



APPENDIX AVAILABLE ON THE HEI WEB SITE

Research Report 184

Advanced Collaborative Emissions Study (ACES): Lifetime Cancer and Non-Cancer Assessment in Rats Exposed to New-Technology Diesel Exhaust

Part 1. Assessment of Carcinogenicity and Biologic Responses in Rats After Lifetime Inhalation of New-Technology Diesel Exhaust in the ACES Bioassay

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Appendix H. Histopathology

This document was reviewed by the HEI ACES Review Panel, but did not undergo the full HEI scientific editing and production process. It was reviewed solely for spelling, grammar, and cross-references to the main text.

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Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR-83467701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. Although specific components of this study were funded by the United States Department of Energy under Assistance Award DE-AC26-05NT42429 to the Health Effects Institute, it has not been subjected to the Department's peer and administrative review and therefore may not necessarily reflect the views of the Department, and no official endorsement by it should be inferred. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

Appendix H. Histopathology

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
ADRENAL GLAND (S); CORTEX; Adenoma								
Incidence ^a	2/138 (1%)	0/6 (0%)	1/7 (14%)	0/132 (0%)	7/138 (5%)	1/9 (11%)	4/12 (33%)	1/133 (1%)
Adjusted Rate ^b	3%	0%	22%	0%	10%	18%	41%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/1 (0%)	0/9 (0%)	2/24 (8%)	1/3 (33%)	1/2 (50%)	0/17 (0%)
First Incidence (Days)	713	--	731	--	529	912	817	667
Poly 3 Test ^d	--	--	--	<i>P</i> =0.307N	--	--	--	<i>P</i> =0.037N*
ADRENAL GLAND (S); Pheochromocytoma; Benign								
Incidence ^a	6/138 (4%)	0/6 (0%)	1/7 (14%)	5/132 (4%)	4/138 (3%)	2/9 (22%)	2/12 (17%)	5/133 (4%)
Adjusted Rate ^b	10%	0%	21%	11%	6%	34%	21%	8%
Terminal Sacrifice Rate ^c	3/16 (19%)	0/0	0/1 (0%)	1/9 (11%)	2/24 (8%)	0/3 (0%)	1/2 (50%)	1/17 (6%)
First Incidence (Days)	779	--	683	511	599	770	881	520
Poly 3 Test ^d	--	--	--	<i>P</i> =0.533	--	--	--	<i>P</i> =0.414
ADRENAL GLAND (S); Pheochromocytoma; Malignant								
Incidence ^a	5/138 (4%)	4/6 (67%)	3/7 (43%)	3/132 (2%)	2/138 (1%)	0/9 (0%)	4/12 (33%)	3/133 (2%)
Adjusted Rate ^b	8%	95%	49%	7%	3%	0%	36%	5%
Terminal Sacrifice Rate ^c	1/16 (6%)	0/0	0/1 (0%)	0/9 (0%)	2/24 (8%)	0/3 (0%)	0/2 (0%)	0/17 (0%)
First Incidence (Days)	615	654	305	479	912	--	467	369
Poly 3 Test ^d	--	--	--	<i>P</i> =0.524N	--	--	--	<i>P</i> =0.421

[‡] Tumors with incidence of three or more in any treatment group were summarized and statistically analyzed. There were no primary lung tumors found in any animal in this study.

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

P* < 0.05, ** *P* < 0.01, **P* < 0.001. "N" indicates negative trend.

Table H.1 (Continued). Histopathologic Results (Tumors)

