

**Summary of Findings Considered Toxicologically Relevant in Rats and Mice Exposed to o-Phthalaldehyde for 3 Months<sup>a</sup>**

	Male Sprague Dawley Rats	Female Sprague Dawley Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
<b>Exposure concentrations</b>	0, 0.44, 0.88, 1.75, 3.5, 7.0 ppm	0, 0.44, 0.88, 1.75, 3.5, 7.0 ppm	0, 0.44, 0.88, 1.75, 3.5, 7.0 ppm	0, 0.44, 0.88, 1.75, 3.5, 7.0 ppm
<b>Survival rates</b>	10/10, 10/10, 10/10, 10/10, 3/10, 0/10	10/10, 10/10, 10/10, 10/10, 8/10, 0/10	10/10, 10/10, 10/10, 10/10, 5/10, 0/10	10/10, 10/10, 10/10, 10/10, 6/10, 0/10
<b>Clinical findings</b>	Abnormal breathing, sneezing, and thinness	Abnormal breathing, sneezing, and thinness	Abnormal breathing, sneezing, thinness, and alopecia	Abnormal breathing, sneezing, thinness, and alopecia
<b>Body weights</b>	0.44, 0.88, 1.75, and 3.5 ppm groups less than chamber control group	1.75 and 3.5 ppm groups less than chamber control group	0.44, 0.88, 1.75, and 3.5 ppm groups less than chamber control group	0.44, 0.88, 1.75, and 3.5 ppm groups less than chamber control group
<b>Organ weights</b>	↓ Cauda epididymis ↓ Epididymis ↓ Testis	None	None	None
<b>Hematology</b> Rats (Day 3, Day 23, Week 14) Mice (Week 14)	Leukocytes (↓,↓,↓); Lymphocytes (↓,↓,↓); Segmented neutrophils (↑,↑,↑); Erythrocytes (↑,↑,-); Hemoglobin (↑,↑,↑); Mean cell volume (↓,↓,-); Packed cell volume (↑,↑,↑); Hematocrit (↑,↑,↑); Platelets (↑,↓,↓); Reticulocytes (↑,-,-)	Leukocytes (↓,-,-); Lymphocytes (↓,↓,↓); Segmented neutrophils (↑,↑,↑); Erythrocytes (↑,↑,↑); Hemoglobin (↑,↑,↑); Mean cell volume (↓,-,-); Packed cell volume (↑,↑,↑); Hematocrit (↑,↑,↑); Platelets (↑,↓,↓); Reticulocytes (↑,↑,-)	Leukocytes (↑); Lymphocytes (↑); Segmented neutrophils (↑); Eosinophils (↑); Erythrocytes (↓); Hemoglobin (↓); Packed cell volume (↓); Hematocrit (↓)	Leukocytes (↑); Segmented neutrophils (↑); Eosinophils (↑); Erythrocytes (↓); Hemoglobin (↓); Packed cell volume (↓); Hematocrit (↓); Mean cell hemoglobin (↓)
<b>Clinical chemistry</b> (Day 3, Day 23, Week 14)	Total protein (↑,↑,-); Albumin (↑,-,-); Globulin (↑,-,-); Alkaline phosphatase (↓,-,↑); Alanine aminotransferase (↓,↑,↑); Bile acids (↓,-,↑); Sorbitol dehydrogenase (↑,-,-); Urea nitrogen (↑,↑,-); Cholesterol (↓,-,↓); Triglycerides (↓,-,-); Glucose (↑,↑,↑); Creatinine kinase (-,↑,↑)	Total protein (↑,-,-); Albumin (-,-,↓); Albumin/globulin ratio (↓,↓,↓); Globulin (↑,-,↑); Alkaline phosphatase (↓,↑,↑); Alanine aminotransferase (↓,-,↑); Bile acids (-,-,↑); Sorbitol dehydrogenase (↑,-,-); Urea nitrogen (↑,↑,-); Cholesterol (↓,-,-); Triglycerides (-,-,↑); Glucose (↑,↑,-); Creatinine kinase (-,↑,↑)	Not assessed	Not assessed
<b>Reproductive effects</b>	↓ Total sperm/cauda ↓ Sperm motility	Not assessed	↓ Sperm motility	Not assessed

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	Male Sprague Dawley Rats	Female Sprague Dawley Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
<b>Nonneoplastic effects</b>	<p><u>Nose</u>: inflammation, suppurative (0/10, 10/10, 10/10, 10/10, 10/10, 10/10); olfactory epithelium, atrophy (2/10, 10/10, 10/10, 10/10, 7/10, 6/10); olfactory epithelium, metaplasia, respiratory (1/10, 1/10, 6/10, 6/10, 2/10, 0/10); olfactory epithelium, regeneration (0/10, 0/10, 1/10, 0/10, 4/10, 0/10); respiratory epithelium, hyperplasia (3/10, 9/10, 9/10, 7/10, 3/10, 0/10); respiratory epithelium, squamous metaplasia (0/10, 10/10, 10/10, 10/10, 10/10, 8/10); respiratory epithelium, necrosis (0/10, 0/10, 3/10, 5/10, 10/10, 10/10); respiratory epithelium, regeneration (0/10, 0/10, 1/10, 0/10, 3/10, 6/10); turbinate, atrophy (0/10, 0/10, 7/10, 10/10, 0/10, 0/10)</p> <p><u>Larynx</u>: inflammation, chronic active (1/10, 2/10, 8/10, 10/10, 10/10, 10/10); metaplasia, squamous (0/10, 1/10, 8/10, 10/10, 10/10, 10/10); necrosis (0/10, 0/10, 1/10, 5/10, 9/10, 10/10); regeneration (0/10, 0/10, 3/10, 2/10, 2/10, 6/10)</p> <p><u>Trachea</u>: fibrosis (0/10, 0/10, 0/10, 5/10, 3/10, 0/10); inflammation, chronic active (0/10, 0/10, 4/10, 8/10, 9/10, 10/10); metaplasia, squamous (0/10, 0/10, 4/10, 10/10, 6/10, 6/10); necrosis (0/10, 0/10, 0/10, 3/10, 8/10, 8/10); regeneration (0/10, 0/10, 0/10, 7/10, 7/10, 6/10)</p>	<p><u>Nose</u>: inflammation, suppurative (0/10, 9/10, 10/10, 10/10, 10/10, 10/10); olfactory epithelium, atrophy (0/10, 9/10, 10/10, 10/10, 10/10, 7/10); olfactory epithelium, metaplasia, respiratory (0/10, 1/10, 2/10, 5/10, 7/10, 1/10); respiratory epithelium, hyperplasia (0/10, 9/10, 7/10, 4/10, 3/10, 3/10); respiratory epithelium, squamous metaplasia (0/10, 10/10, 10/10, 10/10, 10/10, 10/10); respiratory epithelium, necrosis (0/10, 2/10, 6/10, 9/10, 10/10, 10/10); respiratory epithelium, regeneration (0/10, 0/10, 2/10, 0/10, 1/10, 3/10); turbinate, atrophy (0/10, 2/10, 4/10, 10/10, 10/10, 0/10)</p> <p><u>Larynx</u>: inflammation, chronic active (0/10, 1/10, 1/10, 9/10, 10/10, 10/10); metaplasia, squamous (0/10, 1/10, 4/10, 10/10, 10/10, 10/10); necrosis (0/10, 0/10, 0/10, 1/10, 7/10, 8/10)</p> <p><u>Trachea</u>: fibrosis (0/10, 0/10, 0/10, 2/10, 6/10, 0/10); inflammation, chronic active (0/10, 0/10, 3/10, 5/10, 10/10, 10/10); metaplasia, squamous (0/10, 0/10, 3/10, 10/10, 7/10, 7/10); necrosis (0/10, 0/10, 0/10, 3/10, 3/10, 8/10); regeneration (0/10, 0/10, 1/10, 7/10, 10/10, 9/10)</p>	<p><u>Nose</u>: inflammation, suppurative (0/10, 10/10, 10/10, 10/10, 10/10, 10/10); glands, olfactory epithelium, hyperplasia (0/10, 10/10, 10/10, 7/10, 6/10, 0/10); olfactory epithelium, atrophy (0/10, 10/10, 10/10, 10/10, 10/10, 10/10); olfactory epithelium, metaplasia, respiratory (0/10, 1/10, 8/10, 10/10, 4/10, 0/10); respiratory epithelium, metaplasia, squamous (0/10, 10/10, 10/10, 10/10, 10/10, 6/10); respiratory epithelium, necrosis (0/10, 2/10, 6/10, 5/10, 9/10, 10/10); respiratory epithelium, regeneration (0/10, 0/10, 1/10, 0/10, 1/10, 4/10); turbinate atrophy (0/10, 4/10, 6/10, 10/10, 8/10, 0/10)</p> <p><u>Larynx</u>: inflammation, chronic active (0/10, 0/10, 0/10, 4/10, 10/10, 10/10); metaplasia, squamous (0/10, 0/10, 0/10, 3/10, 10/10, 3/10); necrosis (0/10, 0/10, 0/10, 0/10, 1/10, 10/10)</p> <p><u>Trachea</u>: inflammation, chronic active (0/10, 0/10, 0/10, 1/10, 9/10, 10/10); metaplasia, squamous (0/10, 0/10, 0/10, 3/10, 10/10, 3/10); necrosis (0/10, 0/10, 0/10, 0/10, 0/10, 9/10)</p>	<p><u>Nose</u>: inflammation, suppurative (0/10, 10/10, 10/10, 10/10, 10/10, 10/10); glands, olfactory epithelium, hyperplasia (0/10, 10/10, 9/10, 10/10, 8/10, 0/10); olfactory epithelium, atrophy (0/10, 10/10, 10/10, 10/10, 9/10, 9/10); olfactory epithelium, metaplasia, respiratory (0/10, 3/10, 6/10, 3/10, 4/10, 0/10); respiratory epithelium, metaplasia, squamous (0/10, 10/10, 10/10, 10/10, 10/10, 10/10); respiratory epithelium, necrosis (0/10, 2/10, 7/10, 6/10, 8/10, 10/10); respiratory epithelium, regeneration (0/10, 0/10, 0/10, 1/10, 3/10, 6/10); turbinate atrophy (0/10, 7/10, 9/10, 10/10, 7/10, 0/10)</p> <p><u>Larynx</u>: inflammation, chronic active (0/10, 0/10, 0/10, 0/10, 9/10, 10/10); metaplasia, squamous (0/10, 0/10, 3/10, 10/10, 10/10, 8/10); necrosis (0/10, 0/10, 0/10, 0/10, 3/10, 9/10)</p> <p><u>Trachea</u>: inflammation, chronic active (0/10, 0/10, 0/10, 0/10, 10/10, 10/10); metaplasia, squamous (0/10, 0/10, 0/10, 0/10, 9/10, 2/10); necrosis (0/10, 0/10, 0/10, 0/10, 2/10, 10/10)</p>

