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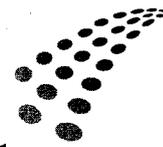


8EHQ-01-14926

Contain NO CBI

August 21, 2002

American
Chemistry
Council *Good Chemistry
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Document Control Office (7407)
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

61365

2002 AUG 22 AM 6:02

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DPPT CBIC

Re: Addendum to an Earlier Submission to TSCA Section 8(e) Docket

Dear Madam or Sir:

On May 18, 2001, the Cumene Panel of the American Chemistry Council submitted abstracts on two studies undertaken by the National Toxicology Program (NTP) to the Environmental Protection Agency (EPA) in accordance with Section 8(e) of the Toxic Substances Control Act (TSCA). The abstracts were from studies conducted by Battelle Laboratories, on cumene (CASRN 98-82-8) entitled "13-Week Subchronic Inhalation Toxicity Study of Cumene -- Mice" and "13-Week Subchronic Inhalation Toxicity Study of Cumene -- Rats." Recently, the Panel obtained additional information on these studies from NTP and is providing the information as an addendum to its earlier letter.

The attachments include: "Pathology Working Group Chairperson's Report: 13-Week Subchronic Study of Cumene (C96011) Administered by Inhalation in Male and Female B6C3F1 Mice"; "Pathology Working Group Chairperson's Report: 13-Week Subchronic Study of Cumene (C96011) Administered by Inhalation in Male and Female F344 Rats"; and two sets of tables entitled "Incidence Rates of Nonneoplastic lesions by Anatomic Site (a) with Average Severity Grades [b] Cumene -- Final #1 Mice" dated 8/27/01; and "Incidence Rates of Nonneoplastic Lesions by Anatomic Site (a) with Average Severity Grades [b] Cumene -- Final #1 Rats," dated 8/27/01.

Members of the Cumene Panel are: Chevron Phillips Chemical Company LP; The Dow Chemical Company; Flint Hills Resources, L.P.; Marathon Ashland Petroleum LLC; Shell Chemical Company; and Sun Company, Inc. A copy of the previous letter, from May 18, 2001, is attached for your convenience.

Please contact Wendy Sherman, Manager of the Cumene Panel, at (703) 741-5639 if you have any questions or require additional information regarding this submission.

Sincerely yours,

Susan Lewis/hcs
Susan E. Lewis,
CHEMSTAR
Managing Director

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Attachments (5)



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2002 SEP 13 AM 10:05

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PWGSC-M
C96011

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**PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT**

**13-WEEK SUBCHRONIC STUDY OF CUMENE (C96011)
ADMINISTERED BY INHALATION
IN MALE AND FEMALE B6C3F1 MICE**

Submitted to:

National Toxicology Program
National Institutes of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Prepared by:

Catherine A. Picut, V.M.D., J.D., DACVP
Pathology Working Group Chairperson
Integrated Laboratory Systems, Inc.

July 19, 2001

The pathologist performing this review has had no involvement in the testing or evaluation of this compound, cumene, for any laboratory or organization other than NTP.

P.O. Box 13501
Research Triangle Park, NC 27709

**PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT**

**13-WEEK SUBCHRONIC STUDY OF CUMENE (C96011C)
ADMINISTERED BY INHALATION
IN MALE AND FEMALE B6C3F1 MICE**

DATE OF PWG: June 16, 2001
LOCATION OF REVIEW: NIEHS, Research Triangle Park, NC

PARTICIPANTS:

Drs. Joel Mahler (NIEHS - NTP Study Pathologist), James Hailey (NIEHS), Ronald Herbert (NIEHS), Amy Brix (EPL), Cynthia Shackelford (EPL-QA Pathologist)), Catherine Picut (ILS-PWG Chairperson), Fiorella Belpoggi (observer), Andrew Suttic (ILS-observer).

SUMMARY OF FINDINGS FROM THE PWG

The PWG was convened to evaluate selected H&E slides from this 13-week study in B6C3F1 mice exposed to whole body inhalation of cumene. The following is a summary of review findings.

- **FORESTOMACH** - There were treatment-related changes in the non-glandular forestomach of female mice, including squamous epithelial hyperplasia and inflammation.
- **THYMUS** - There was diffuse necrosis of the thymus in the high dose female mice that died during the first week of treatment, and this necrosis is considered a pre-terminal agonal change, unrelated to the cause of death.
- **LIVER** - The PWG did not confirm a treatment-related lesion in the liver.

INTRODUCTION

Cumene is isopropylbenzene and a constituent of crude oil used for the production of phenol and acetone. It is a component of high-octane fuel, petroleum-based solvents and paint thinner. The route of human exposure is by inhaling contaminated air from cumene evaporated during production and processing. Cumene is a recognized CNS

depressant, and causes headaches, giddiness, vertigo and ataxia. The carcinogenic potential of cumene has not been determined.

