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Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460



Re: Submission to TSCA Section 8(e) Docket

Dear Madam or Sir:

The Cumene Panel of the American Chemistry Council submits the enclosed abstracts to the Environmental Protection Agency (EPA) in accordance with EPA's interpretation of Section 8(e) of the Toxic Substances Control Act (TSCA). Members of the Cumene Panel are: Chevron Phillips Company LP, The Dow Chemical Company, Equilon Enterprises, LLC, Georgia Gulf Corporation, Koch Petroleum Group - Refining, Marathon Ashland Petroleum, LLC, Shell Chemical Company, and Sunoco, Inc. The Panel has made no determination as to whether substantial injury to health or the environment is actually presented by this information.

On May 9, 2001, the Cumene Panel obtained, from the National Toxicology Program, abstracts of two subchronic inhalation studies conducted on cumene (CASRN 98-82-8) in rats and mice. These abstracts include information, that appears to satisfy EPA's criteria for reporting under TSCA Section 8(e). The abstracts, from Battelle Laboratories, entitled "13-Week Subchronic Inhalation Toxicity Study of Cumene -- Mice" and "13-Week Subchronic Inhalation Toxicity Study of Cumene -- Rats," are attached. We have attached the abstracts as a means of summarizing the reported information. The data presented in the abstract of the rat study are consistent with, although not identical to, those reported by Cushman, J.R., Norris, J.C., Dodd, D.E., Darmer, K.I. and Morris, C.R., "Subchronic Inhalation Toxicity and Neurotoxicity Assessment of Cumene in Fischer 344 Rats." J. of the Am. Coll. of Toxicol., 14(2):129-147 (1995).



Sincerely,

Courtney M. Price

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Attachments



ABSTRACT

Cumene (isopropylbenzene), a constituent of crude oil, was nominated for toxicity study based on its high-production volume, presence as a component of gasoline and other common fuels, high potential for exposure for both workers and consumers, possible mutagenic activity, and lack of carcinogenicity data. This report describes the 13-week inhalation study conducted to characterize the toxicological effects of cumene in male and female B6C3F1 mice.

The bulk test article was analyzed within 30 days before the study. The result for area percent purity was >99.9% by gas chromatography. Other than the cumene peak, no other peaks were detected with an area percent >0.1%. The exposure system delivered cumene vapor to the exposure chambers through a single vapor generator, vapor distribution manifold, and delivery subsystem. Vapor delivery to each chamber was controlled by a metering valve; vapor was further diluted or mixed with conditioned chamber air before entry into the chamber. Exposure chamber concentrations were monitored by gas chromatography once every ~20 minutes throughout each exposure. Exposure concentrations during the study were within the protocol specified range for daily means for all exposures with acceptable relative standard deviations. Cumene was stable in the exposure system and exposure concentration uniformity in exposure chambers was acceptable.

Ten male and female B6C3F1 mice (10/sex/group) were exposed by whole-body inhalation to target concentrations of 0, 62.5, 125, 250, 500 or 1000 ppm cumene for 6 hours/day plus T₆₀, 5 days/week for 13 weeks. Significant toxicological findings are summarized in Tables 1 and 2 for males and females, respectively.

TABLE 1. Summary of Significant Toxicologic Data in Males (Mean ± SD; N = 10)

Parameter	Target Exposure Concentration (ppm)					
	0	62.5	125	250	500	1000
In-Life Observations (Page III-1)						
Mortality	0/10	0/10	0/10	0/10	0/10	0/10
Final body weight mean [g] ± SD (% difference from controls)	38.3 ± 2.1	37.7 ± 2.7 (-1.5)	37.0 ± 2.7 (-3.4)	36.1 ± 2.5 (-5.7)	35.8 ± 2.9* (-6.5)	34.7 ± 1.8** (-9.4)
Necropsy Findings (Page III-2)						
Gross observations	NS	NS	NS	NS	NS	NS
Increased liver weight	NA	NS	NS	NS	NS	+
Increased liver/body weight	NA	+	+	+	+	+
Histopathological Observations (Page III-5)						
Liver, hypertrophy, centrilobular	0/10	NE	NE	NE	0/10	10/10

* $p \leq .05$

** $p \leq .01$

KEY: + = Significantly different from controls; NA = Not applicable; NE = Not examined; NS = Not significant toxicologically; SD = Standard deviation

There appeared to be a difference between males and females in the acute toxicity of cumene. The highest exposure concentration (1000 ppm) was fatal only to females, since eight of ten died during Week 1. Some transient signs of ataxia were noted in the 1000-ppm males and surviving females postexposure during Week 1, which generally disappeared by the following mornings. On the other hand, cumene exposure caused a consistent reduction in body weight compared to the controls, mainly in males (≥ 250 -ppm groups after Week 4). There was no remarkable cumene effect on hematology parameters in either sex when assessed at the end of the study.