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	Male Sprague Dawley Rats	Female Sprague Dawley Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
<b>Nonneoplastic effects</b> (continued)	<u>Lung</u> : alveolus, inflammation, suppurative (0/10, 0/10, 0/10, 0/10, 3/10, 6/10); bronchus, fibrosis (0/10, 0/10, 0/10, 1/10, 2/10, 1/10); bronchus, hyperplasia (0/10, 0/10, 0/10, 2/10, 5/10, 1/10); bronchus, inflammation, chronic active (0/10, 0/10, 0/10, 3/10, 9/10, 8/10); bronchus, metaplasia, squamous (0/10, 0/10, 0/10, 7/10, 6/10, 1/10); bronchus, necrosis (0/10, 0/10, 0/10, 0/10, 5/10, 7/10)	<u>Lung</u> : alveolus, inflammation, suppurative (0/10, 0/10, 0/10, 0/10, 2/10, 4/10); bronchus, fibrosis (0/10, 0/10, 0/10, 1/10, 3/10); bronchus, hyperplasia (0/10, 0/10, 0/10, 1/10, 6/10, 1/10); bronchus, inflammation, chronic active (0/10, 0/10, 0/10, 2/10, 10/10, 10/10); bronchus, metaplasia, squamous (0/10, 0/10, 0/10, 2/10, 9/10, 0/10); bronchus, necrosis (0/10, 0/10, 0/10, 0/10, 2/10, 10/10); bronchus, regeneration (0/10, 0/10, 0/10, 0/10, 1/10, 5/10)	<u>Lung</u> : bronchus, inflammation, chronic active (0/10, 0/10, 0/10, 0/10, 1/10, 6/10); bronchus, necrosis (0/10, 0/10, 0/10, 2/10, 9/10)	<u>Lung</u> : bronchus, inflammation, chronic active (0/10, 0/10, 0/10, 0/10, 6/10, 8/10); bronchus, necrosis (0/10, 0/10, 0/10, 2/10, 8/10)
	<u>Skin</u> : adnexa, degeneration (0/10, 0/10, 0/10, 0/10, 4/10, 10/10); epithelium, hair follicle, parakeratosis (0/10, 7/10, 4/10, 7/10, 3/10, 10/10)	<u>Skin</u> : adnexa, degeneration (0/10, 1/10, 0/10, 0/10, 1/10, 10/10); epithelium, hair follicle, parakeratosis (0/10, 1/10, 1/10, 3/10, 3/10, 6/10)	<u>Skin</u> : hyperplasia, squamous (0/10, 1/10, 0/10, 0/9, 9/10, 4/10); inflammation, chronic active (0/10, 0/10, 0/10, 1/9, 10/10, 9/10); adnexa, degeneration (0/10, 2/10, 0/10, 4/9, 1/10, 6/10); epithelium, hair follicle, parakeratosis (0/10, 3/10, 4/10, 2/9, 2/10, 10/10)	<u>Skin</u> : hyperplasia, squamous (3/10, 0/10, 0/10, 6/10, 9/10, 6/10); inflammation, chronic active (1/10, 1/10, 3/10, 9/10, 9/10, 8/10); adnexa, degeneration (2/10, 0/10, 0/10, 1/10, 0/10, 9/10); epithelium, hair follicle, parakeratosis (0/10, 3/10, 7/10, 9/10, 10/10, 10/10)
	<u>Eye</u> : anterior chamber, inflammation, suppurative (0/10, 0/10, 0/10, 0/10, 4/10, 5/10); cornea, inflammation, suppurative (1/10, 1/10, 1/10, 1/10, 5/10, 6/10); cornea, necrosis (0/10, 0/10, 1/10, 0/10, 2/10, 4/10)	<u>Eye</u> : anterior chamber, inflammation, suppurative (0/10, 0/10, 0/10, 0/10, 1/10, 5/10); cornea, inflammation, suppurative (0/10, 0/10, 1/10, 0/10, 1/10, 8/10); cornea, necrosis (0/10, 0/10, 0/10, 0/10, 0/10, 7/10)	<u>Eye</u> : cornea, inflammation, suppurative (0/10, 1/10, 0/10, 0/10, 1/10, 4/10)	

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	Male Sprague Dawley Rats	Female Sprague Dawley Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
<b>Nonneoplastic effects</b> (continued)	<u>Epididymis</u> : duct, exfoliated germ cell (0/10, 0/10, 1/10, 1/10, 5/10, 4/10); epithelium, apoptosis (0/10, 0/10, 0/10, 0/10, 3/10, 5/10)  <u>Testis</u> : elongated spermatid, degeneration (0/10, 0/10, 0/10, 0/10, 4/10, 0/10); germinal epithelium, apoptosis (0/10, 0/10, 0/10, 0/10, 4/10, 6/10); interstitial cell, atrophy (0/10, 0/10, 0/10, 0/10, 7/10, 10/10); seminiferous tubule, vacuolation (0/10, 0/10, 0/10, 0/10, 3/10, 0/10)		<u>Epididymis</u> : duct, exfoliated germ cell (0/10, 0/10, 0/10, 0/10, 4/10, 1/10);  <u>Testis</u> : germinal epithelium, depletion, cellular, multifocal (0/10, 1/10, 1/10, 0/10, 7/10, 0/10); interstitial cell, atrophy (0/10, 0/10, 0/10, 0/10, 3/10, 0/10)	
<b>Genetic toxicology</b>				
Bacterial gene mutations ( <i>in vitro</i> ):	Positive in <i>Salmonella typhimurium</i> strain TA100 in the absence of exogenous metabolic activation. Negative in <i>Salmonella typhimurium</i> strain TA100 with exogenous activation and in TA98 and <i>Escherichia coli</i> WP2 <i>uvrA</i> /pKM101 with and without exogenous activation.			
Micronucleated reticulocytes ( <i>in vivo</i> ):				
Rat	Negative in males and females.			
Mouse	Equivocal in males and negative in females.			

<sup>a</sup> ↑, ↓, and – represent an increase, a decrease, and no biologically significant change in a parameter, respectively, compared to the chamber control group.

## RESULTS

### RATS

All rats exposed to 7.0 ppm died by the end of week 2 of the study, and seven males and two females exposed to 3.5 ppm died by week 7 of the study (Table 2). In males exposed to 7.0 ppm, eight rats were found dead in week 1 and two were euthanized in weeks 1 and 2. In females exposed to 7.0 ppm, nine rats were found dead, eight in week 1 and one in week 2, and one was euthanized in week 2. In males exposed to 3.5 ppm, four were found dead in weeks 1 and 2, three were euthanized in weeks 6 and 7, and three survived to study completion. In females exposed to 3.5 ppm, two were euthanized in weeks 3 and 7, and eight survived to study completion.

**TABLE 2**  
**Survival and Body Weights of Rats in the 3-Month Inhalation Study of *o*-Phthalaldehyde<sup>a</sup>**

Concentration (ppm)	Survival <sup>b</sup>	Initial Body Weight (g)	Final Body Weight (g)	Change in Body Weight (g)	Final Weight Relative to Controls (%)
<b>Male</b>					
0	10/10	136 ± 2	409 ± 4	273 ± 4	
0.44	10/10	135 ± 3	377 ± 6**	242 ± 6**	92
0.88	10/10	134 ± 2	350 ± 5**	217 ± 6**	86
1.75	10/10	134 ± 2	309 ± 9**	175 ± 9**	76
3.5 <sup>c</sup>	3/10	134 ± 3	222 ± 15**	92 ± 13**	54
7.0 <sup>d</sup>	0/10	134 ± 2	—	—	—
<b>Female</b>					
0	10/10	118 ± 3	239 ± 5	121 ± 4	
0.44	10/10	120 ± 2	238 ± 5	118 ± 5	99
0.88	10/10	118 ± 2	230 ± 3	112 ± 4	96
1.75	10/10	116 ± 2	214 ± 5**	97 ± 4**	89
3.5 <sup>e</sup>	8/10	119 ± 2	205 ± 6**	88 ± 6**	85
7.0 <sup>f</sup>	0/10	118 ± 2	—	—	—

\*\* Significantly different ( $P \leq 0.01$ ) from the chamber control group by Williams' test

<sup>a</sup> Body weights and weight changes are given as mean ± standard error.

<sup>b</sup> Number of animals surviving at 14 weeks/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.