A 2-week inhalation study of cumene in B6C3F1 mice was previously conducted at Battelle. Exposure to 2000 ppm and 4000 ppm for 12 days resulted in ataxia, lethargy and death. At terminal sacrifice, surviving animals had increased liver and kidney weights. Hyaline droplets were observed in exposed male mice.

CONDUCT OF THE PWG

The PWG convened to review selected slides from the B6C3F1 mice that had been administered cumene by whole body inhalation for 13 weeks. The only definitive target organ identified in the study was the forestomach and the thymus in female mice.

Before the PWG, the chairperson reviewed the laboratory reports and the SP's pathology narratives, the summary and individual animal pathology tables, the quality assessment reports, and microslides from the studies. The PWG chairperson selected a set of slides for review by the PWG which included examples of treatment related lesions as well as slides for which there were differences of opinion in diagnosis among the SP, QAP or PWG chair. The PWG consensus opinion for each slide examined, including any additional diagnoses made by the PWG, was recorded on the PWG chairperson's worksheets attached to this report.

STUDY DESIGN

In this inhalation study, cumene was administered at a dose level of 0, 62.5 ppm, 125 ppm, 250 ppm, 500 ppm and 1000 ppm for 13 weeks until the day prior to terminal sacrifice. Doses were administered by whole body inhalation 6 hours/day, 5 days per week, up to 13 weeks.

The doses and numbers of animals examined microscopically per group are summarized below:

Group	Male	Female
Control	10	10
62.5 ppm	10	10
125 ppm	10	10
250 ppm	10	10
500 ppm	10	10
1000 ppm	10	10

The study was conducted at Battelle in Richland, Washington. The Study Pathologist (SP) was Dr. Roger Renne. The Quality Assessment Pathologist (QAP) was Dr. Cynthia Shackelford of EPL.

STUDY RESULTS

Clinical Signs, Mortality, Gross Lesions, Organ Weights, Body Weight

Treatment of mice with cumene resulted in clinical signs of ataxia for several days in the high dose male mice. These male mice recovered and appeared to develop a tolerance by day 3. In the high dose female mice, there were clinical signs of acute toxicity (comatose and ataxia) in 8/10, resulting in eventual death within the first 5 days of the study in these same 8/10 mice.

There were no significant changes in body weight in treated animals compared to controls. The mean body weights for male mice exposed to 500 ppm or 1000 ppm were lower than controls at terminal sacrifice (-7 and -9%, respectively). There was no consistent difference in the mean body weights of exposed groups of female mice compared to the controls throughout the study.

There were no treatment-related gross lesions.

No toxicologically significant effects clinical pathology findings in the exposed mice of either sex when compared to control groups.

Exposure related changes in organ weight (relative and absolute) were limited to the liver in both sexes. Statistically significant increased relative and absolute liver weights were observed in all cumene exposed groups of male mice, and in female mice exposed to 250 ppm or greater.

Histopathology

Forestomach

Squamous epithelial hyperplasia and inflammation of the forestomach mucosa in the female mice were considered potentially related to cumene exposure by the study pathologist. The lesion was always minimal with focal to diffuse thickening of the squamous epithelium to 5-6 cell layers deep. In comparison, normal epithelium was considered to be 3-4 cell layers thick. There was good correlation between the SP and the QAP concerning the lesions in the forestomach of female mice. The QAP identified one animal in the 62.5 ppm dose groups having hyperplasia of the forestomach.

The PWG reviewed and confirmed all of the cases of forestomach epithelial hyperplasia as diagnosed by the SP, including the one additional case of hyperplasia diagnosed by the QAP in an animal in the 62.5 ppm dose group. The PWG discussed the significance of the low incidence of squamous epithelial hyperplasia in the forestomach and concluded that its relationship, if any, to treatment is uncertain.

Inflammation of the forestomach was only seen in association with hyperplasia. This inflammation was of minimal severity and confined to the lamina propria. The inflammation consisted of a mixture of inflammatory cells, primarily neutrophils and macrophages. The study pathologist used the terminology "inflammation" to diagnose this change, and the QAP suggested that the use of qualifiers, such as "chronic active inflammation" or "acute inflammation" was more appropriate. The PWG in reviewing representative examples of inflammation along with hyperplasia agreed that the use of such qualifiers were appropriate.

Thymus

The SP diagnosed necrosis of the thymus of marked severity in and only in the 8/10 female mice of the high dose group that died in the first week of the study. There was excellent correlation in diagnosis between the SP pathologist and the QAP, with a suggestion by the QAP that the changes may be more accurately termed autolysis.

