.45 [2,212.28]	0.0001 – 3.35 [0.49 – 16,469.2]	
Oxidation		0.93 [4,572.05]	0.0001 – 5.58 [0.49 – 27,432.28]	
Laboratory		0.39 [1,917.31]	0.34 – 0.44 [1,671.50 – 2,163.12]	
Repair		1.33 [6,538.52]	0.16 – 2.50 [786.59 – 12,290.45]	
Recovery		0.31 [1,524.02]	0.001 – 1.20 [4.92 – 5,899.42]	
Cumene unit		0.19 [934.07]	0.078 – 0.620 [383.46 – 3,048.03]	
Cumene exposed workers, 1973 – 1984	1,487 air samples			Chemical Manufacturing Association Cumene Program Panel 1985[c]
	6 samples	–	4 – 30 [19,665 – 147,485]	
	4 samples	–	3 – 4 [14,749 – 19,665]	
	25 samples	–	1 – 2 [4,916 – 9,832]	
	Remaining samples	–	< 1 [< 4,916]	
Exposure from solvents, United Kingdom	Not reported	–	Up to 0.6 [2,949.7]	European Communities 2001[a]

Occupational setting	Number of samples	Mean concentration, ppm [µg/m^3]	Concentration range, ppm [µg/m^3]	References
Gasoline delivery truck drivers	Not reported	–	< 0.01 – 0.04 [< 49.16 – 196.65]	American Petroleum Institute 1984[b]

Sources: EC 2001, HSDB 2005, IARC 2012, WHO 1999 (Note: IARC 2012 reported data from the other 3 sources).
[a]As cited by EC 2001.
[b]As cited by HSDB 2005.
[c]As cited by WHO 1999 for an industrial survey submitted to US EPA.

Click here to return to text citing Table B-6.

Regulations and guidelines

Table B-7. Existing standards and guidelines for cumene (ppm)

Type of guideline	Duration of exposure				
	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL – 1 (non-disabling)	50	50	50	50	50
AEGL – 2 (disabling)	550	380	300	190	130
AEGL – 3 (lethal)	1,300	920	730	460	300
Permissible Exposure Limits – Time Weighted Average (OSHA)					50 (skin)[a]
Recommended Exposure Limits – Time Weighted Average (NIOSH)					50 (skin)[a]
Immediately Dangerous to Life and Health (NIOSH)		900			
Threshold Limit Value – Time Weighted Average (ACGIH)					50

Source: NAC-AEGL 2007.
AEGL = Acute Exposure Guideline Level.
[a]The (skin) designation indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of substitution, engineering controls, good work practices, gloves, coveralls, goggles, and other appropriate equipment. This designation is separate from the Permissible Exposure Limit or Recommended Exposure Limit values shown and is not associated with inhalation exposure limits.

The regulations listed below do not contain specific exposure limits for cumene, but their application has the potential to reduce exposure to cumene.

U.S. EPA

Clean Air Act

Standards of Performance for Equipment Leaks of Volatile Organic Compounds (VOC) in the Synthetic Organic Chemical Manufacturing Industry (SOCMI):

Requires all newly constructed, modified, and reconstructed SOCMI process units to use the best demonstrated system of continuous emission reduction for equipment leaks of VOC.

National Emission Standards for Hazardous Air Pollutants:

Requires major and area sources to sharply reduce routine emissions of toxic air pollutants in accordance with specific performance-based standards for all air emission sources that emit one or more of the listed pollutants. Cumene is listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb

Regional Screening Levels (formerly called Preliminary Remediation Goals):

Screening levels for cumene are as follows: Residential soil = 2,100 mg/kg; Industrial soil = 11,000 mg/kg; Residential air = 420 µg/m^3 [0.09 ppm]; Industrial air = 1,800 µg/m3 [0.4 ppm]; Tap water = 390 µg/L.

Resource Conservation and Recovery Act

When cumene becomes a waste, it must be managed according to Federal and/or State hazardous waste regulations. Listed hazardous waste code = U055.

U.S. Food and Drug Administration

In the Federal Register of February 23, 2012 (FR 2012), FDA finalized a recommendation to revise the safety classification of cumene in the guidance for the pharmaceutical industry entitled "Q3C Impurities: Residual Solvents." FDA recommended that cumene be moved from listing as a Class 3 solvent (i.e., a solvent with low toxicity) to a Class 2 solvent with a permitted daily exposure (PDE) of 0.7 mg/day and a concentration limit of 70 ppm.

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Appendix C: Assessment of the Quality of the Individual Animal Cancer Studies

Each primary study was systematically evaluated to determine if it is informative for a cancer assessment. Studies that were given the most weight in the evaluation are those that were of a sufficiently long duration to identify a cancer endpoint, (ideally an exposure approaching the lifetime of the animal), and provided a detailed account of the study design and data collection. Ideally, studies should use an exposure route comparable to human exposure and appropriate statistical methods in reporting of results. Comparison with historical control values is sometimes helpful in assessing the significance of a finding, especially in the case of rare tumors, lower powered studies or assessment of background tumor incidences. The number of animals used in a study, the incidence of tumors in control vs. treated group, and the rarity of a tumor influence the statistical power of a study to detect an effect and are parameters that need to be taken into account in study design and results assessment. *Post hoc* power calculations can be performed. However, rare tumors will be considered in the assessment even if their incidence does not reach significance. Study performance elements for evaluating the different components of study quality are described below.

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NTP TR 542 Inhalation Toxicology and Carcinogenesis Studies of Cumene (CAS No. 98-82-8) in Rats and Mice

Substance characterization	**Independent experiments were conducted in rats and mice at Battelle Toxicology Northwest (Richland, WA)**
Is the chemistry of the substance well characterized? Are the purity, solubility and stability adequate for attributing any adverse effects to the substance?	Yes. Overall purity >99.9% determined, stability of bulk chemical, and vapor concentration throughout the experiment monitored against a standard by gas chromatography.
Animal husbandry	
Are the source, species, and strain of the animals adequately described?	Yes. Rats (F344/N) and mice (B6C3F1) were from Taconic Laboratory Animals and Services
Are the care, diet, housing and maintenance of the animals adequate for attributing any adverse effects to the substance?	Yes. The studies were conducted in and Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) inspected and approved facility; testing was also done on bedding, water and diet for possible chemical contamination; sentinel animals were used and sera tested for subclinical disease.
Were control animals housed in the same room, and tested at the same time under the same conditions as the dosed groups?	Yes. Each animal was housed individually. Animal care and maintenance were described.