<sup>c</sup> Weeks of death: 1, 1, 1, 2, 6, 6, 7

<sup>d</sup> Weeks of death: 1, 1, 1, 1, 1, 1, 1, 1, 1, 2

<sup>e</sup> Weeks of death: 3, 7

<sup>f</sup> Weeks of death: 1, 1, 1, 1, 1, 1, 1, 1, 2, 2

**TABLE 3**  
**Selected Hematology Data for Rats in the 3-Month Inhalation Study of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Male</b>						
n						
Day 3	10	10	10	10	10	9
Day 23	10	10	10	9	5	0
Week 14	10	10	10	10	3	0
Hematocrit (spun) (%)						
Day 3	41.4 ± 0.4	42.5 ± 0.4	42.1 ± 0.3	45.9 ± 0.7**	48.9 ± 0.8**	50.5 ± 0.5**
Day 23	45.1 ± 0.3	45.9 ± 0.5	47.1 ± 0.7*	48.4 ± 0.5**	55.9 ± 1.0**	
Week 14	48.3 ± 0.4	48.8 ± 0.5	50.2 ± 0.4**	49.6 ± 0.6*	51.3 ± 1.1*	
Packed cell volume (%)						
Day 3	39.6 ± 0.4	40.6 ± 0.4	40.0 ± 0.4	44.1 ± 0.6**	47.2 ± 0.9**	49.5 ± 0.5**
Day 23	43.8 ± 0.3	44.2 ± 0.5	45.5 ± 0.6*	47.1 ± 0.5**	53.9 ± 1.1**	
Week 14	46.4 ± 0.4	47.4 ± 0.4	49.1 ± 0.4**	48.2 ± 0.5**	50.3 ± 1.7*	
Hemoglobin (g/dL)						
Day 3	12.7 ± 0.1	13.1 ± 0.1	13.1 ± 0.1	14.4 ± 0.2**	15.3 ± 0.3**	16.2 ± 0.2**
Day 23	14.4 ± 0.1	14.5 ± 0.2	15.0 ± 0.2*	15.5 ± 0.2**	17.7 ± 0.3**	
Week 14	15.6 ± 0.1	15.9 ± 0.1	16.3 ± 0.1**	16.1 ± 0.2**	17.0 ± 0.5**	
Erythrocytes (10 <sup>6</sup> /μL)						
Day 3	6.03 ± 0.07	6.16 ± 0.06	6.23 ± 0.07	6.84 ± 0.11**	7.42 ± 0.15**	7.84 ± 0.11**
Day 23	7.19 ± 0.05	7.18 ± 0.07	7.52 ± 0.11*	7.85 ± 0.08**	9.16 ± 0.23**	
Week 14	8.53 ± 0.08	8.62 ± 0.08	8.87 ± 0.09	8.71 ± 0.12	8.99 ± 0.27	
Reticulocytes (10 <sup>3</sup> /μL)						
Day 3	446 ± 10	413 ± 18	393 ± 17	451 ± 13	515 ± 17*	507 ± 19*
Day 23	281 ± 15	255 ± 10	235 ± 13	265 ± 11	277 ± 28	
Week 14	193 ± 13	205 ± 9	185 ± 13	196 ± 11	270 ± 13	
Platelets (10 <sup>3</sup> /μL)						
Day 3	1,112 ± 29	1,164 ± 30	1,170 ± 30	1,259 ± 45**	1,328 ± 50**	1,355 ± 85**
Day 23	975 ± 33	936 ± 10	941 ± 24	935 ± 19	786 ± 42**	
Week 14	823 ± 23	781 ± 13	770 ± 22	703 ± 23**	697 ± 51*	
Leukocytes (10 <sup>3</sup> /μL)						
Day 3	14.58 ± 0.66	13.44 ± 1.04	13.56 ± 0.93	9.38 ± 0.83**	8.89 ± 1.08**	8.87 ± 0.69**
Day 23	12.02 ± 0.81	10.94 ± 0.44	11.14 ± 0.77	10.04 ± 0.68	7.98 ± 0.73**	
Week 14	11.34 ± 0.49	11.81 ± 0.65	10.73 ± 0.74	9.27 ± 0.60*	6.69 ± 0.30**	
Segmented neutrophils (10 <sup>3</sup> /μL)						
Day 3	1.41 ± 0.12	1.33 ± 0.20	1.46 ± 0.16	1.12 ± 0.11	2.06 ± 0.50	3.28 ± 0.20**
Day 23	1.36 ± 0.20	1.38 ± 0.12	2.76 ± 0.57**	2.30 ± 0.17**	2.95 ± 0.34**	
Week 14	1.35 ± 0.14	1.66 ± 0.11	2.05 ± 0.16**	2.39 ± 0.13**	2.42 ± 0.24**	
Lymphocytes (10 <sup>3</sup> /μL)						
Day 3	12.92 ± 0.58	11.78 ± 0.82	11.81 ± 0.84	8.05 ± 0.83**	6.58 ± 0.61**	5.40 ± 0.69**
Day 23	10.45 ± 0.72	9.28 ± 0.42	8.14 ± 0.36*	7.52 ± 0.64**	4.80 ± 0.49**	
Week 14	9.72 ± 0.39	9.87 ± 0.62	8.42 ± 0.66*	6.67 ± 0.54**	3.84 ± 0.46**	

**TABLE 3**  
**Selected Hematology Data for Rats in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Female</b>						
n						
Day 3	10	10	10	10	10	9
Day 23	10	10	9	10	7	0
Week 14	10	10	10	10	8	0
Hematocrit (spun) (%)						
Day 3	43.9 ± 0.4	44.2 ± 0.3	43.3 ± 0.8	45.3 ± 0.5	48.5 ± 0.7**	51.6 ± 0.7**
Day 23	46.8 ± 0.5	47.2 ± 0.4	48.1 ± 0.6	49.1 ± 0.5**	52.3 ± 1.3**	
Week 14	46.2 ± 0.5	47.4 ± 0.6	47.6 ± 0.5	49.1 ± 0.6**	49.8 ± 1.0**	
Packed cell volume (%)						
Day 3	41.7 ± 0.5	41.9 ± 0.4	40.9 ± 0.7	43.4 ± 0.4*	46.6 ± 0.7**	50.3 ± 0.6**
Day 23	45.2 ± 0.4	45.8 ± 0.4	46.9 ± 0.6*	47.6 ± 0.5**	51.3 ± 1.3**	
Week 14	45.0 ± 0.4	45.6 ± 0.6	46.1 ± 0.5	47.7 ± 0.7**	48.6 ± 1.0**	
Hemoglobin (g/dL)						
Day 3	13.5 ± 0.2	13.7 ± 0.1	13.4 ± 0.2	14.1 ± 0.1**	15.3 ± 0.2**	16.6 ± 0.2**
Day 23	14.9 ± 0.1	15.1 ± 0.1	15.4 ± 0.2*	15.7 ± 0.2**	16.9 ± 0.4**	
Week 14	15.2 ± 0.1	15.4 ± 0.2	15.6 ± 0.1	16.0 ± 0.2**	16.4 ± 0.3**	
Erythrocytes (10 <sup>6</sup> /μL)						
Day 3	6.34 ± 0.11	6.42 ± 0.05	6.42 ± 0.07	6.71 ± 0.10**	7.38 ± 0.13**	8.11 ± 0.10**
Day 23	7.31 ± 0.11	7.47 ± 0.09	7.79 ± 0.09**	7.80 ± 0.09**	8.53 ± 0.23**	
Week 14	7.79 ± 0.10	8.17 ± 0.12*	8.11 ± 0.10*	8.37 ± 0.15**	8.39 ± 0.16**	
Reticulocytes (10 <sup>3</sup> /μL)						
Day 3	423 ± 13	439 ± 25	431 ± 14	465 ± 17	460 ± 18	511 ± 28*
Day 23	182 ± 8	225 ± 10	196 ± 5	223 ± 12*	263 ± 30**	
Week 14	192 ± 8	200 ± 4	206 ± 7	219 ± 9	216 ± 13	
Platelets (10 <sup>3</sup> /μL)						
Day 3	1,309 ± 38	1,182 ± 57	1,309 ± 49	1,305 ± 50	1,435 ± 39	1,550 ± 85*
Day 23	1,006 ± 34	934 ± 28	1,043 ± 45	996 ± 38	859 ± 30*	
Week 14	919 ± 25	943 ± 15	807 ± 43*	829 ± 27*	801 ± 38*	
Leukocytes (10 <sup>3</sup> /μL)						
Day 3	12.51 ± 0.49	12.62 ± 0.51	11.32 ± 0.47	12.62 ± 0.92	11.06 ± 0.97	7.95 ± 0.84**
Day 23	9.21 ± 0.65	7.93 ± 0.60	10.23 ± 0.56	10.42 ± 0.72	8.16 ± 0.79	
Week 14	10.48 ± 0.51	11.59 ± 0.78	10.88 ± 0.56	11.15 ± 1.00	8.29 ± 0.84	
Segmented neutrophils (10 <sup>3</sup> /μL)						
Day 3	1.15 ± 0.10	1.02 ± 0.10	0.98 ± 0.10	1.21 ± 0.12	1.44 ± 0.14	2.71 ± 0.23**
Day 23	1.19 ± 0.17	0.81 ± 0.06	1.61 ± 0.13	2.28 ± 0.29**	3.05 ± 0.75**	
Week 14	1.38 ± 0.15	1.85 ± 0.11**	2.03 ± 0.19**	3.52 ± 0.43**	3.07 ± 0.57**	
Lymphocytes (10 <sup>3</sup> /μL)						
Day 3	11.01 ± 0.51	11.27 ± 0.46	10.01 ± 0.46	11.10 ± 0.85	9.38 ± 0.89	5.11 ± 0.72**
Day 23	7.76 ± 0.64	6.92 ± 0.56	8.34 ± 0.48	7.82 ± 0.68	4.92 ± 0.28**	
Week 14	8.82 ± 0.42	9.41 ± 0.69	8.57 ± 0.62	7.35 ± 0.69	4.88 ± 0.69**	

\* Significantly different (P≤0.05) from the chamber control group by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Data are presented as mean ± standard error. Statistical tests were performed on unrounded data. Due to 100% mortality in clinical pathology and core study rats exposed to 7.0 ppm, no data are available for these groups at day 23 or week 14.

