

# Draft Report on Carcinogens Monograph for Cumene

## Data for Evaluating Alpha-2u Criteria

Gloria D. Jahnke, DVM, DABT  
National Institute of Environmental Health Sciences

NTP Peer Review Meeting  
March 21-22, 2013



**TABLE 6**  
**Selected Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats**  
**In the 3-Month Inhalation Study of Cumene<sup>a</sup>**

	Chamber Control	62.5 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10	10	10
<b>Male</b>						
Necropsy body wt	312 ± 8	313 ± 6	322 ± 5	331 ± 4	314 ± 5	323 ± 5
R. Kidney						
Absolute	0.923 ± 0.024	0.980 ± 0.025	1.010 ± 0.031 <sup>*b</sup>	1.059 ± 0.021**	1.070 ± 0.017**	1.152 ± 0.023**
Relative	2.962 ± 0.032	3.128 ± 0.051**	3.131 ± 0.056 <sup>**b</sup>	3.194 ± 0.036**	3.411 ± 0.045**	3.561 ± 0.029**
Liver						
Absolute	9.518 ± 0.327	10.123 ± 0.267	10.260 ± 0.264	11.170 ± 0.302**	11.589 ± 0.282**	12.637 ± 0.288**
Relative	30.481 ± 0.348	32.279 ± 0.278*	31.792 ± 0.430*	33.660 ± 0.558**	36.895 ± 0.563**	39.068 ± 0.549**
<b>Female</b>						
Necropsy body wt	195 ± 2	190 ± 3	194 ± 4	190 ± 3	185 ± 3	187 ± 4
R. Kidney						
Absolute	0.637 ± 0.016	0.636 ± 0.010	0.649 ± 0.018	0.655 ± 0.017	0.645 ± 0.011	0.675 ± 0.011
Relative	3.263 ± 0.061	3.355 ± 0.049	3.322 ± 0.057	3.439 ± 0.057*	3.486 ± 0.044**	3.612 ± 0.040**
Liver						
Absolute	5.553 ± 0.130	5.669 ± 0.148	5.885 ± 0.204	5.959 ± 0.137	5.979 ± 0.133	6.923 ± 0.227**
Relative	28.442 ± 0.389	29.858 ± 0.458	30.094 ± 0.634*	31.289 ± 0.412**	32.286 ± 0.386**	36.958 ± 0.724**

\* Significantly different ( $P \leq 0.05$ ) from the chamber control group by Williams' test

\*\*  $P \leq 0.01$

<sup>a</sup> Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

<sup>b</sup> n=9

**TABLE 7**  
**Renal Toxicity Data for Male Rats in the 3-Month Inhalation Study of Cumene<sup>a</sup>**

	Chamber Control	62.5 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10	10	10
Cells labeled	60.60 ± 4.25	78.90 ± 5.60	63.80 ± 6.03	54.90 ± 4.50	43.70 ± 6.21	79.40 ± 6.65
Cells counted	2,095 ± 25	2,190 ± 28	2,100 ± 29	2,171 ± 31	2,268 ± 42	2,223 ± 45
Labeling index (%) <sup>b</sup>	2.894 ± 0.204	3.607 ± 0.266	3.051 ± 0.305	2.536 ± 0.219	1.944 ± 0.306	3.614 ± 0.346
Soluble protein (mg/mL)	21.22 ± 1.27	23.43 ± 0.51	23.93 ± 0.93 <sup>c</sup>	25.36 ± 0.69*	25.51 ± 0.73**	26.16 ± 1.09**
α2u-Globulin (nmol/g kidney)	172.2 ± 22.3	328.1 ± 69.6	383.4 ± 46.3** <sup>c</sup>	420.7 ± 50.1**	363.2 ± 41.4**	575.2 ± 74.8**
α2u-Globulin (ng/μg soluble protein)	76.46 ± 9.24	130.98 ± 27.27	150.90 ± 19.23 <sup>c</sup>	154.35 ± 16.98**	133.01 ± 14.25**	209.79 ± 31.34**

\* Significantly different ( $P \leq 0.05$ ) from the chamber control group by Shirley's test

\*\*  $P \leq 0.01$

<sup>a</sup> Data are presented as mean ± standard error.

<sup>b</sup> Labeling index was calculated as the number of labeled cells divided by the total number of cells counted times 100. A minimum of 2,000 cells were counted.