Study design	
Animal model: Are the species and sex appropriate for determination of any exposure-related effect? Were the dose groups randomized?	Yes. Rats and mice of both sexes were tested; there is an adequate historical control database on these species and strains for inhalation studies from this laboratory.
Dosing and observation conditions: Are the study period, dosing period, route of exposure, and doses used adequate for determination of any adverse effect?	Yes. The animals were exposed throughout most of their lifespan (2 yr) by inhalation at a route relevant to human exposure.
Statistical Power: Does the study have adequate number of animals per group to detect an adverse effect, if present?	These studies follow NCI/NTP guidelines with respect to number of animals (Haseman 1984). Whether the adverse effect is statistically significant will depend on 1) what the tumor endpoint is and 2) the incidence of spontaneous tumors for that endpoint. Based on available historical NTP data on control animals, kidney tumors in rats were detected at greater than 50% power, liver tumors in mice at greater than 70% power, and lung tumors in mice at greater than 90% power.
Clinical observations, necropsy and pathology	
Were clinical observations performed?	Yes. A timetable of clinical observations was reported.
Was a full necropsy done on these animals and was histopathology done on tissues from at least all major organs?	Yes. Complete necropsies were done. All organs and tissues were examined for gross lesions and complete histopathology was performed on all rats and mice.
Are pathology procedures well described and adequate for determination for any exposure-related effect?	Yes, tissue fixation method, microscopic evaluations and quality assessment of the data are presented. The rat kidneys from 3-month subchronic study was removed and histopathology. procedures described for proliferating cell nuclear antigen, alpha2u-globulin, and soluble protein.
Data reporting and statistical methods	
Is data reporting well characterized?	Yes. Data are presented in a tabular format; individual animal data are provided in appendices.
Have tumors (benign/malignant) from the same organ been appropriately combined? If so, do they originate from the same cell type? *e.g.*- fibrosarcoma would not be combined with adenoma.	Yes (Rats); Yes (Mice)
Are the statistical methods performed on the data and adequately described?	Yes (Rats); Yes (Mice)

Are appropriate historical control data available?	Historical control values for studies by inhalation and by all routes are reported.
Are these studies informative for cancer assessment?	Yes (Rats) Yes (Mice) No major limitations on cancer study quality were found.

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Appendix D: Genotoxicity Tables

The nine tables on the following pages contain data discussed in the "Mechanisms and Other Relevant Effects" section (Section 5) for genetic and related effects (Section 5.1) and mechanistic considerations (Section 5.2).

Data are reported for *in vitro* studies of cumene mutagenicity in bacteria and yeast (Table D-1), *in vitro* genotoxicity studies of cumene in mammalian cells (Table D-2), *in vivo* studies of cytogenetic effects of cumene in mammals (Table D-3), K-*ras* mutations in spontaneous and cumene-induced lung tumors in mice (Table D-4), *p53* mutations in spontaneous and cumene-induced lung tumors in mice (Table D-5), *in vitro* and *in vivo* genetic toxicology tests results for α-methylstyrene (Table D-6a,b), genes significantly altered in tumors with and without K-*ras* mutations (Table D-7), K-*ras* mutation spectra from mouse lung tumors (Table D-8), and primary K-*ras* mutations in spontaneous and chemically induced mouse lung tumors and DNA adducts (Table D-9).

Table D-1. *In vitro* studies of cumene mutagenicity in bacteria and yeast

Reference	Strain	Method	LED/HID		Results		Cytotoxicity		Evaluation: limitations and conclusions
			– S9	+ S9	– S9	+ S9	– S9	+ S9	
Bacteria: *Salmonella typhimurium*									
Tardiff *et al.* 1976	TA100	Spot test	NR	NT	+	NT	NR	NT	Qualitative assay Incomplete reporting of results[a] Results reported positive in initial test but negative in subsequent tests by coauthor (see Simmon *et al.* 1977)
Simmon *et al.* 1977	TA98, TA100, TA1535, TA1537, TA1538	Plate incorporation	NR 5mg/plate	NR 5mg/plate	–	–	NR	NR	Incomplete reporting of methods (test doses not specified[b]) and results[a] Not mutagenic
	TA98, TA100, TA1535, TA1537, TA1538	Plate incorporation/ closed chamber, test chemical in separate dish	NR	NR	–	–	NR	NR	Closed chamber appropriate for volatile chemical but incomplete reporting of methods (test doses not specified) and results[a] Not mutagenic
Florin *et al.* 1980	TA98, TA100, TA1535, TA1537	Spot test	3 μmol/ plate	3 μmol/ plate	–	–	NR	NR	Qualitative assay Not mutagenic
	TA98, TA100	Plate incorporation	3 μmol/ plate	3 μmol/ plate	–	–	≥ 3 μmol/ plate	≥ 3 μmol/ plate	Incomplete reporting of methods (only high dose provided) and results[a] Not mutagenic
Lawlor and Wagner 1987, cited in EPA 1997, WHO 1999, EC	TA98, TA100, TA1535, TA1537	Preincubation	2000 μg/plate	2000 μg/plate	–	–	2000 μg/plate	2000 μg/plate	Limited information on results provided in review papers. Not mutagenic

Reference	Strain	Method	LED/HID		Results		Cytotoxicity		Evaluation: limitations and conclusions
			– S9	+ S9	– S9	+ S9	– S9	+ S9	
2001									
NTP 2009	TA 97, TA98, TA100, TA1535	Preincubation	166 µg/ plate for TA98, TA100 100 µg/ plate for TA97, TA 1535	333µg/ plate for TA98, TA100 166µg/ plate for TA97, TA 1535	–	–	Toxicity for most strains at highest dose tested	Toxicity for most strains at highest dose tested	S9 from Aroclor 1254-induced rat and hamster liver, 10% and 30%; tested to toxicity (except TA1535, not toxic) Not mutagenic
NTP 2009	TA98, TA100	Preincubation protocol modified by using sealed tubes	TA98: 500 µg/ plate TA100: 250 µg/ plate	TA98: 500 µg/ plate TA100: 500 µg/ plate	– –	– –	TA98: 125 µg/ plate TA100: 100 µg/ plate	TA98: 250 µg/ plate TA100: 250 µg/ plate	S9 from Aroclor 1254-induced rat liver, 10%; tested to toxicity. Not mutagenic
Bacteria: *Escherichia coli*									
NTP 2009	WP2 uvrA (pKM101)	Preincubation protocol modified by using sealed tubes	250 µg/ plate	500 µg/ plate	–	–	100 µg/ plate	500 µg/ plate	S9 from Aroclor 1254-induced rat liver, 10%; tested to toxicity. Not mutagenic
Yeast: *Saccharomyces cerevisiae* D3									
Simmon *et al.* 1977	*S. cerevisiae* D3 (heterozygous in *ade2* of chromosome XV)	Suspension	NR	NR	–	–	NR	NR	Incomplete reporting of methods (test doses not specified) and results[a]. Not mutagenic

LED/HID = lowest effective dose, highest ineffective dose; NR = not reported (although tested); NT = not tested.
[a]Authors only report conclusion of findings (e.g., positive or negative) and do not provide actual data (e.g., number of revertant colonies).
[b]Test doses not specified, authors stated "tested up to 5 mg/plate or a dose which gave a toxic response, whichever was lower

Click here to return to text citing Table D-1.