**TABLE 4**  
**Selected Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Male</b>						
n						
Day 3	10	10	10	10	10	9
Day 23	10	10	10	9	5	0
Week 14	10	10	10	10	3	0
Urea nitrogen (mg/dL)						
Day 3	8.5 ± 0.3	10.2 ± 0.7	9.9 ± 0.8	14.4 ± 0.9**	22.3 ± 1.5**	25.3 ± 0.7**
Day 23	9.3 ± 0.4	8.4 ± 0.4	8.5 ± 0.5	10.8 ± 0.5*	14.2 ± 1.6**	
Week 14	15.4 ± 0.5	15.2 ± 0.4	14.5 ± 0.6	15.1 ± 0.4	18.0 ± 0.6	
Glucose (mg/dL)						
Day 3	142 ± 4	133 ± 3	137 ± 4	157 ± 4*	170 ± 19*	176 ± 7**
Day 23	125 ± 4	136 ± 5	123 ± 7	146 ± 6**	144 ± 12*	
Week 14	121 ± 2	129 ± 4	130 ± 6	128 ± 2*	153 ± 11**	
Total protein (g/dL)						
Day 3	5.5 ± 0.0	5.6 ± 0.0	5.6 ± 0.1	6.1 ± 0.1**	6.3 ± 0.1**	6.0 ± 0.1**
Day 23	6.3 ± 0.1	6.2 ± 0.1	6.3 ± 0.1	6.4 ± 0.1	6.7 ± 0.1*	
Week 14	7.1 ± 0.1	7.1 ± 0.1	7.2 ± 0.1	7.0 ± 0.1	7.0 ± 0.2	
Albumin (g/dL)						
Day 3	4.2 ± 0.0	4.2 ± 0.0	4.2 ± 0.0	4.6 ± 0.1**	4.7 ± 0.1**	4.5 ± 0.1**
Day 23	4.5 ± 0.0	4.4 ± 0.0	4.5 ± 0.1	4.6 ± 0.1	4.7 ± 0.1	
Week 14	4.7 ± 0.0	4.8 ± 0.1	4.8 ± 0.0	4.7 ± 0.1	4.6 ± 0.1	
Globulin (g/dL)						
Day 3	1.3 ± 0.0	1.3 ± 0.0	1.3 ± 0.0	1.5 ± 0.0**	1.6 ± 0.1**	1.5 ± 0.1**
Day 23	1.8 ± 0.0	1.7 ± 0.0	1.9 ± 0.1	1.8 ± 0.1	2.0 ± 0.1	
Week 14	2.4 ± 0.0	2.4 ± 0.0	2.4 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	
Albumin/globulin ratio						
Day 3	3.2 ± 0.1	3.2 ± 0.1	3.2 ± 0.0	3.0 ± 0.1	3.0 ± 0.1	3.1 ± 0.1
Day 23	2.5 ± 0.1	2.6 ± 0.1	2.4 ± 0.1	2.6 ± 0.1	2.3 ± 0.1	
Week 14	1.9 ± 0.0	2.0 ± 0.0	2.0 ± 0.1	2.1 ± 0.1*	1.9 ± 0.1	
Cholesterol (mg/dL)						
Day 3	123 ± 3	117 ± 3	116 ± 3	119 ± 3	118 ± 4	107 ± 4*
Day 23	100 ± 4	93 ± 2	99 ± 3	104 ± 5	116 ± 5	
Week 14	114 ± 4	105 ± 3	107 ± 4	98 ± 4**	86 ± 3**	
Triglycerides (mg/dL)						
Day 3	32 ± 2	28 ± 2	20 ± 1**	18 ± 1**	21 ± 3**	24 ± 2**
Day 23	29 ± 2	26 ± 3	25 ± 2	28 ± 3	39 ± 9	
Week 14	52 ± 4	50 ± 5	48 ± 4	66 ± 5	78 ± 16	
Alanine aminotransferase						
Day 3	72 ± 3	60 ± 3*	57 ± 2**	50 ± 2**	41 ± 2**	48 ± 4**
Day 23	44 ± 1	48 ± 2	51 ± 2**	49 ± 2*	64 ± 10**	
Week 14	55 ± 2	69 ± 6**	69 ± 3**	73 ± 2**	92 ± 12**	
Alkaline phosphatase (IU/L)						
Day 3	312 ± 9	274 ± 11*	265 ± 6**	246 ± 10**	186 ± 4**	172 ± 9**
Day 23	197 ± 7	205 ± 9	214 ± 9	233 ± 9*	206 ± 14	
Week 14	156 ± 5	175 ± 6*	204 ± 7**	216 ± 6**	238 ± 24**	
Creatine kinase (IU/L)						
Day 3	627 ± 111	526 ± 43	518 ± 45	573 ± 91	315 ± 26**	416 ± 39*
Day 23	271 ± 20	352 ± 39	351 ± 34	429 ± 62**	485 ± 63**	
Week 14	196 ± 29	193 ± 21	223 ± 30	242 ± 26	1,014 ± 694**	



**TABLE 4**  
**Selected Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Male (continued)</b>						
n						
Day 3	10	10	10	10	10	9
Day 23	10	10	10	9	5	0
Week 14	10	10	10	10	3	0
Sorbitol dehydrogenase (IU/L)						
Day 3	11 ± 1	11 ± 1	11 ± 1	11 ± 2	15 ± 1*	15 ± 1*
Day 23	12 ± 0	12 ± 1	12 ± 1	11 ± 1	14 ± 1	
Week 14	14 ± 1	12 ± 1	12 ± 1	12 ± 1	12 ± 0	
Bile acids (μmol/L)						
Day 3	32.1 ± 4.4	27.4 ± 4.4	20.6 ± 4.2*	17.3 ± 3.4*	10.1 ± 1.6**	10.9 ± 1.1**
Day 23	12.2 ± 2.1	14.9 ± 2.3	23.4 ± 5.1	14.2 ± 2.8	35.3 ± 16.8	
Week 14	10.6 ± 2.3	29.3 ± 7.1*	26.7 ± 3.7*	26.0 ± 2.3**	24.8 ± 13.8	
<b>Female</b>						
n						
Day 3	10	10	10	10	10	9
Day 23	10	10	9	10	7	0
Week 14	10	10	10	10	8	0
Urea nitrogen (mg/dL)						
Day 3	10.4 ± 0.7	8.9 ± 0.7	11.2 ± 1.1	12.6 ± 1.1	18.1 ± 0.9**	24.4 ± 0.8**
Day 23	10.0 ± 0.3	10.5 ± 0.6	10.3 ± 0.5	14.1 ± 0.8**	17.3 ± 1.1**	
Week 14	15.3 ± 0.7	15.5 ± 0.3	13.1 ± 0.5	16.9 ± 1.0	18.8 ± 1.5	
Glucose (mg/dL)						
Day 3	137 ± 2	138 ± 4	145 ± 3	149 ± 3*	156 ± 4**	163 ± 9**
Day 23	130 ± 5	131 ± 5	141 ± 3	143 ± 5	152 ± 9*	
Week 14	129 ± 4	117 ± 1	127 ± 5	134 ± 4	145 ± 13	
Total protein (g/dL)						
Day 3	5.8 ± 0.1	5.7 ± 0.1	6.0 ± 0.1	6.0 ± 0.0*	6.2 ± 0.1**	6.1 ± 0.1**
Day 23	6.4 ± 0.1	6.3 ± 0.0	6.5 ± 0.1	6.5 ± 0.1	6.6 ± 0.1	
Week 14	7.1 ± 0.1	7.2 ± 0.1	6.8 ± 0.1	7.1 ± 0.1	7.0 ± 0.1	
Albumin (g/dL)						
Day 3	4.6 ± 0.1	4.5 ± 0.1	4.7 ± 0.0	4.6 ± 0.0	4.7 ± 0.1	4.6 ± 0.1
Day 23	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.7 ± 0.1	4.8 ± 0.1	
Week 14	5.1 ± 0.1	5.1 ± 0.1	4.8 ± 0.1**	4.8 ± 0.1**	4.7 ± 0.1**	
Globulin (g/dL)						
Day 3	1.2 ± 0.0	1.2 ± 0.0	1.3 ± 0.0	1.4 ± 0.0**	1.5 ± 0.1**	1.5 ± 0.1**
Day 23	1.7 ± 0.1	1.6 ± 0.0	1.7 ± 0.1	1.8 ± 0.0	1.8 ± 0.1	
Week 14	2.0 ± 0.1	2.1 ± 0.1	2.0 ± 0.1	2.3 ± 0.1**	2.3 ± 0.1**	
Albumin/globulin ratio						
Day 3	3.7 ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.4 ± 0.1*	3.2 ± 0.1**	3.1 ± 0.1**
Day 23	2.9 ± 0.2	3.1 ± 0.1	2.7 ± 0.1	2.6 ± 0.1**	2.6 ± 0.1*	
Week 14	2.6 ± 0.1	2.4 ± 0.1*	2.4 ± 0.1*	2.1 ± 0.1**	2.0 ± 0.1**	
Cholesterol (mg/dL)						
Day 3	114 ± 5	114 ± 4	111 ± 4	111 ± 5	109 ± 4	81 ± 5**
Day 23	102 ± 5	104 ± 5	109 ± 4	105 ± 6	87 ± 6	
Week 14	98 ± 5	110 ± 5	102 ± 3	99 ± 5	80 ± 4	