The changes in the thymus were characterized by thymic lymphocytes with pyknotic (small, shrunken, dense) nuclei. In addition, there were multifocal regions of the thymus having lymphocytes with fragmented or disintegrated nuclei.

The PWG reviewed representative examples of the thymus in these high dose female mice, and all pathologists on the panel confirmed the presence of the changes in the thymus. The consensus of the panel (3 of the 5 pathologists) was of the opinion that necrosis was the appropriate terminology for these changes. The dissenting 2 out of the 5 pathologists believed the changes in the thymus were autolysis.

The thymic necrosis was considered by consensus to be a terminal antemortem change most likely associated with stress and glucocorticoid release, and not associated with the cause of death.

Liver

Centrilobular Hypertrophy

The SP reported centrilobular hypertrophy of the hepatocytes in all 10/10 high dose male mice. This change was reported as a subtle increase in cytoplasmic volume and diffuse pale eosinophilia. The QAP did not confirm this change in any of the 10/10 high dose male mice.

The PWG reviewed representative examples of the livers in this high dose male group along with representative examples of normal livers from the control male rat group. The PWG was unanimous that there was no histologically apparent support for the diagnosis centrilobular hypertrophy and deleted this diagnosis.

Several of the pathologists on the panel noted that while there is no histologic support for this diagnosis, there was likely some change in the liver that would explain the increased liver weights in the male and female mice. Morphometry was recommended as a tool that would likely be more reliable in detecting subtle changes in individual hepatocyte size and volume.

Necrosis

The SP reported liver necrosis with an increased incidence in the 1000 ppm male mice and the 500 ppm female mice when compared to the corresponding controls. This lesion was described as tiny foci of hepatocellular necrosis accompanied by a few inflammatory cells by the SP.

The QAP identified additional cases of these lesions and the resulting incidence or severity was not dose-related. The lesions were graded as minimal to mild.

The PWG reviewed the 12 cases of these lesions which were representative of the spectrum of changes. The lesions ranged from tiny foci of lymphocytes with a few central deeply eosinophilic individualized necrotic hepatocytes, to foci of coagulative or liquefactive necrosis associated with few scattered neutrophils and lymphocytes. The PWG was of the opinion that while the lesions were likely part of the same pathologic continuum, there should be a distinction between those lesions primarily inflammatory and those lesions primarily necrosis.

The PWG used the following criteria in distinguishing these two types of lesions. Those lesions having clusters of lymphocytes with low population (1-5) of necrotic hepatocytes were termed "chronic inflammation". Those lesions having greater than 5 contiguous necrotic hepatocytes and rare to a less prominent inflammatory component were termed "necrosis". "Chronic inflammation" or "necrosis" was not treatment-related and any variation in the incidence between the groups was considered to represent normal biological variation.

Miscellaneous

There was one case of renal tubular necrosis (mild) diagnosed by the SP and confirmed by the QAP in a high dose female mouse. The PWG chairperson was of the opinion that the tubular change was autolysis. The PWG concensus reviewed the case and confirmed the SP's diagnosis of mild renal tubular necrosis.

There was discussion that the cause of death of 8/10 high dose female mice was not identified in this study and there were no histologic lesions to explain the cause of death of these female mice.

HISTOTECHNIQUE QUALITY

The histotechnique quality assessment indicated that the overall histological processing and slide preparation was good, with no artifacts that would interfere with the interpretation of tissue sections.

Catherine A. Picut

Catherine A. Picut, VMD, JD
Diplomate, ACVP
PWG Chairperson

2/19/01

Date

PWGSR
C96011



**PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT**

**THIRTEEN-WEEK SUBCHRONIC STUDY OF
CUMENE (C96011E)
ADMINISTERED BY INHALATION
IN MALE AND FEMALE F344 RATS**

Submitted to:

National Toxicology Program
National Institutes of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709

Prepared by:

Catherine A. Picut, V.M.D., J.D., DACVP
Pathology Working Group Chairperson
Integrated Laboratory Systems, Inc.

July 19, 2001

The pathologist performing this review has had no involvement in the testing or evaluation of this compound, cumene, for any laboratory or organization other than NTP.

P.O. Box 13501
Research Triangle Park, NC 27709

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T-341 P.003/007 F-883

**PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT**

**THIRTEEN-WEEK SUBCHRONIC STUDY OF CUMENE (C96011C)
ADMINISTERED BY INHALATION
IN MALE AND FEMALE F344 RATS**

DATE OF PWG: June 16, 2001
LOCATION OF REVIEW: NIEHS, Research Triangle Park, NC
PARTICIPANTS:

Drs. Joel Mahler (NIEHS - NTP Study Pathologist), James Hailey (NIEHS), Ronald Herbert (NIEHS), Cynthia Shackelford (EPL), Amy Brix (EPL - QA Pathologist), Catherine Picot (ILS-PWG Chairperson), Fiorella Belpoggi (observer), Andrew Suttie (ILS-observer).