Table D-2. *In vitro* genotoxicity studies of cumene in mammalian cells

Reference	Effect	Test system	Concentration (LEC or HIC)	Cytotoxicity (% survival)	Results		Evaluation: limitations and conclusions[a]
					-S9	+S9	
GLSC 1985a, as described in WHO 1999, NTP 2009	Point mutation	Chinese hamster ovary (CHO) cells HGPRT locus	NR	Toxic at ≥ 128 μg/mL (both ±S9)	–	–	Initially called negative, but variable background and colony-forming efficiency warranted retest (see Yang 1987), which also was negative Limited information on methods and results provided in review papers Negative
Yang 1987, as described in EC 2001[b], NTP 2009	Point mutation	Chinese hamster ovary (CHO) cells HGPRT locus	225 μg/mL (both ±S9)	Toxic ≥ 150 μg/mL (–S9); cloning efficiency < 10% at dose ≥ 150 μg/mL (–S9)	–	–	Cloning efficiencies for ≥ 150 μg/mL not valid for evaluation; retest of Gulf Life Sciences Center (1985a) study Limited information on methods and results provided in review papers Negative
Putman 1987a, as described in EC 2001[b]	Chromosomal aberrations	CHO cells	200 μg/mL (–S9) 225 μg/mL (+S9)	Toxic at 200 μg/mL (–S9) 225 μg/mL (+S9)	–	I	Although +S9 treatment with 156 μg/mL showed statistically significant increase in chromosomal aberrations compared with vehicle control, results were within historical control range and were considered negative by authors Limited information on methods and results provided in review papers. Inconclusive

Reference	Effect	Test system	Concentration (LEC or HIC)	Cytotoxicity (% survival)	Results		Evaluation: limitations and conclusions[a]
					-S9	+S9	
GLSC 1984a, as described in EPA 1997	Cell transformation	BALB/3T3 mouse embryo cells	60 μg/mL		+	NT	Limited information on methods and results provided in review paper Initially reported positive but retested, see Putman 1987b Results equivocal because not reproducible
Putman 1987b, as described in EPA 1997, WHO 1999, EC 2001	Cell transformation	BALB/3T3 mouse embryo cells	500 μg/mL	Toxic at ≥ 250 μg/mL	–	NT	HID with acceptable toxicity was 200 μg/mL Retest of Gulf Life Sciences Center (1984a) Limited information provided in review papers Negative
GLSC 1984b, as described in EPA 1997, WHO 1999	Unscheduled DNA synthesis	F344 rat primary hepatocytes	16 μg/mL	Toxic at ≥ 128 μg/mL	+	NA	Limited information on methods and results provided in review papers. Initially reported positive at 16 and 32 μg/mL, but inconsistent response in replicates and high background warranted retesting (see Curren 1987) Results equivocal because not reproducible
Curren 1987, as described in EPA 1997, WHO 1999, EC 2001, NTP 2009	Unscheduled DNA synthesis	F344 rat primary hepatocytes	24 μg/mL	Toxic at ≥ 24 μg/mL	–	NA	Limited information on results and methods provided in review papers Retest of Gulf Life Sciences Center (1984b) study Negative

LEC/HIC = lowest effective concentration/highest ineffective concentration tested, I = inconclusive, NA = not applicable, NT = not tested.
[a]Evaluations of studies presented in this table are limited by the information provided in the cited review papers.
[b]Based on discrepancies or omission in the peer-reviewed report, data was checked in primary (unpublished) report. Click here to return to text citing Table D-2.

Table D-3. *In vivo* studies of cytogenetic effects of cumene in mammals

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
GLSC 1985b, as described in EPA 1997, WHO 1999, EC 2001, NTP 2009	Micronucleus formation bone marrow polychromatic erythrocytes[a]	Crl:CDR-1 (ICR) BR Swiss mice male and female, 10/sex/ group	Gavage 250,500,1000 mg/kg bw Exposure 2 days Sacrificed on d3 and d4	Negative for all treatment doses	Limited information of methods and results provided in review papers. No significant change in PCE:NCE. Negative
NTP 2009	Micronucleus formation peripheral blood erythrocytes	$B6C3F_1$ mice male and female, 9-10/sex/group	Inhalation, two trials Trial 1: 62.5 to 1,000 ppm Trial 2: 62.5 to 500 ppm Exposure for three months	Dose (ppm) / MN-NCEs/ 1000 NCEs Male Air 2.40 ± 0.69 62.5 2.20 ± 0.66 125 2.10 ± 0.48 250 1.80 ± 0.36 500 2.00 ± 0.26 1000 2.20 ± 0.42 Female Air 2.30 ± 0.40 62.5 1.33 ± 0.37 125 1.70 ± 0.30 250 2.10 ± 0.53 500 2.10 ± 0.35	Negative: No increase in MN frequency at all treatment doses in both sexes. No dose-related change in % PCE, an indicator of bone marrow toxicity, was seen.

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
NTP 2009	Micronucleus formation peripheral blood erythrocytes	B6C3F$_1$ mice male and female, 6/sex/group	Gavage Males: 312 to 1,250 mg/kg/day Females: 250 to 1000 mg/kg/day Exposure once daily for four days; final dose was administered 21 hr following third dose, peripheral blood collected 3 hr later	Dose (mg/kg) MN-NCEs/ 1000 NCEs Male 0 1.48 ± 0.04 312 1.47 ± 0.04 625 1.47 ± 0.03 1250 1.51 ± 0.03 Female 0 1.20 ± 0.02 250 1.17 ± 0.02 500 1.16 ± 0.02 1000 1.12 ± 0.01 Dose (mg/kg) MN-PCEs/ 1000 NCEs Male 0 2.75 ± 0.17 312 2.34 ± 0.11 625 2.90 ± 0.23 1250 3.05 ± 0.29 Trend test: $P = 0.067$ Female 0 2.37 ± 0.07 250 2.23 ± 0.12 500 2.44 ± 0.19 1000 1.89 ± 0.14 Trend test: $P = 0.985$	PCE-MN based on evaluating 20,000 reticulocytes (CD71-positive erythrocytes). NCE-MN based on evaluating $1x10^6$ erythrocytes In male mice, the percentage of PCE, a measure of bone marrow toxicity, increased over the dose range examined ($P = 0.031$), although the increase did not reach the level of statistical significance, which was set at $P < 0.025$.[b] PCE-MN are considered more sensitive than NCE-MN values because damaged erythrocytes in the erythrocyte population do not reach peak levels until 28 days of repeat dosing. Negative: No increased in MN frequency for all treatment doses