**TABLE 4**  
**Selected Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Female (continued)</b>						
n						
Day 3	10	10	10	10	10	9
Day 23	10	10	9	10	7	0
Week 14	10	10	10	10	8	0
Triglycerides (mg/dL)						
Day 3	36 ± 2	33 ± 1	32 ± 3	29 ± 3	29 ± 2	31 ± 1
Day 23	32 ± 1	35 ± 3	40 ± 3	34 ± 3	34 ± 4	
Week 14	37 ± 3	43 ± 2	43 ± 2	73 ± 9**	59 ± 8**	
Alanine aminotransferase						
Day 3	57 ± 2	49 ± 3	44 ± 2**	44 ± 2**	35 ± 2**	39 ± 3**
Day 23	42 ± 4	36 ± 1	40 ± 3	45 ± 2	49 ± 4	
Week 14	53 ± 3	54 ± 2	64 ± 6	66 ± 4	88 ± 6**	
Alkaline phosphatase (IU/L)						
Day 3	245 ± 9	222 ± 7	218 ± 9*	197 ± 6**	158 ± 7**	134 ± 6**
Day 23	124 ± 5	121 ± 5	148 ± 8*	156 ± 8**	152 ± 4**	
Week 14	127 ± 6	146 ± 6*	176 ± 23*	184 ± 9**	220 ± 17**	
Creatine kinase (IU/L)						
Day 3	540 ± 74	586 ± 113	651 ± 143	428 ± 81	476 ± 69	417 ± 50
Day 23	370 ± 123	269 ± 35	373 ± 51	316 ± 44	465 ± 52**	
Week 14	188 ± 20	200 ± 26	212 ± 20	258 ± 43	449 ± 123*	
Sorbitol dehydrogenase (IU/L)						
Day 3	10 ± 1	10 ± 1	11 ± 1	10 ± 1	10 ± 1	14 ± 1*
Day 23	14 ± 3	11 ± 0	11 ± 1	12 ± 1	12 ± 1	
Week 14	12 ± 0	11 ± 1	12 ± 1	11 ± 1	11 ± 1	
Bile acids (μmol/L)						
Day 3	19.4 ± 4.5	20.3 ± 5.6	13.9 ± 4.1	9.1 ± 1.5	7.8 ± 0.8*	10.2 ± 1.4
Day 23	9.6 ± 1.6	11.9 ± 1.3	9.4 ± 2.5	13.8 ± 4.2	12.7 ± 2.6	
Week 14	12.5 ± 4.8	18.4 ± 4.0	43.4 ± 13.9**	25.5 ± 3.4**	24.2 ± 3.8**	

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

\*\*  $P \leq 0.01$

<sup>a</sup> Data are presented as mean ± standard error. Statistical tests were performed on unrounded data. Due to 100% mortality in clinical pathology and core study rats exposed to 7.0 ppm, no data are available for these groups at day 23 or week 14.

Significant increases or decreases in cholesterol, glucose, and triglyceride concentrations were observed throughout the study in both male and female rats. In particular, glucose was elevated in males exposed to 1.75 ppm or greater and was most likely due to stress. Alterations in cholesterol and triglycerides were most likely due to changes in lipid metabolism or decreased food intake.

Compared to those of the chamber control groups, the absolute thymus weights were significantly decreased in 0.44 ppm females (18% lower) and 0.88, 1.75, and 3.5 ppm males (14%, 31%, and 56% lower, respectively) and females (10%, 37%, and 44% lower, respectively), as were the relative thymus weights of 1.75 and 3.5 ppm females (Table C1). Lymphoid atrophy of the thymus, diagnosed in the 3.5 and 7.0 ppm groups, likely contributed to the decreased thymus weights. In male rats, there were significant decreases in absolute heart, kidney, and liver weights

**TABLE 5**  
**Incidences of Nonneoplastic Lesions of the Respiratory System in Rats in the 3-Month Inhalation Study**  
**of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Male</b>						
Nose <sup>b</sup>	10	10	10	10	10	10
Inflammation, Suppurative <sup>c</sup>	0	10** (1.6) <sup>d</sup>	10** (2.0)	10** (2.3)	10** (2.7)	10** (2.3)
Glands, Olfactory Epithelium, Hyperplasia	0	0	0	1 (1.0)	2 (1.0)	3 (1.7)
Olfactory Epithelium, Accumulation, Hyaline Droplet	9 (1.3)	10 (2.8)	9 (1.7)	1** (2.0)	0**	0**
Olfactory Epithelium, Atrophy	2 (1.0)	10** (1.9)	10** (2.0)	10** (2.0)	7* (2.0)	6 (1.3)
Olfactory Epithelium, Metaplasia, Respiratory	1 (1.0)	1 (1.0)	6* (1.0)	6* (1.0)	2 (2.0)	0
Olfactory Epithelium, Metaplasia, Squamous	0	0	0	1 (1.0)	1 (2.0)	1 (1.0)
Olfactory Epithelium, Necrosis	0	0	0	1 (2.0)	3 (2.0)	0
Olfactory Epithelium, Regeneration	0	0	1 (1.0)	0	4* (1.8)	0
Respiratory Epithelium, Hyperplasia	3 (1.0)	9** (1.0)	9** (1.2)	7 (1.0)	3 (1.0)	0
Goblet Cell, Respiratory Epithelium, Hyperplasia	0	4* (1.0)	6** (1.7)	2 (2.0)	0	1 (1.0)
Respiratory Epithelium, Metaplasia, Squamous	0	10** (1.9)	10** (2.0)	10** (2.0)	10** (1.7)	8** (1.8)
Respiratory Epithelium, Necrosis	0	0	3 (1.3)	5* (1.4)	10** (2.3)	10** (2.9)
Respiratory Epithelium, Regeneration	0	0	1 (1.0)	0	3 (1.3)	6** (1.5)
Turbinate, Atrophy	0	0	7** (1.0)	10** (1.0)	0	0
Larynx	10	10	10	10	10	10
Inflammation, Chronic Active	1 (1.0)	2 (1.0)	8** (1.4)	10** (1.6)	10** (2.5)	10** (3.0)
Metaplasia, Squamous	0	1 (1.0)	8** (1.0)	10** (1.9)	10** (2.5)	10** (2.7)
Necrosis	0	0	1 (1.0)	5* (1.0)	9** (1.9)	10** (2.6)
Regeneration	0	0	3 (1.7)	2 (1.5)	2 (2.0)	6** (2.0)
Trachea	10	10	10	10	10	10
Fibrosis	0	0	0	5* (1.0)	3 (1.7)	0
Inflammation, Chronic Active	0	0	4* (1.0)	8** (1.8)	9** (1.9)	10** (2.7)
Metaplasia, Squamous	0	0	4* (1.0)	10** (1.0)	6** (2.0)	6** (1.8)
Necrosis	0	0	0	3 (1.3)	8** (1.8)	8** (2.6)
Regeneration	0	0	0	7** (2.9)	7** (2.3)	6** (2.2)
Ulcer	0	0	0	0	1 (1.0)	2 (2.5)
Lung	10	10	10	10	10	10
Alveolus, Infiltration Cellular, Histiocyte	0	1 (1.0)	0	3 (1.3)	9** (1.4)	1 (1.0)
Alveolus, Inflammation, Suppurative	0	0	0	0	3 (1.0)	6** (1.0)
Bronchus, Fibrosis	0	0	0	1 (1.0)	2 (1.5)	1 (2.0)
Bronchus, Hyperplasia	0	0	0	2 (1.0)	5* (1.8)	1 (1.0)
Bronchus, Inflammation, Chronic Active	0	0	0	3 (1.3)	9** (1.7)	8** (2.4)
Bronchus, Metaplasia, Squamous	0	0	0	7** (1.0)	6** (1.5)	1 (1.0)
Bronchus, Necrosis	0	0	0	0	5* (1.6)	7** (2.7)
Bronchus, Regeneration	0	0	0	0	3 (1.0)	1 (2.0)

**TABLE 5**  
**Incidences of Nonneoplastic Lesions of the Respiratory System in Rats in the 3-Month Inhalation Study**  
**of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Female</b>						
Nose	10	10	10	10	10	10
Inflammation, Suppurative	0	9** (1.1)	10** (1.5)	10** (2.4)	10** (2.9)	10** (2.4)
Glands, Olfactory Epithelium, Hyperplasia	0	2 (1.0)	0	2 (1.0)	2 (1.0)	2 (1.0)
Olfactory Epithelium, Accumulation, Hyaline Droplet	9 (1.2)	10 (2.6)	8 (2.5)	4* (1.5)	0**	0**
Olfactory Epithelium, Atrophy	0	9** (1.8)	10** (2.0)	10** (2.0)	10** (1.9)	7** (1.6)
Olfactory Epithelium, Metaplasia, Respiratory	0	1 (1.0)	2 (1.0)	5* (1.2)	7** (1.4)	1 (1.0)
Respiratory Epithelium, Hyperplasia	0	9** (1.0)	7** (1.1)	4* (1.3)	3 (1.0)	3 (1.0)
Respiratory Epithelium, Metaplasia, Squamous	0	10** (1.9)	10** (2.0)	10** (1.9)	10** (2.1)	10** (1.7)
Respiratory Epithelium, Necrosis	0	2 (1.0)	6** (1.2)	9** (1.1)	10** (1.8)	10** (2.3)
Respiratory Epithelium, Regeneration	0	0	2 (1.5)	0	1 (2.0)	3 (1.7)
Turbinate, Atrophy	0	2 (1.0)	4* (1.0)	10** (1.0)	10** (1.0)	0
Larynx	10	10	10	10	10	10
Inflammation, Chronic Active	0	1 (1.0)	1 (2.0)	9** (1.4)	10** (1.8)	10** (2.6)
Metaplasia, Squamous	0	1 (1.0)	4* (1.0)	10** (1.9)	10** (3.0)	10** (3.0)
Necrosis	0	0	0	1 (2.0)	7** (1.3)	8** (2.5)
Trachea	10	10	10	10	10	10
Fibrosis	0	0	0	2 (1.0)	6** (1.2)	0
Inflammation, Chronic Active	0	0	3 (1.0)	5* (1.2)	10** (1.8)	10** (2.9)
Metaplasia, Squamous	0	0	3 (1.0)	10** (1.0)	7** (1.7)	7** (1.4)
Necrosis	0	0	0	3 (1.0)	3 (1.0)	8** (2.0)
Regeneration	0	0	1 (2.0)	7** (2.6)	10** (2.9)	9** (1.8)
Ulcer	0	0	0	0	1 (2.0)	2 (2.0)