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
ADRENAL GLAND (S); Pheochromocytoma; Malignant, Complex, or Benign								
Incidence ^a	11/138 (8%)	4/6 (67%) ^e	4/7 (57%) ^e	8/132 (6%)	6/138 (4%)	2/9 (22%) ^e	6/12 (50%) ^e	8/133 (6%)
Adjusted Rate ^b	18%	95%	60%	18%	9%	34%	53%	13%
Terminal Sacrifice Rate ^c	4/16 (25%)	0/0	0/1 (0%)	1/9 (11%)	4/24 (17%)	0/3 (0%)	1/2 (50%)	1/17 (6%)
First Incidence (Days)	615	654	305	479	599	770	467	369
Poly 3 Test ^d	--	--	--	<i>P</i> =0.555N	--	--	--	<i>P</i> =0.319
BRAIN; Granular Cell Tumor								
Incidence ^a	1/138 (1%)	1/141 (1%)	1/134 (1%)	2/132 (2%)	1/139 (1%)	4/142 (3%)	1/139 (1%)	4/133 (3%)
Adjusted Rate ^b	2%	2%	2%	5%	2%	6%	1%	7%
Terminal Sacrifice Rate ^c	0/15 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	1/29 (3%)	0/17 (0%)	1/17 (6%)
First Incidence (Days)	654	698	501	514	882	732	367	595
Poly 3 Test ^d	<i>P</i> =0.401	<i>P</i> =0.934N	<i>P</i> =0.791	<i>P</i> = 0.374	<i>P</i> =0.265	<i>P</i> =0.360	<i>P</i> =0.766N	<i>P</i> = 0.129
CLITORAL GLAND (S); Squamous Cell Papilloma								
Incidence ^a	0/0	0/0	0/0	0/0	1/131 (1%)	1/8 (13%) ^e	0/5 (0%) ^e	4/130 (3%)
Adjusted Rate ^b	--	--	--	--	2%	17%	0%	7%
Terminal Sacrifice Rate ^c	0/0	0/0	0/0	0/0	0/23 (0%)	0/2 (0%)	0/2 (0%)	1/16 (6%)
First Incidence (Days)	--	--	--	--	731	880	--	740
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> = 0.137

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
HARDERIAN GLAND (S); Adenoma								
Incidence ^a	5/139 (4%)	0/0	0/0	2/132 (2%)	0/139 (0%)	0/0	0/0	2/134 (1%)
Adjusted Rate ^b	8%	--	--	5%	0%	--	--	3%
Terminal Sacrifice Rate ^c	2/16 (13%)	0/0	0/0	0/9 (0%)	0/24 (0%)	0/0	0/0	0/17 (0%)
First Incidence (Days)	367	--	--	520	--	--	--	711
Poly 3 Test ^d	--	--	--	<i>P</i> =0.369N	--	--	--	<i>P</i> =0.168
MAMMARY GLAND (S); Adenocarcinoma								
Incidence ^a	0/65 (0%)	0/0	1/2 (50%)	0/61 (0%)	9/137 (7%)	11/46 (24%)	12/47 (26%)	16/127 (13%)
Adjusted Rate ^b	0%	--	50%	0%	13%	34%	36%	25%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	0/23 (0%)	4/13 (31%)	2/5 (40%)	3/17 (18%)
First Incidence (Days)	--	--	713	--	466	618	275	535
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.048 *
MAMMARY GLAND (S); Adenoma								
Incidence ^a	0/65 (0%)	0/0	0/2 (0%)	0/61 (0%)	2/137 (1%)	2/46 (4%)	2/47 (4%)	4/127 (3%)
Adjusted Rate ^b	0%	--	0%	0%	3%	7%	7%	7%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	0/23 (0%)	1/13 (8%)	1/5 (20%)	1/17 (6%)
First Incidence (Days)	--	--	--	--	749	647	840	648
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.253