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
NTP 2009	Micronucleus formation bone marrow polychromatic erythrocytes	F344/N rats male, 5/group	Intraperitoneal injection, two trials Trial 1: 78 to 2,500 mg/kg for three days, sacrificed d4 Trial 2: 312 to 2,500 mg/kg for three days, sacrificed d4 Exposure three times at 24-hour intervals	Dose (mg/kg) MN-PCEs/ 1000 PCEs [bc] Trial 1 0 0.50 ± 0.16 78.13 1.20 ± 0.25 156.25 1.20 ± 0.34 312.5 1.30 ± 0.54* 625 0.80 ± 0.41 1,250 2.60 ± 0.29*** 2,500 1.25 ± 0.25 Trend test: $P < 0.001$*** Trial 2 0 0.50 ± 0.27 312 1.70 ± 0.20** 625 1.40 ± 0.33* 1,250 1.80 ± 0.34*** 2,500 1.50 ± 1.00* Trend test: $P = 0.085$	Data from high dose (2,500 mg/kg) excluded from trend test in both trials due to high animal mortality (survival 2/5 in Trial 1 and 3/5 in Trial 2). No dose-related change in the percent PCE was seen. Positive
NTP 2012	Micronucleus formation peripheral blood erythrocytes	F344/DuCrl rats male, 6/group	Gavage 200 to 800 mg/kg/day Exposure once daily for four days; final dose was administered 21 hr following third dose, peripheral blood collected 3 hr later	Dose (mg/kg) MN-PCEs/ 1000 PCEs 0 0.33 ± 0.03 200 0.27 ± 0.05 400 0.33 ± 0.05 800 0.18 ± 0.06	PCE-MN restricted to youngest reticulocytes (cells with the highest CD71 expression using cell cytometry); 20,000 evaluated PCE (20,000). Technique considered as sensitive as measuring bone marrow PCE for short term studies in rats. NCEs were measured but are not presented because

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
					no increase was seen with EMS, the positive control. The PCE results are the more valid population to evaluate because they are the least altered by the efficient action by the rat spleen in sequestering and destroying micronucleated erythrocytes. In rats, the percentage of PCE was reduced significantly (30% reduction from control) at the top dose, indicating that this dose of cumene induced bone marrow toxicity over the 4-day treatment period. However, the degree of reduction was not excessive (OECD Guideline 474 permits a reduction to a level of 20% of the control value). Negative: no increased MN frequency at all treatment doses

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
Kim *et al.* 2008	Fpg/Endo III FLARE Assay oxidative damage Hepatocytes Lymphocytes Olive tail moment (OTM) Tail length (TL) Conditions: Buffer Fpg excision repair enzyme (Fpg) Endonuclease III (Endo)	Sprague-Dawley rats male, 20/group	Inhalation (whole body) 0, 8, 80, 800 ppm 6 hours/day for up to13 weeks; Buffer (no enzyme), Fpg:Endo II: olive tail moment and tail length measured in hepatocytes and lympocytes and OGG1 mRNA expression measured in hepatocytes at 1, 14, 28, and 90 days	For hepatocytes with endonuclease, OTM values for 1 and 90 day exposures were significantly increased for 8 ppm (compared with control) but reduced for 800 ppm (compared with 8 ppm). There was little effect on TL values under any conditions. For lymphocytes, both OTM and TL values were reported to have several statistically significant results under various conditions. However, any pattern of results is obscured by an incomplete and inconsistent statistical analyses and no clear conclusions can be drawn from the results of this study.	Unacceptably high measures of background (0 ppm treatment) of DNA damage in controls; wide variation in DNA damage of controls across time periods; large standard deviations for all data. Inappropriate and inconsistent statistical analyses: reference group changes with no rationale (e.g., sometimes is unexposed only and other times is a combined group of the unexposed and low or unexposed, low and medium exposure groups). No adjustment made for multiple comparisons. Inadequate documentation (i.e., incomplete and unclear reporting of methods and disussion of findings).

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
NTP 2012	DNA damage (Comet assay)	F344/DuCrl rats male, 6/group	Gavage 200 to 800 mg/kg/day Exposure once daily for four days; final dose was administered 21 hr following third dose, peripheral blood, liver, lung and kidney tissue collected 3 hr later	Tissue / mg/kg / %Tail DNA [bc] Blood 0: 3.664 ± 0.394 Blood 200: 3.575 ± 0.195 Blood 400: 4.188 ± 0.402 Blood 800: 4.011 ± 0.416 Liver 0: 5.876 ± 0.616 Liver 200: 6.967 ± 0.415 Liver 400: 7.505 ± 0.637 Liver 800: 8.465 ± 0.730*** Trend test: *P* = 0.002*** Lung 0: 6.374 ± 0.327 Lung 200: 6.344 ± 0.696 Lung 400: 7.201 ± 1.029 Lung 800: 7.395 ± 0.450 Kidney 0: 8.176 ± 0.474 Kidney 200: 7.530 ± 1.005 Kidney 400: 7.681 ± 0.910 Kidney 800: 7.085 ± 0.393	Positive responses: Liver: Statistically significant for high dose pairwise comparison to control group (*P* = 0.004) and for trend test (*P* = 0.002).[c]

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
NTP 2012	DNA damage (Comet assay)	$B6C3F_1$ mice male and female. 6/sex/group	Gavage Males: 312 to 1,250 mg/kg/day Females: 250 to 1000 mg/kg/day Exposure once daily for four days; final dose was administered 21 hr following third dose, peripheral blood, liver, lung and kidney tissue collected 3 hr later.	Male Tissue / mg/kg / %Tail DNA [bc] Blood 0: 2.409 ± 0.375 312: 2.442 ± 0.248 625: 2.580 ± 0.511 1250: 2.006 ± 0.274 Liver 0: 7.498 ± 0.784 312: 9.284 ± 0.351 625: 7.632 ± 0.546 1250: 8.333 ± 1.067 Lung 0: 11.875 ± 1.212 312: 12.145 ± 0.800 625: 13.676 ± 1.330 1250: 12.983 ± 1.252 Kidney 0: 3.497 ± 0.198 312: 4.037 ± 0.456 625: 3.385 ± 0.261 1250: 3.753 ± 0.483	