**TABLE 5**  
**Incidences of Nonneoplastic Lesions of the Respiratory System in Rats in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Female (continued)</b>						
Lung	10	10	10	10	10	10
Alveolus, Infiltration Cellular, Histiocyte	0	2 (1.0)	1 (1.0)	3 (1.3)	9** (2.0)	3 (1.0)
Alveolus, Inflammation, Suppurative	0	0	0	0	2 (1.5)	4* (1.5)
Bronchus, Fibrosis	0	0	0	1 (1.0)	1 (1.0)	3 (2.3)
Bronchus, Hyperplasia	0	0	0	1 (2.0)	6** (2.0)	1 (2.0)
Bronchus, Inflammation, Chronic Active	0	0	0	2 (1.5)	10** (1.6)	10** (2.0)
Bronchus, Metaplasia, Squamous	0	0	0	2 (1.0)	9** (1.6)	0
Bronchus, Necrosis	0	0	0	0	2 (1.0)	10** (2.3)
Bronchus, Regeneration	0	0	0	0	1 (1.0)	5* (1.6)
Interstitial, Inflammation, Granulomatous	0	0	0	0	0	2 (1.5)
Perivascular, Inflammation, Chronic Active	0	0	1 (1.0)	1 (2.0)	6** (1.7)	0

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

\*\*  $P \leq 0.01$

<sup>a</sup> All males and females exposed to 7.0 ppm died by the end of week 2, and seven male and two female 3.5 ppm rats died by week 7. This limited exposure duration may have affected lesion incidence rates.

<sup>b</sup> Number of animals with tissue examined microscopically

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

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

detection or formation of hyaline droplets could have been obscured or decreased by inflammation or reparative or adaptive changes in the higher exposure groups. Reparative or adaptive changes observed in the olfactory epithelium of the nose included hyperplasia, atrophy, metaplasia, and regeneration. There were low numbers of exposed males and females with minimal hyperplasia of the glands of the olfactory epithelium of the nose. All exposed groups of rats, except 7.0 ppm males, had significantly increased incidences of olfactory epithelium atrophy. The incidences of respiratory metaplasia of the olfactory epithelium in males exposed to 0.88 or 1.75 ppm and females exposed to 1.75 or 3.5 ppm were significantly increased. A few male rats exposed to 0.88 ppm or greater had squamous metaplasia or regeneration of the olfactory epithelium of the nose; the incidence of regeneration was significantly increased in 3.5 ppm males.

Microscopically, olfactory epithelial necrosis was noted as focal to focally extensive areas of shrunken, fragmented, or partially sloughed epithelium along either the dorsal aspect in level II histologic sections of the nose or along the dorsal aspect and ethmoid turbinates of level III. Hyaline droplet accumulation was microscopically noted as bright, eosinophilic material in the cytoplasm of olfactory epithelial cells. Hyperplasia of the glands of the olfactory epithelium, present along the nasal septum and the dorsal aspect of level II, was characterized by Bowman's glands

**TABLE 7**  
**Reproductive System Parameters of Male Rats in the 3-Month Inhalation Study of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
n	10	10	10	10	0	0
L. Cauda Epididymis Weight	0.2555 ± 0.0092	0.2697 ± 0.0109	0.2140 ± 0.0103**	0.1956 ± 0.0072**		
L. Epididymis Weight	0.6692 ± 0.0100	0.6559 ± 0.0197	0.5721 ± 0.0254**	0.5405 ± 0.0133**		
L. Testis Weight	2.0070 ± 0.0294	1.9794 ± 0.0590	1.7603 ± 0.1211*	1.7549 ± 0.0316*		
Sperm Motility (%)	83.1 ± 1.5	75.2 ± 1.5**	67.1 ± 8.1**	65.6 ± 2.5**		
Sperm (10 <sup>6</sup> /cauda epididymis)	81.19 ± 2.44	87.24 ± 6.47	69.88 ± 10.56	66.68 ± 5.57		
Epididymis <sup>b</sup>	10	10	10	10	10	10
Duct, Exfoliated Germ Cell <sup>c</sup>	0	0	1 (2.0) <sup>d</sup>	1 (2.0)	5 <sup>▲</sup> (1.6)	4 <sup>▲</sup> (2.5)
Epithelium, Apoptosis	0	0	0	0	3 (1.3)	5 <sup>▲</sup> (1.2)
Testes	10	10	10	10	10	10
Exfoliated Germ Cell	0	0	0	0	1 (2.0)	2 (2.0)
Elongated Spermatid, Degeneration	0	0	0	0	4 <sup>▲</sup> (1.3)	0
Germinal Epithelium, Apoptosis	0	0	0	0	4 <sup>▲</sup> (1.3)	6 <sup>▲▲</sup> (1.0)
Interstitial Cell, Atrophy	0	0	0	0	7 <sup>▲▲</sup> (2.9)	10 <sup>▲▲</sup> (2.9)
Seminiferous Tubule, Vacuolation	0	0	0	0	3 (1.3)	0

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

\*\* Significantly different (P≤0.01) from the chamber control group by Williams' (tissue weights) or Shirley's (motility) test

▲ Significantly different from the chamber control group (P≤0.05) by the Fisher exact test

▲▲ P≤0.01

<sup>a</sup> Tissue weights and sperm data are presented as mean ± standard error. Tissue weights and sperm data were not available for the 3.5 and 7.0 ppm groups due to excessive mortality.

<sup>b</sup> Number of animals with tissue examined microscopically

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

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

## MICE

All mice exposed to 7.0 ppm died during week 1 of the study, and five males and four females exposed to 3.5 ppm died by week 6 of the study (Table 8). In males exposed to 7.0 ppm, eight mice were found dead and two were euthanized. In females exposed to 7.0 ppm, nine mice were found dead and one was euthanized. In males exposed to 3.5 ppm, five were euthanized (during weeks 5 and 6), and five survived to study completion. In females exposed to 3.5 ppm, four were euthanized (in weeks 1, 3, and 6), and six survived to study completion.

Clinical findings in males and females exposed to 3.5 or 7.0 ppm included abnormal breathing, sneezing, and thinness. One or more of these clinical findings were present in animals that were euthanized prior to study completion. Of the mice that were found dead, there were no clinical findings that preceded death. The probable cause of death for all mice that died in the two highest exposure groups was undetermined; however, it was noted for nine mice that the nasal cavity could not be flushed with formalin. Necrosis and inflammation in the respiratory tract may have led to respiratory compromise and death in mice prior to study completion, as for rats. Alopecia was also observed in 3.5 ppm mice on day 44, but the condition had resolved by the end of the study. Exposure

**TABLE 8**  
**Survival and Body Weights of Mice in the 3-Month Inhalation Study of o-Phthalaldehyde<sup>a</sup>**

Concentration (ppm)	Survival <sup>b</sup>	Initial Body Weight (g)	Final Body Weight (g)	Change in Body Weight (g)	Final Weight Relative to Controls (%)
<b>Male</b>					
0	10/10	22.3 ± 0.3	35.6 ± 0.9	13.3 ± 0.7	
0.44	10/10	22.4 ± 0.2	29.5 ± 0.4**	7.1 ± 0.3**	83
0.88	10/10	22.4 ± 0.2	27.2 ± 0.4**	4.9 ± 0.3**	76
1.75	10/10	22.3 ± 0.2	25.8 ± 0.3**	3.5 ± 0.3**	73
3.5 <sup>c</sup>	5/10	22.6 ± 0.3	21.6 ± 0.8**	-0.8 ± 0.5**	61
7.0 <sup>d</sup>	0/10	22.4 ± 0.2	—	—	—
<b>Female</b>					
0	10/10	19.1 ± 0.4	29.8 ± 0.9	10.7 ± 0.7	
0.44	10/10	18.8 ± 0.1	25.5 ± 0.3**	6.7 ± 0.3**	86
0.88	10/10	19.1 ± 0.2	23.3 ± 0.3**	4.2 ± 0.3**	78
1.75	10/10	19.0 ± 0.3	22.8 ± 0.4**	3.7 ± 0.4**	76
3.5 <sup>e</sup>	6/10	19.0 ± 0.2	20.7 ± 0.8**	1.6 ± 1.0**	69
7.0 <sup>d</sup>	0/10	19.2 ± 0.2	—	—	—

\*\* Significantly different (P≤0.01) from the chamber control group by Williams' test

<sup>a</sup> Body weights and weight changes are given as mean ± standard error.

<sup>b</sup> Number of animals surviving at 14 weeks/number initially in group. Subsequent calculations are based on animals surviving to the end of the study.