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
MAMMARY GLAND (S); Adenoma or Adenocarcinoma								
Incidence ^a	0/65 (0%)	0/0	1/2 (50%)	0/61 (0%)	11/137 (8%)	13/46 (28%)	13/47 (28%)	20/127 (16%)
Adjusted Rate ^b	0%	--	50%	0%	16%	40%	39%	31%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	0/23 (0%)	5/13 (38%)	2/5 (40%)	4/17 (24%)
First Incidence (Days)	--	--	713	--	466	618	275	535
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.023 *
MAMMARY GLAND (S); Fibroadenoma								
Incidence ^a	0/65 (0%)	0/0	0/2 (0%)	0/61 (0%)	27/137 (20%)	25/46 (54%)	20/47 (43%)	23/127 (18%)
Adjusted Rate ^b	0%	--	0%	0%	38%	69%	57%	34%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	10/23 (43%)	8/13 (62%)	0/5 (0%)	4/17 (24%)
First Incidence (Days)	--	--	--	--	590	456	640	460
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.377N
MAMMARY GLAND (S); Fibroadenoma, Adenocarcinoma, or Adenoma								
Incidence ^a	0/65 (0%)	0/0	1/2 (50%)	0/61 (0%)	36/137 (26%)	36/46 (78%)	31/47 (66%)	42/127 (33%)
Adjusted Rate ^b	0%	--	50%	0%	47%	91%	79%	57%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	10/23 (43%)	12/13 (92%)	2/5 (40%)	8/17 (47%)
First Incidence (Days)	--	--	713	--	466	456	275	460
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.121

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ***P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
OVARY (IES); Granulosa Cell Tumor; Benign								
Incidence ^a	0/0	0/0	0/0	0/0	6/139 (4%)	7/141 (5%)	4/136 (3%)	3/133 (2%)
Adjusted Rate ^b	--	--	--	--	9%	10%	6%	5%
Terminal Sacrifice Rate ^c	0/0	0/0	0/0	0/0	4/24 (17%)	5/29 (17%)	2/17 (12%)	1/17 (6%)
First Incidence (Days)	--	--	--	--	641	754	703	732
Poly 3 Test ^d	--	--	--	--	<i>P</i> =0.194N	<i>P</i> =0.648	<i>P</i> =0.395N	<i>P</i> =0.256N
PANCREAS; Islet Cell; Adenoma								
Incidence ^a	4/138 (3%)	1/2 (50%) ^e	1/1 (100%) ^e	2/131 (2%)	4/139 (3%)	1/3 (33%) ^e	1/3 (33%) ^e	2/134 (1%)
Adjusted Rate ^b	7%	82%	100%	5%	6%	33%	48%	3%
Terminal Sacrifice Rate ^c	1/16 (6%)	0/0	0/0	1/9 (11%)	0/24 (0%)	0/2 (0%)	0/0	1/17 (6%)
First Incidence (Days)	677	625	730	731	667	900	871	893
Poly 3 Test ^d	--	--	--	<i>P</i> =0.500N	--	--	--	<i>P</i> =0.342N
PANCREAS; Islet Cell; Carcinoma or Adenoma								
Incidence ^a	5/138 (4%)	1/2 (50%) ^e	1/1 (100%) ^e	2/131 (2%)	4/139 (3%)	2/3 (67%) ^e	2/3 (67%) ^e	2/134 (1%)
Adjusted Rate ^b	8%	82%	100%	5%	6%	67%	74%	3%
Terminal Sacrifice Rate ^c	1/16 (6%)	0/0	0/0	1/9 (11%)	0/24 (0%)	1/2 (50%)	0/0	1/17 (6%)
First Incidence (Days)	633	625	730	731	667	900	653	893
Poly 3 Test ^d	--	--	--	<i>P</i> =0.379N	--	--	--	<i>P</i> =0.342N