Reference	Endpoint	Species/sex/#	Exposure	Results (mean ± S.E.)	Evaluation: limitations and conclusions
				Female Tissue mg/kg %Tail DNA [bc] Blood 0 2.097 ± 0.175 250 2.362 ± 0.357 500 1.949 ± 0.210 1000 2.063 ± 0.245 Liver 0 10.417 ± 1.676 250 11.182 ± 1.913 500 10.993 ± 0.958 1000 9.303 ± 1.834 Lung 0 6.785 ± 0.324 250 7.328 ± 0.551 500 7.787 ± 0.698 1000 8.723 ± 0.660* Trend test: P = 0.008* [c] Kidney 0 5.646 ± 0.746 250 4.416 ± 0.275 500 4.406 ± 0.436 1000 5.512 ± 0.301	Positive responses: Female: Lung: Statistically significant for high dose pairwise comparison to control group (P = 0.016) and for trend test (P = 0.008).[c]

Endo = endonuclease, detects oxidized pyrimidines; FLARE = Fragment Length Analysis using Repair Enzymes; Fpg = formamidopyrimidine-DNA glycosylase, detects altered (oxidized and ring opened) purines; OGG1 = 8-Oxoguanine glycosylase; OTM = olive tail moment; MN = micronucleated; NCE = normochromatic erythrocyte; PCE = polychromatic erythrocyte; TL = tail length.

*P < 0.05 (compared with controls unless otherwise noted), ** P < 0.006, *** P < 0.005.

[a]Not specified in peer-reviewed reports, so cell type determined from primary (unpublished) report.

[b] Dose-related trend; significant at $P \leq 0.025$;Pairwise comparison with the control group; significant at P <= 0.025.

[c] Levene's test is used to determine if variance among groups are equal. If equal, linear regression analysis and pairwise differences are evaluated using William's test. When variances are unequal, Jonckheere's test is used to evaluate linear trend data and Dunn's test is used used for pairwise comparisons with control group.

Click here to return to text citing Table D-3.

Table D-4. K-*ras* mutations in spontaneous and cumene-induced lung tumors in mice

Treatment (ppm)	N	No. with K-*ras* (%)	Codon 12 - GGT (%)[a]			Codon 61 – CAA (%)[a]		
			GAT	TGT GTT	CGT	CGA	CAT CTA	CAC
Controls								
Historical	117	33 (28)	14 (42)	6 (18)	0	2 (6)	4 (12)	1 (3)
Concurrent	7	1 (14)	0	0	0	1 (100)	0	0
Cumene								
125	4	1 (25)	0	1 (100)	0	0	0	0
250	13	10 (77)	0	1 (10)	2 (20)	5 (50)	0	2 (20)
500	18	17 (94)	4 (24)	7 (41)	0	4 (24)	0	0
1,000	17	17 (100)	2 (12)	7 (41)	1 (6)	4 (24)	1 (6)	0
Total	52	45 (87)	6 (13)	16 (36)	3 (7)	13 (29)	1 (2)	2 (4)

Source: Hong *et al.* 2008.
[a]Number of tumors with a specific K-*ras* mutation/total number of tumors with K-*ras* mutations.

Click here to return to text citing Table D-4.

Table D-5. *p53* Mutations in spontaneous and cumene-induced lung tumors in mice

Treatment (ppm)[a]	N	Activated *p53* (%)	Tumors with mutations (%)[b]		*p53* protein expression
			Exon 5	Exon 7	
0	7	0	0	0	1 (14)
125	4	0	0	0	1 (25)
250	13	5 (38)	4 (80)	1 (20)	6 (46)
500	18	11 (61)	10 (91)	1 (9)	8 (44)
1,000	17	11 (65)	10 (91)	1 (9)	14 (82)
Total	52	27 (52)	24 (89)	3 (11)	29 (56)

Source: Hong *et al.* 2008.
[a]125 ppm (females only), 1,000 ppm (males only).
[b]Number of tumors with a specific *p53* mutation/total number of tumors with *p53* mutations. No mutation detected in exons 6 and 8.

Click here to return to text citing Table D-5.

Table D-6a. *In vitro* genetic toxicology test results for α-methylstyrene

Reference	Effect	Test system	Results	Concentration or dose (LEC or LED HIC or HID)	Cytotoxicity (% survival)	Evaluation: limitations and conclusions
NTP 2007	Reverse mutation	*Salmonella typhimurium* (TA97, TA98, TA100, TA1535) preincubation assay	Negative for both ±S9, both rat and hamster S9 (10% and 30%)	–S9: 100 µg/plate +S9: 333 µg/plate	–S9: toxic at 333 µg/plate for TA98 and TA100; not tested > 100 µg/plate for TA97 and TA1535 (not toxic at these doses) +S9 (rat or hamster 10%): toxic > 333 µg/plate for all strains	Results were similar for all bacteria strains; tests were conducted up to 3,333 µg/plate for strains TA98 and TA100, both with 30% rat or 30% hamster S9: all showed toxicity but were not mutagenic.
NTP 2007	Chromosomal aberrations	Chinese hamster ovary (CHO) cells	Negative for both ±S9	Negative at HID 200 µg/ml (toxic at higher dose tested)	Toxic at 251.3 µg/mL for both ±S9	
Norppa and Vainio 1983	Sister chromatid exchange	Human whole blood lymphocytes	Weakly positive (for treatment –S9; did not test +S9)	Positive response at ~3 mM[a] (response ≥ 20% increase over solvent control)	> ~3 mM[a]	Data in graphical format Results not double the mean # SCEs/cell; decreased response at higher concentrations may be related to toxicity
NTP 2007	Sister chromatid exchange	CHO cells	–S9: Negative at 50 µg/mL +S9: Positive for 50, 124.4, 149.9 µg/mL	–S9: 166.7 50 µg/mL (HID) +S9: 50 µg/mL (LED)	For both ±S9: toxic at 166.7 µg/mL	For –S9, negative at 50 µg/mL but toxic at next dose of 166.7 µg/mL (no intermediate doses tested)

LED or LEC, HID or HIC = lowest effective dose or concentration/highest ineffective dose or concentration tested, NT = not tested.
[a]Dose level estimated from figure. Click here to return to text citing Table D-6a.

Table D-6b. *In vivo* genetic toxicology test results for α-methylstyrene

Reference	Effect	Test system	Exposure (ppm)	Results[a] NCEs	Dose (LED or HID)	Evaluation: limitations and conclusions
NTP 2007	Micronucleus induction	Females $B6C3F_1$ mice 3-month inhalation exposure peripheral blood	0 75 150 300 600 1000 Trend test	5.10 ± 0.46 2.40 ± 0.43 2.90 ± 0.90 3.60 ± 0.48 5.30 ± 0.42 9.13 ± 0.77*** $P < 0.001$	1,000 ppm	Positive response at highest dose tested and for trend test; 1,000 normochromatic (NCEs) and 1,000 polychromatic erythrocytes (PCEs) scored in 10 animals/exposure group No increase in MN-PCE seen at the 1000 ppm dose. No dose-related change in the percent PCE was seen.
		Males $B6C3F_1$ mice 3-month inhalation exposure peripheral blood	0 75 150 300 600 1000 Trend test	5.30 ± 0.50 5.80 ± 0.44 5.80 ± 0.63 5.00 ± 0.65 4.60 ± 0.45 6.30 ± 1.02 $P = 0.346$	1,000 ppm	Negative response; 1,000 normochromatic (NCEs) and 1,000 polychromatic erythrocytes (PCEs) scored in 10 animals/exposure group. No increase in MN-PCE seen at the 1000 ppm dose. No dose-related change in the percent PCE was seen.