TABLE 2. Summary of Significant Toxicologic Data in Females (Mean \pm SD; N = 10)

Parameter	Target Exposure Concentration (ppm)					
	0	62.5	125	250	500	1000 ^a
In-Life Observations (Page III-1)						
Mortality	0/10	0/10	0/10	0/10	0/10	8/10
Final body weight: mean (g) \pm SD (% difference from controls)	32.4 \pm 3.5	31.0 \pm 3.8 (-4.3)	31.4 \pm 3.6 (-3.1)	31.5 \pm 3.4 (-2.9)	29.8 \pm 2.1 (-8.2)	30.8 \pm 1.8 (-5.2)
Necropsy Findings (Page III-2)						
Gross observations	NS	NS	NS	NS	NS	NS
Increased liver weight	NA	NS	NS	NS	NS	+ ^{**}
Increased liver:body weight	NA	NS	NS	+ ^{**}	+ ^{**}	+ ^{**}
Histopathological Observations (Page III-5)						
Forestomach, hyperplasia, squamous	0/10	NE	NE	0/10	2/10	1/10
Forestomach, inflammation	0/10	NE	NE	0/10	2/10	1/10

^aN = 2; eight died before terminal sacrifice

* $p \leq .05$

** $p \leq .01$

KEY: + = Significantly different from controls; NA = Not applicable; NE = Not examined; NS = Not significant toxicologically; SD = Standard deviation

Pathological changes from 13 weeks of exposure to cumene in both sexes of mice were minimal. The most notable finding at necropsy was an exposure-related increase in the relative liver weights in both sexes, which were significant for all exposed males and for females exposed at ≥ 250 ppm. Microscopically, minimal centrilobular hypertrophy of hepatocytes may account for the increased liver weights, although such change was subtle and observed in livers only in the male 1000-ppm group. Cumene exposure also caused low incidences of hyperplasia and/or inflammation of the mucosa of the forestomach in females.

ABSTRACT

Cumene (isopropylbenzene), a constituent of crude oil, was nominated for toxicity study based on its high-production volume, presence as a component of gasoline and other common fuels, high potential for exposure for both workers and consumers, possible mutagenic activities, and lack of carcinogenicity data. This report describes the 13-week inhalation study conducted to characterize the toxicological effects of cumene in male and female Fischer 344/N (F344) rats.

The bulk test article was analyzed within 30 days before the study. The result for area percent purity was >99.9% by gas chromatography. Other than the cumene peak, no other peaks were detected with an area percent >0.1%. The exposure system delivered cumene vapor to the exposure chambers through a single vapor generator, vapor distribution manifold, and delivery subsystem. Vapor delivery to each chamber was controlled by a metering valve; vapor was further diluted or mixed with conditioned chamber air before entry into the chamber. Exposure chamber concentrations were monitored by gas chromatography once every ~20 minutes throughout each exposure. Exposure concentrations during the study were within the protocol specified range for daily means for all exposures with acceptable relative standard deviations. Cumene was stable in the exposure system and exposure concentration uniformity in exposure chambers was acceptable.

Twenty male and female F344 rats (20/sex/group) were exposed by whole-body inhalation to target concentrations of 0, 62.5, 125, 250, 500, or 1000 ppm cumene 6 hours/day plus T₆₃, 5 days/week for up to 13 weeks. Significant toxicological findings are summarized in Tables 1 and 2 for males and females, respectively.

The 13-week inhalation exposure of rats up to 1000 ppm cumene caused minimal toxicological effects, except for renal lesions in males. Survival was 100% for all groups and there was no significant impact of exposure on mean body weight gain in either sex. Minimal signs of ataxia were occasionally observed postexposure in the 1000-ppm groups only during the early exposure days. Changes in hematology parameters as the result of cumene exposure were not remarkable. The most notable effect on serum chemistry parameters was an increase in total bile acid concentration in both sexes at Days 3 and 23.

Gross lesions related to cumene exposure were not observed in either sex at necropsy. The most significant finding at terminal sacrifice was an increase in liver and kidney weights, particularly in males. The kidney weight increase in exposed males was accompanied by an increase in hyaline droplets and tubular regeneration in renal cortical tubules and granular casts in tubules in the corticomedullary junction area. There was a clear exposure-related increase in incidence and severity of granular casts, indicating that degeneration and necrosis of renal tubules occurred as a result of cumene exposure. These renal lesions were similar to those resulting from exposure to chemicals that induce accumulation of $\alpha_2\mu$ -globulin in renal cortical tubular cytoplasm. The amount of $\alpha_2\mu$ -globulin in kidneys of males exposed to cumene increased as a function of exposure, although there was no clear difference in renal cortical cell turnover rates between exposed and controls, as measured using proliferating cell nuclear antigen immunohistochemistry. There was no microscopic lesion in the livers of exposed rats of either sex to account for the increase in liver weights.