<sup>c</sup> Weeks of death: 5, 5, 5, 6, 6

<sup>d</sup> Week of deaths: 1 (all)

<sup>e</sup> Weeks of death: 1, 3, 3, 6

**TABLE 9**  
**Selected Hematology Data for Mice in the 3-Month Inhalation Study of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm
<b>Male</b>					
n	10	10	10	10	5
Hematocrit (spun) (%)	50.2 ± 0.4	50.3 ± 0.3	50.3 ± 0.4	49.0 ± 0.3*	47.5 ± 0.9*
Packed cell volume (%)	49.8 ± 0.4	50.3 ± 0.5	49.7 ± 0.3	47.9 ± 0.3**	46.4 ± 1.0**
Hemoglobin (g/dL)	16.0 ± 0.1	16.4 ± 0.1	16.1 ± 0.1	15.6 ± 0.1*	15.0 ± 0.3*
Erythrocytes (10 <sup>6</sup> /μL)	10.38 ± 0.07	10.66 ± 0.12	10.52 ± 0.08	10.04 ± 0.09*	9.72 ± 0.14**
Reticulocytes (10 <sup>3</sup> /μL)	256 ± 9	257 ± 14	258 ± 9	224 ± 10	228 ± 28
Mean cell volume (fL)	47.9 ± 0.2	47.2 ± 0.1	47.2 ± 0.2*	47.8 ± 0.2	47.7 ± 0.5
Mean cell hemoglobin (pg)	15.5 ± 0.1	15.4 ± 0.1	15.3 ± 0.1	15.5 ± 0.1	15.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	32.2 ± 0.1	32.6 ± 0.1	32.5 ± 0.2	32.5 ± 0.1	32.3 ± 0.1
Leukocytes (10 <sup>3</sup> /μL)	2.32 ± 0.19	3.32 ± 0.21**	3.08 ± 0.12**	4.61 ± 0.42**	6.15 ± 1.22**
Segmented neutrophils (10 <sup>3</sup> /μL)	0.30 ± 0.04	0.42 ± 0.02	0.41 ± 0.03	0.87 ± 0.08**	2.90 ± 1.14**
Lymphocytes (10 <sup>3</sup> /μL)	1.91 ± 0.15	2.82 ± 0.19**	2.57 ± 0.13**	3.57 ± 0.35**	2.83 ± 0.21**
Eosinophils (10 <sup>3</sup> /μL)	0.02 ± 0.00	0.02 ± 0.01	0.05 ± 0.01	0.12 ± 0.02**	0.19 ± 0.06**
<b>Female</b>					
n	10	10	10	10	6
Hematocrit (spun) (%)	50.7 ± 0.6	50.2 ± 0.3	48.8 ± 0.4**	49.3 ± 0.7*	46.0 ± 1.0** <sup>b</sup>
Packed cell volume (%)	50.1 ± 0.6	50.2 ± 0.3	48.6 ± 0.4**	48.7 ± 0.6*	47.1 ± 0.4**
Hemoglobin (g/dL)	16.5 ± 0.2	16.3 ± 0.1	15.8 ± 0.1**	15.9 ± 0.2**	15.2 ± 0.2**
Erythrocytes (10 <sup>6</sup> /μL)	10.33 ± 0.08	10.44 ± 0.05	10.10 ± 0.07	10.16 ± 0.11	9.70 ± 0.11**
Reticulocytes (10 <sup>3</sup> /μL)	285 ± 23	279 ± 16	299 ± 16	276 ± 13	243 ± 13
Mean cell volume (fL)	48.4 ± 0.3	48.1 ± 0.2	48.1 ± 0.1	48.0 ± 0.2	48.5 ± 0.3
Mean cell hemoglobin (pg)	15.9 ± 0.1	15.7 ± 0.1*	15.7 ± 0.0*	15.7 ± 0.1**	15.6 ± 0.1*
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.1	32.5 ± 0.1	32.6 ± 0.1	32.7 ± 0.1	32.2 ± 0.2*
Leukocytes (10 <sup>3</sup> /μL)	3.80 ± 0.51	2.78 ± 0.18	3.37 ± 0.34	4.01 ± 0.36	5.31 ± 0.36*
Segmented neutrophils (10 <sup>3</sup> /μL)	0.69 ± 0.23	0.47 ± 0.08	0.61 ± 0.06	0.84 ± 0.12	2.14 ± 0.31**
Lymphocytes (10 <sup>3</sup> /μL)	3.03 ± 0.32	2.27 ± 0.14	2.65 ± 0.30	3.04 ± 0.24	2.94 ± 0.37
Eosinophils (10 <sup>3</sup> /μL)	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.07 ± 0.01*	0.19 ± 0.05**

\* Significantly different (P≤0.05) from the chamber control group by Dunn's or Shirley's test

\*\* P≤0.01

<sup>a</sup> Data are presented as mean ± standard error. Statistical tests were performed on unrounded data. Due to 100% mortality in mice exposed to 7.0 ppm, no data are available for this group.

<sup>b</sup> n=5



**TABLE 10**  
**Incidences of Nonneoplastic Lesions of the Respiratory System in Mice in the 3-Month Inhalation Study**  
**of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Male</b>						
Nose <sup>b</sup>	10	10	10	10	10	10
Inflammation, Suppurative <sup>c</sup>	0	10** (2.1) <sup>d</sup>	10** (2.7)	10** (4.0)	10** (3.2)	10** (1.9)
Glands, Olfactory Epithelium, Hyperplasia	0	10** (1.5)	10** (1.6)	7** (1.7)	6** (1.5)	0
Olfactory Epithelium, Accumulation, Hyaline Droplet	0	10** (2.9)	10** (3.0)	10** (2.2)	9** (2.2)	0
Olfactory Epithelium, Atrophy	0	10** (2.3)	10** (1.9)	10** (2.6)	10** (2.3)	10** (1.5)
Olfactory Epithelium, Metaplasia, Respiratory	0	1 (2.0)	8** (1.4)	10** (1.9)	4* (1.5)	0
Olfactory Epithelium, Metaplasia, Squamous	0	0	2 (2.0)	1 (1.0)	2 (1.5)	0
Olfactory Epithelium, Necrosis	0	0	0	0	0	5* (2.2)
Respiratory Epithelium, Accumulation, Hyaline Droplet	0	10** (3.0)	10** (3.5)	10** (3.8)	10** (2.0)	0
Glands, Respiratory Epithelium, Accumulation, Hyaline Droplet	0	7** (2.0)	10** (2.4)	6** (1.0)	0	0
Respiratory Epithelium, Metaplasia, Squamous	0	10** (1.7)	10** (2.1)	10** (2.7)	10** (2.4)	6** (1.2)
Respiratory Epithelium, Necrosis	0	2 (1.0)	6** (1.3)	5* (1.2)	9** (1.9)	10** (2.8)
Respiratory Epithelium, Regeneration	0	0	1 (1.0)	0	1 (2.0)	4* (1.3)
Turbinate Atrophy	0	4* (1.0)	6** (1.7)	10** (2.8)	8** (2.4)	0
Larynx	10	10	9	10	10	10
Inflammation, Chronic Active	0	0	0	4* (1.0)	10** (1.3)	10** (3.0)
Metaplasia, Squamous	0	0	1 (1.0)	10** (2.4)	10** (4.0)	8** (3.5)
Necrosis	0	0	0	0	1 (2.0)	10** (3.1)
Trachea	10	10	10	10	10	10
Inflammation, Chronic Active	0	0	0	1 (1.0)	9** (1.3)	10** (1.6)
Metaplasia, Squamous	0	0	0	3 (1.0)	10** (2.8)	3 (2.0)
Necrosis	0	0	0	0	0	9** (2.7)
Regeneration	0	0	0	0	0	5* (1.6)
Lung	10	10	10	10	10	10
Bronchiole, Goblet Cell, Hyperplasia	0	0	0	0	4* (1.0)	0
Bronchus, Inflammation, Chronic Active	0	0	0	0	1 (2.0)	6** (1.5)
Bronchus, Necrosis	0	0	0	0	2 (1.0)	9** (2.4)

**TABLE 10**  
**Incidences of Nonneoplastic Lesions of the Respiratory System in Mice in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Female</b>						
Nose	10	10	10	10	10	10
Inflammation, Suppurative	0	10** (2.0)	10** (3.2)	10** (4.0)	10** (3.0)	6** (1.5)
Glands, Olfactory Epithelium, Hyperplasia	0	10** (2.1)	9** (2.1)	10** (1.5)	8** (2.0)	0
Olfactory Epithelium, Accumulation, Hyaline Droplet	0	10** (3.0)	10** (2.8)	10** (2.0)	6** (1.3)	0
Olfactory Epithelium, Atrophy	0	10** (2.3)	10** (2.1)	10** (2.6)	9** (2.4)	9** (1.8)
Olfactory Epithelium, Metaplasia, Respiratory	0	3 (1.3)	6** (1.2)	3 (1.0)	4* (2.3)	0
Respiratory Epithelium, Accumulation, Hyaline Droplet	0	10** (3.0)	10** (3.3)	10** (3.6)	8** (2.0)	0
Glands, Respiratory Epithelium, Accumulation, Hyaline Droplet	0	9** (2.1)	10** (2.1)	6** (2.0)	2 (1.0)	0
Respiratory Epithelium, Metaplasia, Squamous	0	10** (2.0)	10** (2.7)	10** (2.7)	8** (2.6)	0
Respiratory Epithelium, Necrosis	0	2 (1.0)	7** (1.1)	6** (1.3)	8** (1.5)	10** (2.5)
Respiratory Epithelium, Regeneration	0	0	0	1 (1.0)	3 (2.0)	6** (1.7)
Respiratory Epithelium, Ulcer	0	0	0	0	0	2 (1.0)
Turbinate Atrophy	0	7** (1.0)	9** (2.1)	10** (3.3)	7** (3.1)	0
Larynx	10	10	10	10	10	10
Inflammation, Chronic Active	0	0	0	0	9** (1.9)	10** (3.1)
Metaplasia, Squamous	0	0	3 (1.3)	10** (2.1)	10** (3.9)	8** (3.8)
Necrosis	0	0	0	0	3 (2.0)	9** (2.6)
Regeneration	0	0	0	0	0	3 (1.7)
Trachea	10	10	10	10	10	10
Inflammation, Chronic Active	0	0	0	0	10** (1.9)	10** (1.3)
Metaplasia, Squamous	0	0	0	0	9** (3.1)	2 (1.5)
Necrosis	0	0	0	0	2 (1.5)	10** (3.5)
Regeneration	0	0	0	0	1 (1.0)	2 (2.0)
Lung	10	10	10	10	10	10
Bronchiole, Goblet Cell, Hyperplasia	0	0	0	0	6** (1.5)	0
Bronchus, Inflammation, Chronic Active	0	0	0	0	6** (1.2)	8** (1.4)
Bronchus, Necrosis	0	0	0	0	2 (2.0)	8** (2.8)
Bronchus, Ulcer	0	0	0	0	0	2 (2.5)