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
PITUITARY GLAND; PARS DISTALIS; Adenoma								
Incidence ^a	37/134 (28%)	26/28 (93%)	22/28 (79%)	42/131 (32%)	75/136 (55%)	58/61 (95%)	53/58 (91%)	60/133 (45%)
Adjusted Rate ^b	52%	93%	85%	66%	84%	97%	94%	70%
Terminal Sacrifice Rate ^c	6/16 (38%)	8/9 (89%)	3/4 (75%)	4/9 (44%)	20/23 (87%)	14/15 (93%)	8/9 (89%)	10/17 (59%)
First Incidence (Days)	366	261	305	396	296	303	310	369
Poly 3 Test ^d	--	--	--	<i>P</i> =0.045 *	--	--	--	<i>P</i> =0.009N**
PITUITARY GLAND; PARS DISTALIS; Carcinoma or Adenoma								
Incidence ^a	37/134 (28%)	26/28 (93%)	23/28 (82%)	43/131 (33%)	75/136 (55%)	59/61 (97%)	55/58 (95%)	62/133 (47%)
Adjusted Rate ^b	52%	93%	87%	67%	84%	98%	97%	72%
Terminal Sacrifice Rate ^c	6/16 (38%)	8/9 (89%)	3/4 (75%)	4/9 (44%)	20/23 (87%)	14/15 (93%)	8/9 (89%)	10/17 (59%)
First Incidence (Days)	366	261	305	292	296	303	310	369
Poly 3 Test ^d	--	--	--	<i>P</i> =0.038 *	--	--	--	<i>P</i> =0.019N*
PITUITARY GLAND; PARS INTERMEDIA; Adenoma								
Incidence ^a	7/134 (5%)	0/28 (0%)	1/28 (4%)	2/131 (2%)	0/136 (0%)	2/61 (3%)	0/58 (0%)	2/133 (2%)
Adjusted Rate ^b	12%	0%	6%	5%	0%	5%	0%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/9 (0%)	0/4 (0%)	0/9 (0%)	0/23 (0%)	1/15 (7%)	0/9 (0%)	1/17 (6%)
First Incidence (Days)	316	--	814	415	--	705	--	776
Poly 3 Test ^d	--	--	--	<i>P</i> =0.180N	--	--	--	<i>P</i> =0.174

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
SKIN; Lipoma								
Incidence ^a	0/138 (0%)	3/7 (43%)	0/7 (0%)	0/133 (0%)	0/139 (0%)	0/11 (0%)	1/11 (9%)	0/134 (0%)
Adjusted Rate ^b	0%	54%	0%	0%	0%	0%	15%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	3/4 (75%)	0/0	0/9 (0%)	0/24 (0%)	0/1 (0%)	0/2 (0%)	0/17 (0%)
First Incidence (Days)	--	845	--	--	--	--	881	--
Poly 3 Test ^d	--	--	--	--	--	--	--	--
SKIN; Malignant Schwannoma								
Incidence ^a	2/138 (1%)	1/7 (14%)	3/7 (43%)	1/133 (1%)	0/139 (0%)	1/11 (9%)	0/11 (0%)	0/134 (0%)
Adjusted Rate ^b	3%	18%	52%	2%	0%	19%	0%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	1/4 (25%)	0/0	0/9 (0%)	0/24 (0%)	0/1 (0%)	0/2 (0%)	0/17 (0%)
First Incidence (Days)	418	845	537	710	--	513	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.606N	--	--	--	--
THYMUS; Hibernoma								
Incidence ^a	0/122 (0%)	0/3 (0%)	1/3 (33%)	3/120 (3%)	0/129 (0%)	0/9 (0%)	0/18 (0%)	0/122 (0%)
Adjusted Rate ^b	0%	0%	38%	8%	0%	0%	0%	0%
Terminal Sacrifice Rate ^c	0/12 (0%)	0/1 (0%)	0/1 (0%)	0/9 (0%)	0/22 (0%)	0/4 (0%)	0/3 (0%)	0/17 (0%)
First Incidence (Days)	--	--	305	291	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.081	--	--	--	--