SUMMARY OF FINDINGS FROM THE PWG

The PWG was convened to evaluate selected H&E slides from this 13-week study in F344 rats exposed to whole body inhalation of cumene. The following is a summary of review findings.

- **KIDNEY**- There were treatment-related changes in the kidney compatible with alpha 2u-globulin nephropathy. These changes included hyaline droplet accumulation (NOEL = 62.5), granular casts (NOEL = 62.5), and tubular regeneration (NOEL = 125 ppm).

INTRODUCTION

Cumene is isopropylbenzene and a constituent of crude oil used for the production of phenol and acetone. It is a component of high-octane fuel, petroleum-based solvents, and paint thinner. The most probable route of human exposure is by inhaling contaminated air from cumene evaporated during production and processing. Cumene is a recognized CNS depressant, and causes headaches, giddiness, vertigo and ataxia. The carcinogenic potential of cumene has not been determined.

A 2-week inhalation study of cumene in F344/N rats was previously performed at Battelle. Exposure to 2000 ppm and 4000 ppm for 12 days resulted in ataxia, lethargy and death. At terminal sacrifice, surviving animals had increased liver and kidney weights. Hyaline droplets were observed in exposed male rats.

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CONDUCT OF THE PWG

The PWG convened to review selected slides from the F344 rats that had been administered cumene by whole body inhalation for 13 weeks. The only definitive target organ identified in the study was the kidney.

Before the PWG, the chairperson reviewed the laboratory reports and the SP's pathology narratives, the summary and individual animal pathology tables, the quality assessment reports, and microslides from the studies. The PWG chairperson selected a set of slides for review by the PWG which included examples of treatment related lesions as well as slides for which there were differences of opinion in diagnosis among the SP, QAP or PWG chair. The PWG consensus opinion for each slide examined, including any additional diagnoses made by the PWG, was recorded on the PWG chairperson's worksheets attached to this report.

STUDY DESIGN

In this inhalation study, cumene was administered at a dose level of 0, 62.5 ppm, 125 ppm, 250 ppm, 500 ppm and 1000 ppm for 13 weeks until the day prior to terminal sacrifice. Doses were administered by whole body inhalation 6 hours/day, 5 days per week, up to 13 weeks.

The doses and numbers of animals examined microscopically per group are summarized below:

Group	Male	Female
Control	10	10
62.5 ppm	10	10
125 ppm	10	10
250 ppm	10	10
500 ppm	10	10
1000 ppm	10	10

At necropsy, the left kidney was fixed in neutral buffered formalin and sections were stained with hematoxylin and eosin (H&E) and Mallory Heidenhein (MH) stains. In addition, immunohistochemistry of the left kidney to quantitate proliferating cell nuclear antigen (PCNA) was performed.

The right kidney was frozen for alpha 2u-globulin quantitation.

The study was conducted at Battelle in Richland, Washington. The Study Pathologist (SP) was Dr. Roger Renne. The Quality Assessment Pathologist (QAP) was Dr. Amy Brix of EPL.

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STUDY RESULTS

Clinical Signs, Mortality, Gross Lesions, Organ Weights, Body Weight

Treatment of rats with cumene resulted in clinical signs of ataxia for several days in the high dose male rats. These male rats recovered and appeared to develop a tolerance by day 3. The female rats exhibited no clinical signs.

There were no significant changes in mean body weights for either male or female rats when compared to controls.

There were no changes in the clinical pathology parameters that were clearly treatment related. The male rats had elevated white blood cell counts in the 62.5, 500 and 1000 ppm groups, and the females had elevated white blood cell counts in the 500 and 1000 ppm groups at terminal sacrifice. There was an increase in the total bile acid concentration in the high dose male rats at terminal sacrifice.

There were no treatment-related gross lesions.

Exposure related changes in organ weight (relative and absolute) were limited to the liver in males and females, and to the kidneys in male rats. Statistically significant increases in the liver and kidney weights were noted in the male rats (250, 500 and 1000 ppm dose group), and a statistically significant increase in liver weights was noted in the female rats (250, 500 and 1000 ppm groups).

Histopathology

Kidney

The kidney was considered the target organ in male rats. The study pathologist reported an exposure related increase in incidence and severity of hyaline droplets in the renal cortical tubules (no NOEL), a slight increase in mean severity and incidence of regeneration of renal cortical tubules (NOEL = 125 ppm), and in the presence of granular casts (no NOEL).