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

\*\*  $P \leq 0.01$

<sup>a</sup> All mice exposed to 7.0 ppm died during week 1 of the study, and five males and four females exposed to 3.5 ppm died by week 6 of the study. This limited exposure duration may have affected lesion incidence rates.

<sup>b</sup> Number of animals with tissue examined microscopically

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

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

**TABLE 11**  
**Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Inhalation Study of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Male</b>						
Skin <sup>b</sup>	10	10	10	9	10	10
Hyperplasia, Squamous <sup>c</sup>	0	1 (2.0) <sup>d</sup>	0	0	9** (1.7)	4* (2.0)
Inflammation, Chronic Active	0	0	0	1 (1.0)	10** (1.8)	9** (1.1)
Adnexa, Degeneration	0	2 (1.5)	0	4* (2.0)	1 (1.0)	6** (2.0)
Epidermis, Necrosis	0	0	0	0	0	3 (2.0)
Epithelium, Hair Follicle, Parakeratosis	0	3 (1.0)	4* (1.0)	2 (1.0)	2 (1.5)	10** (1.8)
Skin, Pinna	10	0	0	0	0	10
Adnexa, Degeneration	0					10** (2.0)
Epithelium, Hair Follicle, Parakeratosis	0					10** (2.1)
Hyperplasia, Squamous	0					10** (2.0)
Inflammation, Chronic Active	0					10** (1.8)
Eye	10	10	10	10	10	10
Cornea, Inflammation, Suppurative	0	1 (2.0)	0	0	1 (1.0)	4* (1.0)
Bone Marrow	10	0	0	10	10	10
Hyperplasia	0			2 (1.0)	5* (1.4)	7** (1.9)
Spleen	10	0	0	10	10	10
Atrophy, Lymphoid	0			0	0	10** (1.9)
Thymus	10	10	10	10	9	10
Atrophy, Lymphoid	0	0	0	0	5* (1.4)	10** (2.7)
<b>Female</b>						
Skin	10	10	10	10	10	10
Hyperplasia, Squamous	3 (1.3)	0	0	6 (1.3)	9** (1.7)	6 (1.0)
Inflammation, Chronic Active	1 (1.0)	1 (1.0)	3 (1.0)	9** (1.1)	9** (1.9)	8** (1.3)
Adnexa, Degeneration	2 (1.0)	0	0	1 (1.0)	0	9** (1.3)
Epidermis, Necrosis	0	0	0	0	0	5* (2.2)
Epithelium, Hair Follicle, Parakeratosis	0	3 (1.0)	7** (1.0)	9** (1.1)	10** (1.1)	10** (2.1)
Skin, Pinna	10	0	0	0	0	10
Adnexa, Degeneration	0					10** (1.7)
Epithelium, Hair Follicle, Parakeratosis	0					10** (2.0)
Hyperplasia, Squamous	0					10** (1.5)
Inflammation, Chronic Active	0					10** (1.4)

**TABLE 11**  
**Incidences of Selected Nonneoplastic Lesions in Mice in the 3-Month Inhalation Study of o-Phthalaldehyde**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
<b>Female (continued)</b>						
Eye	10	10	10	10	10	8
Cornea, Inflammation, Suppurative	0	0	0	0	2 (1.0)	3 (1.0)
Cornea, Necrosis	0	0	0	0	0	2 (1.5)
Bone Marrow	10	0	0	0	10	7
Hyperplasia	0				8** (2.0)	0
Spleen	10	0	0	0	10	8
Atrophy, Lymphoid	0				1 (1.0)	8** (1.6)
Thymus	10	10	9	10	10	10
Atrophy, Lymphoid	0	0	0	0	6** (2.0)	10** (2.6)

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

\*\*  $P \leq 0.01$

<sup>a</sup> All mice exposed to 7.0 ppm died during week 1 of the study, and five males and four females exposed to 3.5 ppm died by week 6 of the study. This limited exposure duration may have affected lesion incidence rates.

<sup>b</sup> Number of animals with tissue examined microscopically

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

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

Adnexa degeneration was characterized by the accumulation of pale basophilic homogenous material in the cytoplasm of multiple follicular and adnexal epithelial cells that often surrounded and compressed the nucleus (Plate 6). Electron microscopy, performed on an affected skin sample, showed that the cytoplasmic accumulations were inconsistently membrane bound and varied from diffusely electron lucent particles to small dense bodies that resemble glycogen. In addition to the cytoplasmic accumulations, adnexa degeneration also encompassed an increase in apoptosis, seen as small cells with dark eosinophilic cytoplasm and multiple small round, dark pyknotic bodies (apoptotic debris) within scattered individual hair follicle epithelial cells. Necrosis in the epidermis was noted as decreased staining and loss of cellular detail involving the entire thickness of the epidermis, with occasional cleft formation between the epidermis and dermis. Hair follicle epithelium parakeratosis was characterized by increased layers of brightly eosinophilic material (keratin) with retention of nuclei (parakeratosis) that collected into plaques along the epithelial surface, with preferential involvement of follicular regions over interfollicular areas.

Evaluation of skin included additional evaluation of the left pinna in control and 7.0 ppm male and female mice (pinnae were not available in rats). The additional evaluation was based on lesions noted in routine inguinal skin sections in mice during peer review, clinical findings of black pigmentation noted on appendages (pinnae and/or feet) during in-life exposure in rats, and technical information and scientific literature on contact dermatitis/chemical burns associated with o-phthalaldehyde exposure in humans. Squamous hyperplasia, chronic active inflammation,

**Male Reproductive System:** Mice exposed to 0.44, 0.88, or 1.75 ppm o-phthalaldehyde exhibited lower sperm motility (10% to 21% lower) (Tables 12 and D2). No histopathologic lesions were attributed to exposure concentrations less than 3.5 ppm. However, as was observed in rats, at the two highest exposure concentrations (at which morbidity and mortality were observed), testicular and epididymal histopathologic lesions were noted. Sperm parameter data were not available in the 3.5 and 7.0 ppm groups due to excessive mortality.

A significantly increased incidence of cellular depletion of the germinal epithelium of the testis occurred in 3.5 ppm males (Tables 12 and A3). In addition, three of the early death mice from the 3.5 ppm group had mild interstitial cell atrophy. There was a significantly increased incidence of exfoliated germ cell in the epididymal duct in males exposed to 3.5 ppm. These changes in the testis and epididymis in the 3.5 ppm group (partial depletion of germ cells, interstitial cell atrophy, and exfoliated germ cells in the epididymis) could be due to decreased body weight gain secondary to treatment, but an effect of o-phthalaldehyde cannot be ruled out.

Microscopically, germinal epithelium cellular depletion of the testis was minimal to mild and characterized by small numbers of seminiferous tubules with partial depletion of one or more generations of germ cells. Four of the seven mice with germinal epithelium cellular depletion also had minimal to mild accumulations of exfoliated germ cells and debris present in the duct of the epididymis. Interstitial cell atrophy resembled the lesion in rats but was less severe in mice.

**TABLE 12**  
**Reproductive System Parameters of Male Mice in the 3-Month Inhalation Study of o-Phthalaldehyde<sup>a</sup>**

	Chamber Control	0.44 ppm	0.88 ppm	1.75 ppm	3.5 ppm	7.0 ppm
n	10	10	10	10	0	0
Sperm Motility (%)	74.7 ± 8.4	69.5 ± 7.8*	68.8 ± 7.7**	41.8 ± 9.6**		
Epididymis <sup>b</sup>	10	10	10	10	10	10
Duct, Exfoliated Germ Cell <sup>c</sup>	0	0	0	0	4 <sup>▲</sup> (1.3) <sup>d</sup>	1 (1.0)
Testes	10	10	10	10	10	10
Germinal Epithelium, Depletion Cellular, Multifocal	0	1 (1.0)	1 (1.0)	0	7 <sup>▲▲</sup> (1.3)	0
Interstitial Cell, Atrophy	0	0	0	0	3 (2.0)	0

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

\*\* P≤0.01

▲ Significantly different from the chamber control group (P≤0.05) by the Fisher exact test

▲▲ P≤0.01

<sup>a</sup> Sperm motility is presented as mean ± standard error. Sperm motility was not available for the 3.5 and 7.0 ppm groups due to excessive mortality.

<sup>b</sup> Number of animals with tissue examined microscopically

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

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