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding (Tumors)	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
THYMUS; Thymoma								
Incidence ^a	2/122 (2%)	2/3 (67%) ^e	2/3 (67%) ^e	3/120 (3%)	11/129 (9%)	8/9 (89%) ^e	16/18 (89%) ^e	17/122 (14%)
Adjusted Rate ^b	4%	79%	98%	8%	17%	96%	94%	28%
Terminal Sacrifice Rate ^c	2/12 (17%)	1/1 (100%)	1/1 (100%)	1/9 (11%)	1/22 (5%)	4/4 (100%)	3/3 (100%)	5/17 (29%)
First Incidence (Days)	845	731	731	628	548	747	627	651
Poly 3 Test ^d	--	--	--	<i>P</i> =0.383	--	--	--	<i>P</i> =0.085
THYROID GLAND (S); C-Cell; Adenoma								
Incidence ^a	15/134 (11%)	11/89 (12%) ^f	8/86 (9%) ^f	7/131 (5%)	11/138 (8%)	7/94 (7%) ^f	8/93 (9%) ^f	8/132 (6%)
Adjusted Rate ^b	24%	21%	18%	16%	16%	12%	13%	13%
Terminal Sacrifice Rate ^c	3/14 (21%)	2/23 (9%)	4/14 (29%)	2/9 (22%)	4/24 (17%)	3/28 (11%)	1/16 (6%)	3/17 (18%)
First Incidence (Days)	367	396	305	483	326	706	534	601
Poly 3 Test ^d	<i>P</i> =0.173N	<i>P</i> =0.484N	<i>P</i> =0.291N	<i>P</i> =0.188N	<i>P</i> =0.422N	<i>P</i> =0.398N	<i>P</i> =0.432N	<i>P</i> =0.379N
THYROID GLAND (S); C-Cell; Carcinoma								
Incidence ^a	3/134 (2%)	0/89 (0%) ^f	2/86 (2%) ^f	5/131 (4%)	1/138 (1%)	0/94 (0%) ^f	1/93 (1%) ^f	1/132 (1%)
Adjusted Rate ^b	5%	0%	5%	11%	2%	0%	2%	2%
Terminal Sacrifice Rate ^c	1/14 (7%)	0/23 (0%)	1/14 (7%)	2/9 (22%)	0/24 (0%)	0/28 (0%)	0/16 (0%)	0/17 (0%)
First Incidence (Days)	391	--	814	396	863	--	506	520
Poly 3 Test ^d	<i>P</i> =0.166	<i>P</i> =0.343N	<i>P</i> =0.656N	<i>P</i> =0.210	<i>P</i> =0.559	<i>P</i> =0.815N	<i>P</i> =0.713	<i>P</i> =0.673

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

^f Thyroid glands from low- and mid-exposure animals in 1-, 3-, 12-, and 24-month interim sacrifice groups were not examined microscopically (see text Results). Reported rates and *P* values reflect exclusion of these animals from statistical analysis.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
THYROID GLAND (S); C-Cell; Carcinoma or Adenoma								
Incidence ^a	18/134 (13%)	11/89 (12%)	10/86 (12%)	12/131 (9%)	12/138 (9%)	7/94 (7%)	9/93 (10%)	9/132 (7%)
Adjusted Rate ^b	29%	21%	23%	25%	17%	12%	15%	14%
Terminal Sacrifice Rate ^c	4/14 (29%)	2/23 (9%)	5/14 (36%)	4/9 (44%)	4/24 (17%)	3/28 (11%)	1/16 (6%)	3/17 (18%)
First Incidence (Days)	367	396	305	396	326	706	506	520
Poly 3 Test ^d	P=0.392N	P=0.268N	P=0.300N	P=0.413N	P=0.456N	P=0.314N	P=0.437N	P=0.383N
THYROID GLAND (S); Follicular Cell; Adenoma								
Incidence ^a	6/134 (4%)	10/89 (11%)	3/86 (3%)	3/131 (2%)	0/138 (0%)	3/94 (3%)	4/93 (4%)	6/132 (5%)
Adjusted Rate ^b	10%	20%	7%	7%	0%	5%	7%	10%
Terminal Sacrifice Rate ^c	1/14 (7%)	6/23 (26%)	2/14 (14%)	1/9 (11%)	0/24 (0%)	1/28 (4%)	1/16 (6%)	0/17 (0%)
First Incidence (Days)	677	549	845	314	--	779	621	720
Poly 3 Test ^d	P=0.231N	P=0.179	P=0.434N	P=0.402N	P=0.018 *	P=0.218	P=0.042 *	P=0.010 *
THYROID GLAND (S); Follicular Cell; Carcinoma								
Incidence ^a	2/134 (1%)	2/89 (2%)	1/86 (1%)	0/131 (0%)	1/138 (1%)	5/94 (5%)	4/93 (4%)	2/132 (2%)
Adjusted Rate ^b	3%	4%	2%	0%	2%	8%	7%	3%
Terminal Sacrifice Rate ^c	1/14 (7%)	2/23 (9%)	0/14 (0%)	0/9 (0%)	0/24 (0%)	3/28 (11%)	1/16 (6%)	0/17 (0%)
First Incidence (Days)	678	845	814	--	732	848	781	814
Poly 3 Test ^d	P=0.305N	P=0.812	P=0.626N	P=0.299N	P=0.459	P=0.143	P=0.128	P=0.402