Hyaline Droplets

Hyaline droplets were visible on H&E stained slides as brightly eosinophilic globules of varying size in the renal cortical tubular epithelium. With the MH stain, the droplets were magenta. There was excellent correlation between the diagnosis of hyaline droplet accumulation between the SP and QAP and the severity ranges from minimal to moderate. The PWG reviewed both the H&E stained and MH stained slides of selected cases of hyaline droplet accumulations, including control animals. The PWG was of the consensus that the droplets were more easily visualized with the MH stain and

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this stain was acceptable to grade the droplet accumulation. The PWG decided unanimously that there should not be a threshold used in the diagnosis of hyaline droplet accumulation and that all 10/10 control male rats had minimal to mild hyaline droplet accumulation recognizable with the MH stain.

The PWG discussed the NOEL and determined it should be at 62.5 ppm. In setting this NOEL, the panel noted that moderate severity of hyaline droplet accumulation only occurred in the 125 ppm dose group and higher. Further the amount of alpha 2u-globulin quantitated from the right kidneys is increased to a statistically significant degree in dose groups 125 ppm and higher.

Granular Casts

Granular casts were generally present at the corticomedullary junction and caused dilation of the tubular lumen with lightly eosinophilic granular acellular material. The SP based the grading of casts on the "the number of tubules containing casts and the degree of dilatation of these tubules." There was no threshold used for making the diagnosis of casts and there was good correlation between the SP and QAP with regards to the incidence and severity of casts. The PWG reviewed selected cases of casts from minimal to marked severity and concurred with the severity grading. The PWG noted that the range of "minimal" to "marked" as it pertained to casts, represented the full range of severity of the casts as seen in this study. They further remarked that the term of "marked" in this study may not necessarily be "marked" in any other study. The grading scheme used for casts in this study was as follows:

Minimal - grade 1 - 1 dilated tubule containing cast
 Mild - grade 2 - 2-3 dilated tubules containing casts
 Moderate - grade 3 - 4-5 dilated tubules containing casts
 Marked - grade 4 - 6 or more dilated tubules containing casts

The PWG concluded by unanimous opinion that a diagnosis of casts could not be supported in any of the 62.5 ppm group of animals. The one cast diagnosed by the SP and confirmed by the QAP in this low dose group (62.5 ppm) contained basophilic material and was not located at the corticomedullary junction as were the other casts in this study. The NOEL for granular casts was set by the PWG at 62.5 ppm

Tubular Regeneration

Tubular regeneration was diagnosed by the SP and was characterized by tubules lined by more basophilic epithelium and having larger nuclei than surrounding tubules. Tubular regeneration was typically seen in clusters. There was good correlation between SP and QAP, and the PWG generally agreed with the diagnoses of tubular regeneration when shown representative examples of the H&E and PCNA stained slides.

The PWG discussed that the PCNA stained slides were not helpful in identifying or grading tubular regeneration, and the H&E stained slides were more reliable. The

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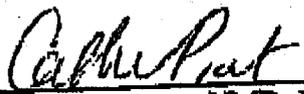
PWG discussed that the NOEL was appropriately set at 125 ppm, since moderate grades of tubular regeneration were seen only in the 250 ppm dose group and greater. The PWG also discussed the lack of correlation of tubular regeneration on the H&E stained tissue with the labeling index of PCNA positive cells reported in this study. There was no statistically significant increase in the number of PCNA positive cells in the treated versus control animals. There was no definitive explanation of this lack of correlation.

Liver

The QAP reviewed the livers from the control and high dosed male and female rats, in order to identify a histological basis for the increased liver weights in both sexes. Chronic inflammation of minimal to mild severity was coded by the QAP in several female livers but there was no difference between the control and high dose female groups. The diagnosis of chronic inflammation as added by the QAP was deleted, since this inflammation was a background lesion and only a portion of the study animals were examined for this change.

HISTOTECHNIQUE QUALITY

The histotechnique quality assessment indicated that the overall histological processing and slide preparation was good, with no artifacts that would interfere with the interpretation of tissue sections.



Catherine A. Picut, VMD, JD
Diplomate, ACVP
PWG Chairperson



Date

NTP Experiment-Test: 96011-04
Study Type: SUBCHRON 90-DAY
Route: RESPIRATORY EXPOSURE WHOLE BODY

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
WITH AVERAGE SEVERITY GRADES [b]
CUMENE

Report: PEIRPT03
Date: 08/27/01
Time: 14:01:01

FINAL#1/MICE

Facility: Battelle Northwest
Chemical CAS #: 98-82-8
Lock Date: 02/05/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

- a Number of animals examined microscopically at site and number of animals with lesion
- b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

NTP Experiment-Test: 96011-04
 Study Type: SUBCHRON 90-DAY
 Route: RESPIRATORY EXPOSURE WHOLE BODY

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 WITH AVERAGE SEVERITY GRADES (b)
 CUMENE