<sup>c</sup> n=9

**TABLE 8**  
**Incidences of Nonneoplastic Lesions in the Kidney of Male Rats**  
**in the 3-Month Inhalation Study of Cumene**

	Chamber Control	62.5 ppm	125 ppm	250 ppm	500 ppm	1,000 ppm
Number Examined Microscopically	10	10	10	10	10	10
Cortex Renal Tubule, Accumulation, Hyaline Droplet <sup>a</sup>	10 (1.1) <sup>b</sup>	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	0	0	2 (1.0)	8** (1.5)	10** (2.5)	9** (2.2)

\*\* Significantly different ( $P < 0.01$ ) from the chamber control group by the Fisher exact test

<sup>a</sup> Number of animals with lesion

<sup>b</sup> Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

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

<b>Sex</b>	<b>Conc. (ppm)</b>	<b>Renal tubule hyperplasia</b>	<b>Renal papilla mineralization</b>	<b>Renal pelvis transitional epithelium hyperplasia</b>	<b>Nephropathy</b>
Male	0	0	5 (1.0)	3 (1.7)	47 (2.3)
	250	3 <sup>a</sup> (3.3) <sup>b</sup>	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).

\*\* $P \leq 0.01$ .

<sup>a</sup>Number of animals with lesion (50 animals examined per group).

<sup>b</sup>Average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

**TABLE B4**  
**Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Cumene**

	Chamber Control	250 ppm	500 ppm	1,000 ppm
<b>Special Senses System</b>				
Eye	(50)	(49)	(50)	(50)
Bilateral, lens, cataract	1 (2%)			
Bilateral, retina, atrophy	1 (2%)	1 (2%)	1 (2%)	
Cornea, epithelium, hyperplasia				1 (2%)
Cornea, inflammation				1 (2%)
Cornea, inflammation, suppurative	1 (2%)			
Lens, cataract	5 (10%)	2 (4%)	5 (10%)	3 (6%)
Retina, atrophy	3 (6%)	5 (10%)	8 (16%)	2 (4%)
Harderian gland	(50)	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		1 (2%)	1 (2%)
Zymbal's gland	(1)		(1)	(1)
<b>Urinary System</b>				
Kidney	(50)	(50)	(50)	(50)
Infarct, multiple			1 (2%)	
Nephropathy	38 (76%)	37 (74%)	41 (82%)	44 (88%)
Artery, inflammation, chronic active				1 (2%)
Papilla, mineralization	6 (12%)	3 (6%)	4 (8%)	6 (12%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)	1 (2%)	6 (12%)	1 (2%)
Pelvis, transitional epithelium, mineralization	23 (46%)	27 (54%)	27 (54%)	22 (44%)
Pelvis, dilatation	1 (2%)			
Renal tubule, accumulation, hyaline droplet	1 (2%)		1 (2%)	
Renal tubule, cyst	1 (2%)		1 (2%)	1 (2%)
Renal tubule, pigmentation	1 (2%)			
Urinary bladder	(50)	(49)	(50)	(50)
Transitional epithelium, hyperplasia	1 (2%)	2 (4%)	2 (4%)	1 (2%)

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

<b>Sex</b>	<b>Conc. (ppm)</b>	<b>Renal tubule hyperplasia</b>	<b>Renal papilla mineralization</b>	<b>Renal pelvis transitional epithelium hyperplasia</b>	<b>Nephropathy</b>
Male	0	0	5 (1.0)	3 (1.7)	47 (2.3)
	250	3 <sup>a</sup> (3.3) <sup>b</sup>	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).

\*\* $P \leq 0.01$ .

<sup>a</sup>Number of animals with lesion (50 animals examined per group).

<sup>b</sup>Average severity grade: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

**TABLE A4**  
**Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Cumene**

	Chamber Control	250 ppm	500 ppm	1,000 ppm
<b>Urinary System</b>				
Kidney	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Infarct		1 (2%)	2 (4%)	1 (2%)
Infarct, multiple		1 (2%)		
Nephropathy	47 (94%)	47 (94%)	47 (94%)	50 (100%)
Bilateral, renal tubule, cyst			1 (2%)	
<b>Urinary System (continued)</b>				
Kidney (continued)	(50)	(50)	(50)	(50)
Bilateral, infarct		1 (2%)		
Capsule, dilatation			1 (2%)	
Glomerulus, inflammation, suppurative		1 (2%)		
Papilla, mineralization	5 (10%)	35 (70%)	44 (88%)	41 (82%)
Pelvis, transitional epithelium, hyperplasia	3 (6%)	5 (10%)	14 (28%)	15 (30%)
Pelvis, dilatation			1 (2%)	1 (2%)
Renal tubule, accumulation, hyaline droplet			1 (2%)	1 (2%)
Renal tubule, cyst		1 (2%)	3 (6%)	2 (4%)
Renal tubule, hyperplasia		3 (6%)	8 (16%)	6 (12%)
Renal tubule, hypertrophy				1 (2%)
Renal tubule, mineralization	1 (2%)			