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Thyroid glands from low- and mid-exposure animals in 1-, 3-, 12-, and 24-month interim sacrifice groups were not examined microscopically (see text Results).

Reported rates and *P* values reflect exclusion of these animals from statistical analysis.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
THYROID GLAND (S); Follicular Cell; Carcinoma or Adenoma								
Incidence ^a	8/134 (6%)	11/89 (12%) ^c	4/86 (5%) ^c	3/131 (2%)	1/138 (1%)	8/94 (9%) ^c	8/93 (9%) ^c	8/132 (6%)
Adjusted Rate ^b	14%	22%	9%	7%	2%	13%	14%	13%
Terminal Sacrifice Rate ^c	2/14 (14%)	7/23 (30%)	2/14 (14%)	1/9 (11%)	0/24 (0%)	4/28 (14%)	2/16 (13%)	0/17 (0%)
First Incidence (Days)	677	549	814	314	732	779	621	720
Poly 3 Test ^d	P=0.140N	P=0.247	P=0.382N	P=0.225N	P=0.037 *	P=0.023 *	P=0.009 **	P=0.010 *
UTERUS; Endometrial Stromal Polyp								
Incidence ^a	0/0	0/0	0/0	0/0	7/138 (5%)	6/20 (30%) ^c	5/18 (28%) ^c	5/134 (4%)
Adjusted Rate ^b	--	--	--	--	10%	41%	38%	8%
Terminal Sacrifice Rate ^c	0/0	0/0	0/0	0/0	1/24 (4%)	3/8 (38%)	0/3 (0%)	1/17 (6%)
First Incidence (Days)	--	--	--	--	366	602	654	323
Poly 3 Test ^d	--	--	--	--	--	--	--	P=0.406N
ALL ORGANS Hemangiosarcoma								
Incidence ^a	5/139 (4%)	0/141 (0%)	0/136 (0%)	1/133 (1%)	0/139 (0%)	1/142 (1%)	0/139 (0%)	0/134 (0%)
Adjusted Rate ^b	8%	0%	0%	2%	0%	1%	0%	0%
Terminal Sacrifice Rate ^c	2/16 (13%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	601	--	--	500	--	602	--	--
Poly 3 Test ^d	P=0.181N	P=0.985N	P=0.836N	P=0.196N	--	--	--	--

^a Number of tumor-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Thyroid glands from low- and mid-exposure animals in 1-, 3-, 12-, and 24-month interim sacrifice groups were not examined microscopically (see text Results). Reported rates and *P*-values reflect exclusion of these animals from statistical analysis.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
ALL ORGANS Histiocytic Sarcoma								
Incidence ^a	1/139 (1%)	1/141 (1%)	1/136 (1%)	0/133 (0%)	2/139 (1%)	1/142 (1%)	3/139 (2%)	1/134 (1%)
Adjusted Rate ^b	2%	2%	2%	0%	3%	1%	4%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	1/17 (6%)	0/17 (0%)
First Incidence (Days)	710	630	747	--	438	852	597	788
Poly 3 Test ^d	<i>P</i> =0.578N	<i>P</i> =0.934N	<i>P</i> =0.790	<i>P</i> =0.547N	<i>P</i> =0.619N	<i>P</i> =0.722N	<i>P</i> =0.507	<i>P</i> =0.466N
ALL ORGANS Malignant Lymphoma								
Incidence ^a	7/139 (5%)	2/141 (1%)	2/136 (1%)	5/133 (4%)	3/139 (2%)	2/142 (1%)	0/139 (0%)	3/134 (2%)
Adjusted Rate ^b	11%	3%	3%	11%	4%	3%	0%	5%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	1/29 (3%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	494	657	305	314	726	900	--	323
Poly 3 Test ^d	<i>P</i> =0.443N	<i>P</i> =0.139N	<i>P</i> =0.106N	<i>P</i> =0.586N	<i>P</i> =0.531N	<i>P</i> =0.673N	<i>P</i> =0.127N	<i>P</i> =0.582
ALL ORGANS Mesothelioma								
Incidence ^a	1/139 (1%)	1/141 (1%)	3/136 (2%)	2/133 (2%)	1/139 (1%)	1/142 (1%)	0/139 (0%)	0/134 (0%)
Adjusted Rate ^b	2%	2%	5%	5%	2%	1%	0%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	1/26 (4%)	1/18 (6%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	830	845	501	487	639	882	--	--
Poly 3 Test ^d	<i>P</i> =0.224	<i>P</i> =0.935N	<i>P</i> =0.330	<i>P</i> =0.373	<i>P</i> =0.290N	<i>P</i> =0.925N	<i>P</i> =0.518N	<i>P</i> =0.404N