Report: PEIRPT03
 Date: 08/27/01
 Time: 14:01:01

B6C3F1 MICE FEMALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

DISPOSITION SUMMARY

Animals Initially In Study	10	10	10	10	10	10
Early Deaths						
Natural Death						8
Survivors	10	10	10	10	10	2
Terminal Sacrifice						
Animals Examined Microscopically	10	10	10	10	10	10

ALIMENTARY SYSTEM

Liver	(10)	(10)	(10)	(10)	(10)	(10)
Inflammation, Chronic, Focal	1 [1.0]	10 [1.0]	10 [1.0]	9 [1.0]	7 [1.0]	2 [1.0]
Necrosis	4 [1.3]	(10)	(10)	(10)	2 [1.5]	(10)
Stomach, Forestomach	(10)	(10)	(10)	(10)	(10)	(10)
Hyperplasia, Squamous		1 [1.0]			2 [2.0]	1 [1.0]
Inflammation, Acute						1 [1.0]
Inflammation, Chronic Active				2 [1.0]	2 [1.0]	

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

None

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

Uterus	(10)					(10)	(8)
Endometrium, Hyperplasia, Cystic	1 [1.0]						

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

	CONTROL	62.5 PPM	125 PPM	250 PPM	500 PPM	1000 PPM
HEMATOPOIETIC SYSTEM						
Spleen	(10)	(1)			(10)	(8)
Hyperplasia, Lymphoid		1 [2.0]				
Thymus	(10)	(10)	(10)	(10)	(10)	(10)
Necrosis						8 [4.0]
INTEGUMENTARY SYSTEM						
Skin	(10)				(10)	(10)
Hair Follicle, Infiltration Cellular, Mixed Cell					1 [1.0]	
MUSCULOSKELETAL SYSTEM						
None						
NERVOUS SYSTEM						
None						
RESPIRATORY SYSTEM						
Larynx	(10)				(10)	(10)
Inflammation, Suppurative					1 [1.0]	1 [1.0]
Metaplasia, Squamous		1 [1.0]			(10)	2 [1.0]
Lung	(10)	(10)			(10)	(10)
Inflammation, Acute						1 [3.0]
Nose	(10)				(10)	(10)
Inflammation, Suppurative						2 [1.0]
SPECIAL SENSES SYSTEM						
Eye	(10)				(10)	(6)
Infiltration Cellular, Polymorphonuclear	2 [1.5]				8 [1.0]	1 [1.0]
URINARY SYSTEM						

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal; 2-mild; 3-moderate; 4-marked)

NTP Experiment-Test: 96011-04
 Study Type: SUBCHRON 90-DAY
 Route: RESPIRATORY EXPOSURE WHOLE BODY

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 WITH AVERAGE SEVERITY GRADES(b)
 CUMENNE

Report: PEIRPT03
 Date: 08/27/01
 Time: 14:01:01

B6C3F1 MICE FEMALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

URINARY SYSTEM - CONT	CONTROL	62.5 PPM	125 PPM	250 PPM	500 PPM	1000 PPM
Kidney	(10)	(10)	(10)	(10)	(10)	(10)
Renal Tubule, Necrosis	1 [1.0]		2 [1.0]	1 [1.0]	2 [1.0]	1 [2.0]
Renal Tubule, Regeneration						1 [1.0]

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

B6C3F1 MICE MALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

DISPOSITION SUMMARY

Animals Initially In Study	10	10	10	10	10	10
Early Deaths						
Survivors	10	10	10	10	10	10
Terminal Sacrifice						
Animals Examined Microscopically	10	10	10	10	10	10

ALIMENTARY SYSTEM

Liver	(10)	(10)	(10)	(10)	(10)	(10)
Basophilic Focus			1			
Inflammation, Chronic, Focal	4 [1.0]	3 [1.0]	2 [1.0]	3 [1.0]	5 [1.0]	4 [1.0]
Necrosis		1 [1.0]		1 [1.0]	1 [1.0]	5 [1.2]
Mesentery					(1)	
Fat, Necrosis					1 [1.0]	
Salivary Glands						(10)
Inflammation, Chronic	(10)					1 [2.0]

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

None

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

None

HEMATOPOIETIC SYSTEM

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

NTP Experiment-Test: 96011-04 INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 Study Type: SUBCHRON 90-DAY WITH AVERAGE SEVERITY GRADES [b]
 Route: RESPIRATORY EXPOSURE WHOLE BODY CUMENE

Report: PEIRPT03
 Date: 08/27/01
 Time: 14:01:01

B6C3F1 MICE MALE	CONTROL	62.5 PPM	125 PPM	250 PPM	500 PPM	1000 PPM
------------------	---------	----------	---------	---------	---------	----------