TABLE 1. Summary of Significant Toxicologic Data in Males (Mean ± SD; N = 10)

Parameter	Target Exposure Concentration (ppm)					
	0	62.5	125	250	500	1000
In-Life Observations (Page III-1)						
Mortality	0/10	0/10	0/10	0/10	0/10	0/10
Final body weight: mean (g) ± SD (% difference from controls)	311.7 ± 24.4	313.3 ± 19.3 (0.5)	322.4 ± 15.5 (3.4)	331.4 ± 12.5 (5.3)	314.0 ± 16.7 (0.7)	323.3 ± 15.9 (3.7)
Necropsy Findings (Page III-3)						
Gross observations	NS	NS	NS	NS	NS	NS
Increased liver weight	NA	NS	NS	NS	NS	NS
Increased liver:body weight	NA	+	NS	NS	NS	NS
Increased kidney weight	NA	NS	NS	NS	NS	NS
Increased kidney:body weight	NA	+	+	NS	NS	NS
Clinical Pathology Findings (Page III-6)						
Day 3: Increased reticulocytes	NA	NS	NS	+	NS	NS
Day 3: Decreased lymphocytes	NA	NS	NS	NS	NS	NS
Day 3: Decreased leukocytes	NA	NS	NS	NS	NS	NS
Day 3: Increased bile acid	NA	NS	NS	NS	NS	NS
Day 3: Increased blood urea nitrogen	NA	NS	NS	NS	NS	NS
Day 23: Increased lymphocytes	NA	+	NS	NS	NS	NS
Day 23: Increased leukocytes	NA	NS	NS	NS	NS	NS
Day 23: Increased blood urea nitrogen	NA	NS	NS	NS	NS	NS
Day 23: Increased bile acid	NA	NS	NS	NS	NS	NS
Day 23: Decreased alanine aminotransferase	NA	NS	NS	NS	NS	NS
TSAC: Increased lymphocytes	NA	NS	NS	NS	NS	NS
TSAC: Decreased alanine aminotransferase	NA	NS	NS	NS	NS	NS
TSAC: Increased bile acid	NA	NS	NS	NS	NS	NS
Renal Toxicity Findings (Page III-14)						
α ₂ -Globulin (mean [nmol/g kidney] ± SD)	172 ± 71	326 ± 220	363 ± 139**	421 ± 158**	363 ± 131**	575 ± 237**
PCNA (% labeled nuclei)	2.9 ± 0.64	3.6 ± 0.84	3.1 ± 0.86	2.5 ± 0.69	1.9 ± 0.97	3.6 ± 1.1
Histopathological Observations (Page III-4)						
Renal cortex, hyaline droplets	3/10	8/10	10/10	10/10	10/10	10/10
Renal cortex, tubular regeneration	7/10	7/10	8/10	9/10	10/10	10/10
Renal tubules, granular casts	0/10	1/10	2/10	8/10	10/10	9/10

N = 9

* p ≤ .05
** p ≤ .01

KEY: + = Significantly different from controls; NA = Not applicable; NS = Not significant toxicologically; PCNA = Proliferating cell nuclear antigen; SD = Standard deviation; TSAC = Terminal sacrifice

TABLE 2. Summary of Significant Toxicologic Data in Females (Mean ± SD; N = 10)

Parameter	Target Exposure Concentration (ppm)					
	0	62.5	125	250	500	1000
Mortality	In-Life Observations [Page III-1]					
Final body weight: mean [g] ± SD (% difference from controls)	0/10 195.0 ± 6.6	0/10 189.7 ± 7.9 (-2.8)	0/10 194.4 ± 14.3 (-0.3)	0/10 190.4 ± 10.7 (-2.4)	0/10 185.1 ± 8.9 (-5.1)	0/10 187.1 ± 11.7 (-4.1)
Gross observations	Necropsy Findings [Page III-3]					
Increased liver:body weight	NS	NS	NS	NS	NS	NS
Increased kidney:body weight	NA	NS	NS	NS	NS	NS
Day 3: Decreased lymphocytes	Clinical Pathology Findings [Page III-6]					
Day 3: Increased bile acid	NA	NS	NS	NS	NS	NS
Day 23: Increased lymphocytes	NA	NS	NS	NS	NS	NS
Day 23: Increased bile acid	NA	NS	NS	NS	NS	NS
Day 23: Increased leukocytes	NA	NS	NS	NS	NS	NS
TSAC: Decreased alanine aminotransferase	NA	NS	NS	NS	NS	NS

* p ≤ .05
** p ≤ .01

KEY: += Significantly different from controls; NA = Not applicable; NS = Not significant toxicologically; SD = Standard deviation