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
ADRENAL GLAND (S); CORTEX; Angiectasis	Control	Low ^e	Mid ^e	High	Control	Low ^e	Mid ^e	High
Incidence ^a	0/138 (0%)	0/6 (0%)	0/7 (0%)	0/132 (0%)	3/138 (2%)	0/9 (0%)	0/12 (0%)	1/133 (1%)
Adjusted Rate ^b	0%	0%	0%	0%	4%	0%	0%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/1 (0%)	0/9 (0%)	0/24 (0%)	0/3 (0%)	0/2 (0%)	1/17 (6%)
First Incidence (Days)	--	--	--	--	641	--	--	912
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.291N
Mean Lesion Severity Score	--	--	--	--	2.7	--	--	3.0
ADRENAL GLAND (S); CORTEX; Congestion								
Incidence ^a	0/138 (0%)	1/6 (17%)	0/7 (0%)	1/132 (1%)	6/138 (4%)	2/9 (22%)	1/12 (8%)	5/133 (4%)
Adjusted Rate ^b	0%	25%	0%	2%	9%	31%	11%	8%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/1 (0%)	0/9 (0%)	0/24 (0%)	0/3 (0%)	0/2 (0%)	0/17 (0%)
First Incidence (Days)	--	396	--	458	326	318	876	595
Poly 3 Test ^d	--	--	--	<i>P</i> =0.410	--	--	--	<i>P</i> =0.525N
Mean Lesion Severity Score	--	3.0	--	3.0	3.2	3.5	3.0	3.8
ADRENAL GLAND (S); CORTEX; Degeneration								
Incidence ^a	0/138 (0%)	1/6 (17%)	0/7 (0%)	1/132 (1%)	17/138 (12%)	3/9 (33%)	1/12 (8%)	21/133 (16%)
Adjusted Rate ^b	0%	29%	0%	2%	26%	54%	11%	33%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/1 (0%)	0/9 (0%)	9/24 (38%)	2/3 (67%)	0/2 (0%)	8/17 (47%)
First Incidence (Days)	--	725	--	458	853	880	891	740
Poly 3 Test ^d	--	--	--	<i>P</i> =0.410	--	--	--	<i>P</i> =0.208
Mean Lesion Severity Score	--	2.0	--	3.0	2.4	2.7	2.0	2.3

[‡] Non-neoplastic lesions with incidence of three or more in any treatment group were summarized and statistically analyzed.