None

INTEGUMENTARY SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

None

RESPIRATORY SYSTEM

Larynx	(10)				(10)	
Metaplasia, Squamous	1 [1.0]					(10)
Lung	(10)		(1)			(10)
Hemorrhage			1 [2.0]			

SPECIAL SENSES SYSTEM

Eye	(10)					(10)
Infiltration Cellular, Polymorphonuclear	6 [1.0]					10 [1.2]

URINARY SYSTEM

Kidney	(10)				(1)	(10)
Renal Tubule, Regeneration	3 [1.0]					

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

NTP Experiment-Test: 96011-03
Study Type: SUBCHRON 90-DAY
Route: RESPIRATORY EXPOSURE WHOLE BODY

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
WITH AVERAGE SEVERITY GRADES [b]
↓
CUMENE

FINAL#1/RATS

Report: PEIRPT03
Date: 08/27/01
Time: 13:58:00

Facility: Battelle Northwest
Chemical CAS #: 98-82-8
Lock Date: 02/05/01
Cage Range: All
Reasons For Removal: All
Removal Date Range: All
Treatment Groups: Include All

- a Number of animals examined microscopically at site and number of animals with lesion
- b Average severity grade (1-minimal; 2-mild; 3-moderate; 4-marked)

NTP Experiment-Test: 96011-03
 Study Type: SUBCHRON 90-DAY
 Route: RESPIRATORY EXPOSURE WHOLE BODY

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 WITH AVERAGE SEVERITY GRADES[b]
 CUMENE

Report: PEIRPT03
 Date: 08/27/01
 Time: 13:58:00

FISCHER 344 RATS FEMALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

DISPOSITION SUMMARY

	CONTROL	62.5 PPM	125 PPM	250 PPM	500 PPM	1000 PPM
Animals Initially In Study	10	10	10	10	10	10
Early Deaths						
Survivors	10	10	10	10	10	10
Terminal Sacrifice						
Animals Examined Microscopically	10		2		2	10

ALIMENTARY SYSTEM

Liver	(10)		(1)			(10)
Hepatodiaphragmatic Nodule			1			
Stomach, Forestomach	(9)				(1)	(10)
Serosa, Foreign Body					1 [4.0]	
Serosa, Inflammation, Granulomatous					1 [4.0]	

CARDIOVASCULAR SYSTEM

None

ENDOCRINE SYSTEM

None

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

Ovary	(10)		(1)		(10)	
Cyst			1 [2.0]		2 [1.0]	

HEMATOPOIETIC SYSTEM

Lymph Node, Mediastinal	(5)					(4)
Hyperplasia, Lymphoid	1 [1.0]					

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

FISCHER 344 RATS FEMALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

INTEGUMENTARY SYSTEM

Skin (10) (1) (10)
 Subcutaneous Tissue, Hair Follicle, Cyst,
 Squamous (1) [2.0]

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

None

RESPIRATORY SYSTEM

Lung (10) (10)
 Alveolus, Infiltration Cellular 1 [1.0]
 Alveolus, Infiltration Cellular, Histocyte 1 [1.0]

SPECIAL SENSES SYSTEM

None

URINARY SYSTEM

None

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

NTP Experiment-Test: 96011-03
 Study Type: SUBCHRON 90-DAY
 Route: RESPIRATORY EXPOSURE WHOLE BODY

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 WITH AVERAGE SEVERITY GRADES[b]
 CUMENE

Report: PEIRPT03
 Date: 08/27/01
 Time: 13:58:00

FISCHER 344 RATS MALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

DISPOSITION SUMMARY	CONTROL	62.5 PPM	125 PPM	250 PPM	500 PPM	1000 PPM
Animals Initially In Study	10	10	10	10	10	10
Early Deaths						
Survivors	10	10	10	10	10	10
Terminal Sacrifice						
Animals Examined Microscopically	10	10	10	10	10	10

ALIMENTARY SYSTEM

Liver	(10)			(1)		(10)
Hepatodiaphragmatic Nodule				1		
Mesentery					(1)	
Inflammation, Chronic				1 [3.0]		(10)
Pancreas	(10)					(10)
Infiltration Cellular, Lymphocyte	1 [1.0]					1 [1.0]

CARDIOVASCULAR SYSTEM

Heart	(10)					(10)
Inflammation, Chronic	1 [1.0]					

ENDOCRINE SYSTEM

None

GENERAL BODY SYSTEM

None

GENITAL SYSTEM

None

HEMATOPOIETIC SYSTEM

None

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

FISCHER 344 RATS MALE CONTROL 62.5 PPM 125 PPM 250 PPM 500 PPM 1000 PPM

INTEGUMENTARY SYSTEM

None

MUSCULOSKELETAL SYSTEM

None

NERVOUS SYSTEM

None

RESPIRATORY SYSTEM

Lung

Alveolar Epithelium, Hyperplasia	(10)							(10)
Alveolus, Hemorrhage	1 [1.0]							1 [2.0]
Alveolus, Infiltration Cellular, Histiocyte	1 [1.0]							2 [1.0]