NCE = normochromatic erythrocytes; NR = none reported.
[a]Mean ± standard error.
*** $P < 0.005$ compared with chamber controls.

Click here to return to text citing Table D-6b.

Table D-7. Genes significantly altered in tumors with and without K-*ras* mutations

Gene class	Genes	K-*ras* mutation	
		With	Without
Promote MAPK activation	*Mif, Avpi, Map2K1, Ereg, Mapbpip, Klf5*	↑	nc
Activated by MAPK signaling	*Ccnd1, Ptges, Areg*	↑	nc
Inactivate MAPK signaling	*Dusp14, Dusp3*	↓	nc
	Reck, Dusp1, Dusp4, Cav1, Loxl1	↓	↓
Anti-apoptosis	*Clu*	↑	↑
	Areg, Cks1b	↑	nc
Enhance tumor cell metastasis	*Krt18, Krt8, Lasp1, Mif, MMP14, Tacstd1*	↑	nc
Increased tumor malignancy	*Eno1, Gpr30, Srd5a1, Slc2a1*	↑	nc
Induce angiogenesis	*Slc2a1, Gnb2l1, Ptges*	↑	nc
Increased in metastatic tumors	*Sdc1, Ccnd1*	↑	nc
Invasion inhibitors	*Reck, Gsn, Lims2, Cav1, Gpx3*	↓	↓
Tumor suppressors	*Ptprd, Igsf4a, Fhl1, Pdzd2, Cdkn2d, Cdh5, Loxl1, Akap12*	↓	↓
Tumor suppressors, cell motility and proliferation inhibitors	*IGFBP4, Sod3, Rb1, Cebpd, Vwf, Dlc1*	↓	nc

Source: Wakamatsu *et al.* 2008.
nc = no change.

Click here to return to text citing Table D-7.

Table D-8. K-*ras* mutation spectra from mouse lung tumors

Chemical	Tumors with mutations/total tumors examined	Mutation (%)		Other prominent mutations (%)
		GC > TA (codon 12)	AT > GC (codon 61)	
Ethyl carbamate (urethane)	278/421	0	31	AT > TA (64)
Vinyl carbamate	58/71	8	42	AT > TA (33)
Diethylnitrosamine (DEN)	28/42	11	71	GC > AT (18)
N-Ethyl-*N*-nitrosourea (ENU)	11/11	0	64	GC > AT (27)
N-Nitrosodimethylamine (NDMA)	103/137	1	5	GC > AT (94)
4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	221/273	2	1	GC > AT (96)
Cyclopenta[cd]pyrene	20/27	40	0	GC > CG (50)
Benz[j]aceanthrylene	23/23	35	0	GC > CG (65)

Chemical	Tumors with mutations/total tumors examined	Mutation (%)		Other prominent mutations (%)
		GC > TA (codon 12)	AT > GC (codon 61)	
Benzo[b]fluoranthene	25/29	92	0	GC > CG (4) GC > AT (4)
Benzo[*a*]pyrene	43/51	81	0	GC > AT (19)
5-Methylchrysene	44/49	73	0	GC > CG (27)
1-Nitropyrene	12/35	0	83	GC > AT (17)
Spontaneous[a]	181/368	18	23	GC > AT (28) AT > TA (19)
Spontaneous[b]	33/117	18	6	GC > AT (42) AT > TA (12)

Source: Jackson *et al.* 2006.
% = Number of tumors with a specific K-*ras* mutation/total number of tumors with K-*ras* mutations
[a] Genetic Alterations in Cancer Knowledge System (Accessed on July 6, 2012, available at: http://tools.niehs.nih.gov/gac/datamining/genetics/).
[b] From Hong *et al.* 2008.

Click here to return to text citing Table D-8.

Part 2

Draft RoC Substance Profile

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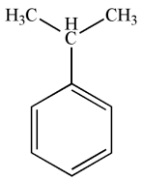
Cumene

CAS No. 98-82-8



Also known as isopropylbenzene

Carcinogenicity

Cumene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. Although cancer at some tissue sites may have been caused by species-specific mechanisms, there is no compelling data that the mechanisms by which cumene causes cancer in animals would not also operate in humans. Although information on cumene metabolism in humans is limited, there is at least one urinary metabolite of cumene has been identified in humans and experimental animals, indicating potential for similar metabolism. There is some evidence that cumene causes DNA damage. In addition, at least one metabolite of cumene (α-methylstyrene) is genotoxic, and other metabolites of cumene are potentially genotoxic. Furthermore, mutations of the K-*ras* oncogene and *p53* tumor-suppressor gene observed in cumene-induced lung tumors in mice, along with altered expression of many genes, resemble molecular alterations found in human lung and other cancers. Therefore, all occurrences of malignant tumors in experimental animals following cumene exposure are considered potentially relevant to carcinogenicity in humans.

Cancer Studies in Experimental Animals

Inhalation exposure to cumene caused tumors in two rodent species and at several different tissue sites (NTP 2009). Cumene caused benign and malignant lung tumors (alveolar/bronchiolar adenoma, carcinoma, and adenoma and carcinoma combined) in mice of both sexes. In female mice, the increased incidences of benign or malignant liver tumors (hepatocellular adenoma alone or combined with carcinoma) showed significant dose-related trends. In male rats, cumene increased the combined incidence of benign and malignant kidney tumors (renal tubule adenoma and carcinoma).

These findings are supported by statistically increased incidences of benign nasal tumors (adenoma of the respiratory epithelium of the nose) in both sexes of rats, and a significant dose-related trend in males. Additional tumors that may have been related to cumene exposure included malignant blood-vessel tumors (hemangiosarcoma, primarily of the spleen) and benign thyroid-gland tumors (follicular-cell adenoma) in male mice and benign tumors of the testes (interstitial-cell adenoma) in male rats.