SPECIAL SENSES SYSTEM

None

URINARY SYSTEM

Kidney

Cortex, Renal Tubule, Accumulation, Hyaline	(10)	(10)	(10)	(10)	(10)	(10)	(10)
Droplet	10 [1.1]	10 [1.4]	10 [1.9]	10 [2.4]	10 [3.0]	10 [2.9]	
Cortex, Renal Tubule, Regeneration	8 [1.0]	6 [1.2]	8 [1.5]	10 [1.8]	10 [2.1]	10 [2.1]	
Medulla, Casts Granular			2 [1.0]	8 [1.5]	10 [2.5]	9 [2.2]	
Papilla, Mineralization						1 [1.0]	
Papilla, Transitional Epithelium, Mineralization			1 [1.0]				
Urinary Bladder	(10)		(1)				(10)
Calculus Gross Observation			1				
Calculus Micro Observation Only			1 [1.0]				

a Number of animals examined microscopically at site and number of animals with lesion
 b Average severity grade (1-minimal;2-mild;3-moderate;4-marked)

END OF REPORT

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

May 18, 2001


**American
Chemistry
Council**
*Good Chemistry
Makes It Possible*

BY MESSENGER

Document Control Office (7407)
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

2002 AUG 22 AM 6:02

RECEIVED
OPPT/CBIC

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 /efw

Attachments



Responsible Care®

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 T₉₀, 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 ≤ .05

** p ≤ .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 T₉₀, 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 α_{2u} -globulin in renal cortical tubular cytoplasm. The amount of α_{2u} -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 \pm 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] \pm SD (% difference from controls)	311.7 \pm 24.4	313.3 \pm 19.3 (0.5)	322.4 \pm 15.5 (3.4)	331.4 \pm 12.5 (6.3)	314.0 \pm 16.7 (0.7)	323.3 \pm 15.9 (3.7)
Necropsy Findings [Page III-3]						
Gross observations	NS	NS	NS	NS	NS	NS
Increased liver weight	NA	NS	NS	++	++	++
Increased liver:body weight	NA	+	NS	++	++	++
Increased kidney weight	NA	NS	NS	++	++	++
Increased kidney:body weight	NA	+	+	++	++	++
Clinical Pathology Findings [Page III-6]						
Day 3: Increased reticulocytes	NA	NS	NS	+	++	++
Day 3: Decreased lymphocytes	NA	NS	NS	NS	NS	++
Day 3: Decreased leukocytes	NA	NS	NS	NS	NS	++
Day 3: Increased bile acid	NA	NS	++	++	++	++
Day 3: Increased blood urea nitrogen	NA	NS	NS	NS	NS	++
Day 23: Increased lymphocytes	NA	+	NS	NS	+	++
Day 23: Increased leukocytes	NA	NS	NS	NS	++	++
Day 23: Increased blood urea nitrogen	NA	NS	NS	NS	NS	++
Day 23: Increased bile acid	NA	NS	NS	++	++	++
Day 23: Decreased alanine aminotransferase	NA	++	++	++	++	++
TSAC: Increased lymphocytes	NA	NS	NS	NS	++	NS
TSAC: Decreased alanine aminotransferase	NA	NS	NS	++	++	++
TSAC: Increased bile acid	NA	NS	NS	NS	NS	++
Renal Toxicity Findings [Page III-14]						
α_2 -Globulin (mean [nmol/g kidney] \pm SD)	172 \pm 71	328 \pm 220	383 \pm 139 ^{***}	421 \pm 158 ^{**}	363 \pm 131 ^{**}	575 \pm 237 ^{**}
PCNA (% labeled nuclei)	2.9 \pm 0.64	3.6 \pm 0.84	3.1 \pm 0.96	2.5 \pm 0.69	1.9 \pm 0.97	3.6 \pm 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 \leq .05** p \leq .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
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)	195.0 ± 6.6	189.7 ± 7.9 (-2.8)	194.4 ± 14.3 (-0.3)	190.4 ± 10.7 (-2.4)	185.1 ± 8.9 (-5.1)	187.1 ± 11.7 (-4.1)
Necropsy Findings [Page III-3]						
Gross observations	NS	NS	NS	NS	NS	NS
Increased liver:body weight	NA	NS	NS	NS	NS	NS
Increased kidney:body weight	NA	NS	NS	NS	NS	NS
Clinical Pathology Findings [Page III-6]						
Day 3: Decreased lymphocytes	NA	NS	NS	NS	NS	NS
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