Studies on Mechanisms of Carcinogenesis and Other Relevant Data

Cumene is readily absorbed following inhalation or oral exposure, and studies in rats and rabbits showed that cumene is also absorbed through the skin (Chen *et al.* 2011, EC 2001,

WHO 1999). Cumene is extensively metabolized by cytochrome P450 (isoforms not identified) in liver and other tissues, including the lung. Sixteen cumene metabolites were identified in rat urine. The most abundant metabolite in rat and mouse urine and rat bile was 2-phenyl-2-propanol glucuronide, and 2-phenyl-2-propanol was found in the urine of humans exposed to cumene vapor for 8 hours (Sećzuk and Litewka 1976). Cumene metabolism proceeds primarily through side-chain oxidation, but ring oxidation also occurs *in vivo.* Metabolism of cumene to electrophilic intermediates by side-chain oxidation of α-methylstyrene to α-methylstyrene oxide or by ring oxidation to arene oxides could potentially cause DNA damage.

The mechanisms by which cumene causes cancer in experimental animals are not known. Differences between species in the types of tumors observed may be due, in part, to species differences in metabolism and disposition. Several potential modes of action or molecular alterations associated with carcinogenesis have been identified, including genetic and epigenetic effects, metabolic activation to cytotoxic metabolites and cell proliferation,, and α_{2u}-globulin nephropathy.

Chemical agents that cause cancer at several tissue sites in more than one species frequently are genotoxic carcinogens. Although cumene was not mutagenic or genotoxic in most of the standard *in vitro* and *in vivo* assays, single-cell gel electrophoresis (the comet assay) provided some evidence that cumene caused DNA damage in the liver of male rats and the lungs of female mice (NTP 2012). Although α-methylstyrene was not mutagenic in bacteria, there is some evidence that it may cause chromosomal damage in rodents and cultured cells, and its proposed metabolite, α-methylstyrene oxide, is mutagenic in bacteria. Therefore, a genotoxic mechanism of action for cumene (presumably via its conversion to α-methylstyrene or to other metabolites) cannot be ruled out.

The mutation spectra of K-*ras* and *p53* in lung tumors from mice exposed to cumene differ from those observed in spontaneous lung tumors, suggesting the involvement of DNA damage (either direct damage from adduct formation or indirect damage through reactive oxygen species) and genomic instability (Hong *et al.* 2008). The K-*ras* and *p53* mutations observed in cumene-induced lung tumors, along with the altered expression of many genes (e.g., alteration of mitogen-activated protein kinase/extracellular signal-regulated kinase signaling, invasion and metastasis, inhibition of apoptosis, increased angiogenesis, and increased metastatic potential), resemble molecular alterations found in human lung and other cancers.

The occurrence of alveolar/bronchiolar neoplasms in mice but not in rats may be partly explained by differences in disposition and metabolism. Following administration of ^{14}C-labelled cumene, ^{14}C concentrations in lung tissue were highest in female mice after seven consecutive daily doses, but did not increase with repeated dosing in rats. *In vitro* studies with mouse and rat lung and liver microsomes found that mouse lung microsomes were the most efficient at metabolizing cumene, which is consistent with the accumulation of cumene metabolites in mouse lung (Chen *et al.* 2011). Based on a comparison with other compounds that also induced lung tumors in mice but not in rats, including ethylbenzene and styrene, Cruzan *et al.* (2009, 2012) proposed that species-specific metabolism by the cytochrome P450 isoform CYP2F2 in the Clara cells of mouse lung results in the production of cytotoxic metabolites that cause tumors. However, very few data are available to indicate which P450 isoforms are responsible for

metabolizing cumene. CYP2E1 and CYP2F2 are likely candidates, based on similarities between cumene and other alkylbenzenes, but metabolism of cumene by CYP2F2 in mouse lung has not been demonstrated to date. The orthologous isozyme CYP2F1 is found in human lung. Therefore, these data are insufficient to support the conclusion that cumene's induction of lung tumors in mice is not relevant to human carcinogenicity because of its dependence on species-specific metabolism to cytotoxic metabolites. In a two-year carcinogenicity study (NTP 2009), bronchiolar hyperplasia and alveolar epithelial bronchiolar metaplasia were significantly increased in mice of both sexes; however, there was no evidence of cytotoxicity (e.g., necrosis or inflammation) in the lung in the two-year study or in a three-month study. As discussed above, gene expression data provide some evidence that cumene's molecular targets in the mouse are similar to molecular alterations found in human lung tumors. Therefore, none of the available experimental evidence argues against the relevance of the mouse lung tumor observations to human carcinogenicity.

α_{2u}-Globulin nephropathy is a recognized mode of action associated with kidney tumors in male rats and is not considered relevant to humans. Both the International Agency for Research on Cancer (IARC 1999) and the U.S. Environmental Protection Agency (EPA 1991c) identified specific criteria and a sequence of events for evaluating whether this mechanism is responsible for carcinogenicity. Although the available data are consistent with an α_{2u}-globulin nephropathy mode of action playing a role in induction of kidney tumors by cumene, not all of the criteria were met. Criteria for which the evidence is questionable include nongenotoxicity, male-rat specificity for nephropathy, and evidence of sustained cell proliferation in the renal cortex. Some data, although limited, suggest genotoxic activity for cumene, and female rats exposed to cumene showed evidence of nephropathy. Although cumene exposure has been shown to induce α_{2u}-globulin-associated nephropathy in male rats, other mechanisms of carcinogenesis could not be unequivocally ruled out. Therefore, the relevance of cumene's induction of kidney tumors in male rats to human carcinogenicity cannot be dismissed.

At least one metabolite of cumene (α-methylstyrene) is carcinogenic in experimental animals. Under exposure conditions similar to those used with cumene, α-methylstyrene caused kidney tumors in male rats and liver tumors in male and female mice, but did not cause lung tumors or benign nasal tumors (NTP 2007). Because both the toxicity and the carcinogenicity of cumene were more widespread than those of α-methylstyrene, it was concluded that this metabolite cannot be solely responsible for the carcinogenicity of cumene (NTP 2009).

Cancer Studies in Humans

No epidemiological studies or case reports were identified that evaluated the relationship between human cancer and exposure specifically to cumene.

Properties

Cumene is an alkylated benzene that exists at room temperature as a volatile, colorless liquid with a sharp, penetrating aromatic or gasoline-like odor (NTP 2009). It is a flammable liquid that is stable under normal conditions but may become unstable at high temperatures and pressures. It forms cumene hydroperoxide when exposed to air for long

periods and is incompatible with oxidizers, nitric acid, and sulfuric acid. Decomposition of cumene may result in the release of toxic gases and vapors, such as carbon monoxide. Physical and chemical properties of cumene are listed in the following table.

Property	Information
Molecular weight	120.2[a]
Specific gravity	0.862 at 20°C/4°C[a]
Melting point	–96°C[b]
Boiling point	152.4°C[b]
Log K_{ow}	3.66[b]
Water solubility	61.3 mg/L at 25°C[b]
Vapor pressure	4.5 mm Hg at 25°C[b]
Vapor density relative to air	4.1[a]

Sources: [a] HSDB 2005, [b] ChemIDplus 2012.

Use

Cumene is used primarily in the manufacture of phenol and acetone (accounting for 98% of all use) and in the manufacture of acetophenone, α-methylstyrene, diisopropylbenzene, and dicumylperoxide (HSDB 2005). It is used as a constituent of some petroleum-based solvents, such as naphtha; as a catalyst for acrylic and polyester resins; and as a raw material for peroxides and oxidation catalysts (NTP 2009). Other, direct uses are as a thinner for paints, enamels, and lacquers and as a solvent for fats and resins; as such, cumene has been suggested as a replacement for benzene. Cumene is also used as a starting material in the manufacture of aspirin and penicillin (APPE 2012b). In addition, cumene has been used in gasoline blending, diesel fuel, and high-octane motor fuels, particularly as an aviation fuel (Advameg 2012, HSDB 2005, NTP 2009).

Production

Cumene is a high-production-volume chemical. In 2011, cumene was manufactured by at least 50 companies worldwide, including at least 8 in the United States (SRI 2011). Demand for cumene from 1986 to 2003 ranged from 3.7 billion to 8.0 billion pounds per year (HSDB 2005). Because the vast majority of cumene is used to make phenol and acetone, demand is strongly tied to the phenol derivatives market (ICIS 2010a). Recent growth in global demand for cumene has been largely attributed to the rebounding automobile and construction industries (ICIS 2010). Reported recent and historical volumes of U.S. production, imports, and exports are listed in the following table.

Category		Year	Quantity (lb)
Production + imports (EPA Chemical Data Reporting Rule[a])		2006	> 1 billion
U.S. imports:[b]	recent	2011	2.3 billion
	historical	1989	325 million
U.S. exports:[b]	recent	2011	127 million
	historical	1989	124 million

Sources: [a] EPA 2010, 2011a; formerly the "Inventory Update Rule."
[b] USITC 2011.

Exposure

In the United States, significant exposure to cumene results from the use of fossil fuels and solvents and from cigarette smoke. The major source of cumene exposure is environmental, via inhalation of ambient air. Exposure also can occur in the workplace through the production and use of cumene in the chemical industry. Cumene has been detected in blood, alveolar air, and urine from blood donors or people without occupational exposure to cumene (Brugnone *et al.* 1989, Perbellini *et al.* 1988) and in expired air samples from non-smoking individuals living in an urban environment (Krotoszynski *et al.* 1977).

The general population is exposed to cumene via inhalation of ambient air in industrial and urban areas of the United States. Because cumene is a natural component of petroleum (typically 0.1% to 1% by weight in crude oil), its emissions from petroleum-product-related sources, such as combustion of fossil fuels by land transportation vehicles, evaporative losses from gasoline stations, and refuelling losses, are ubiquitous in the environment. From 1990 to 2012, approximately 180 spill incidents involving cumene were reported to the National Response Center (NRC 2012).

Cumene has been measured in the atmosphere in many locations throughout the United States; however, levels are several-fold higher in industrial and urban settings than in rural areas, presumably because of cumene's presence in petroleum emissions. Cumene may also be released from cumene manufacturing and processing. According to EPA's Toxics Release Inventory, reported on- and off-site releases of cumene in 2010 totalled slightly over 1 million pounds from more than 300 facilities across the United States (TRI 2012). Releases to air accounted for 94.1% of total releases, releases to land for 4.4%, off-site disposal for 1.3%, disposal by underground injection for 0.2%, and releases to water for 0.1%. The European Union System for the Evaluation of Substances model indicated that about 97% of total estimated human environmental exposure to cumene is via the air (EC 2001).

The U.S. general population is not likely to be exposed to cumene via ingestion of water. Concentrations of cumene are several-fold lower in surface water and drinking water than in groundwater near industrial sources, in industrial effluents, or in sediments and biota. U.S. drinking water only rarely contains cumene at concentrations above 0.5 μg/L (EPA 1987, WHO 1999). The main source of soil contamination by cumene is point emissions from garage spills or near gasoline stations (EC 2001).

Cumene has also been detected at low levels in fruits, vegetables, meats, honey, dairy products, wine, and prepared foods (HSDB 2005). In the U.S. Food and Drug Administration Total Diet Study, conducted from 1991–3 through 2003–4, cumene was found at levels ranging from 0.002 to 0.063 ppm in 18 foods, including fruit-flavored popsicles and sherbet, cake doughnuts, sweet rolls and Danish pastries, and raw oranges (FDA 2006). Cumene in food may be from environmental or processing sources or may occur naturally (EPA 1987). Cumene levels in condensates of cigarette smoke were reported to range from 7 to 14 μg/cigarette (WHO 1999). Cumene is present at concentrations ranging from 1% to 5% (or not quantified) in several consumer products, including automobile fuel-injector-system cleaners, roof adhesives, some agricultural herbicides, fabric softener pads, and crib mattresses (Anderson and Anderson 2000a, 2000b, HPDB 2011).

In occupational settings, the main route of exposure to cumene is via inhalation during cumene manufacturing, processing, and use, primarily in the manufacture of phenol and acetone. Dermal exposure to cumene may occur at manufacturing and processing facilities during activities such as cleaning and maintenance. End users of products containing cumene outside of the manufacturing industry (e.g., for painting and car repair) may also be exposed.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

Standards of Performance for Equipment Leaks of Volatile Organic Compounds (VOCs) in the Synthetic Organic Chemical Manufacturing Industry (SOCMI): All newly constructed, modified, and reconstructed SOCMI process units must use the best demonstrated system of continuous emission reduction for equipment leaks of VOCs.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of cumene = U055.

U.S. Food and Drug Administration (FDA)

Q3C Impurities: Residual Solvents: Class 2 solvent; permitted daily exposure (PDE) = 0.7 mg; concentration limit = 70 ppm.

Occupational Safety and Health Administration (OSHA)

Permissible exposure limit (PEL) = 50 ppm.

Potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 50 ppm.

National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL)

AEGL-1 (non-disabling) = 50 ppm; AEGL-2 (disabling) = 130 ppm; AEGL-3 (lethal) = 300 ppm (8-h TWAs).

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (ILDH) limit = 900 ppm.

Recommended exposure limit (REL) (8-h TWA) = 50 ppm.

Potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.

Environmental Protection Agency (EPA)

Regional Screening Levels (formerly called Preliminary Remediation Goals):

Screening levels for cumene are as follows: Residential soil = 2,100 mg/kg; Industrial soil = 11,000 mg/kg; Residential air = 420 µg/m^3 [0.09 ppm]; Industrial air = 1,800 µg/m3 [0.4 ppm]; Tap water = 390 µg/L.

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