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^e	Mid ^e	High	Control	Low ^e	Mid ^e	High
ADRENAL GLAND (S); CORTEX; Fatty Change; Focal								
Incidence ^a	41/138 (30%)	0/6 (0%)	1/7 (14%)	28/132 (21%)	19/138 (14%)	3/9 (33%)	1/12 (8%)	18/133 (14%)
Adjusted Rate ^b	59%	0%	24%	54%	27%	46%	11%	27%
Terminal Sacrifice Rate ^c	11/16 (69%)	0/0	1/1 (100%)	3/9 (33%)	4/24 (17%)	1/3 (33%)	0/2 (0%)	3/17 (18%)
First Incidence (Days)	569	--	845	506	611	660	881	520
Poly 3 Test ^d	--	--	--	<i>P</i> =0.318N	--	--	--	<i>P</i> =0.547
Mean Lesion Severity Score	1.6	--	2.0	1.8	1.7	2.7	2.0	1.8
ADRENAL GLAND (S); CORTEX; Hypertrophy; Focal								
Incidence ^a	24/138 (17%)	0/6 (0%)	1/7 (14%)	4/132 (3%)	26/138 (19%)	4/9 (44%)	1/12 (8%)	17/133 (13%)
Adjusted Rate ^b	36%	0%	24%	9%	35%	61%	11%	25%
Terminal Sacrifice Rate ^c	8/16 (50%)	0/0	1/1 (100%)	0/9 (0%)	7/24 (29%)	2/3 (67%)	1/2 (50%)	3/17 (18%)
First Incidence (Days)	366	--	845	537	590	660	912	617
Poly 3 Test ^d	--	--	--	<i>P</i> =0.001N**	--	--	--	<i>P</i> =0.116N
Mean Lesion Severity Score	1.6	--	2.0	2.0	1.7	2.8	2.0	2.0
ADRENAL GLAND (S); CORTEX; Thrombosis								
Incidence ^a	0/138 (0%)	0/6 (0%)	0/7 (0%)	0/132 (0%)	3/138 (2%)	0/9 (0%)	0/12 (0%)	1/133 (1%)
Adjusted Rate ^b	0%	0%	0%	0%	4%	0%	0%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/1 (0%)	0/9 (0%)	0/24 (0%)	0/3 (0%)	0/2 (0%)	0/17 (0%)
First Incidence (Days)	--	--	--	--	730	--	--	731
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.288N
Mean Lesion Severity Score	--	--	--	--	2.0	--	--	2.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^e	Mid ^e	High	Control	Low ^e	Mid ^e	High
ADRENAL GLAND (S); MEDULLA; Hyperplasia								
Incidence ^a	9/138 (7%)	0/6 (0%)	0/7 (0%)	10/132 (8%)	3/138 (2%)	0/9 (0%)	2/12 (17%)	5/133 (4%)
Adjusted Rate ^b	15%	0%	0%	22%	4%	0%	21%	8%
Terminal Sacrifice Rate ^c	4/16 (25%)	0/0	0/1 (0%)	4/9 (44%)	1/24 (4%)	0/3 (0%)	0/2 (0%)	1/17 (6%)
First Incidence (Days)	367	--	--	292	639	--	817	369
Poly 3 Test ^d	--	--	--	<i>P</i> =0.231	--	--	--	<i>P</i> =0.283
Mean Lesion Severity Score	1.7	--	--	2.1	1.7	--	2.0	2.4
CLITORAL GLAND (S); Inflammation; Suppurative								
Incidence ^a	--	--	--	--	5/131 (4%)	0/8 (0%)	1/5 (20%)	2/130 (2%)
Adjusted Rate ^b	--	--	--	--	8%	0%	23%	3%
Terminal Sacrifice Rate ^c	--	--	--	--	2/23 (9%)	0/2 (0%)	0/2 (0%)	1/16 (6%)
First Incidence (Days)	--	--	--	--	691	--	844	864
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.212N
Mean Lesion Severity Score	--	--	--	--	2.8	--	3.0	3.0
EPIDIDYMIUM (S); Exfoliated Cells								
Incidence ^a	13/139 (9%)	2/3 (67%)	0/0	11/132 (8%)	--	--	--	--
Adjusted Rate ^b	20%	76%	--	23%	--	--	--	--
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	--	--	--	--
First Incidence (Days)	439	661	--	396	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.426	--	--	--	--
Mean Lesion Severity Score	1.9	2.5	--	1.9	--	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
EPIDIDYMIDE (S); Hypospermia	Control	Low ^e	Mid ^e	High	Control	Low ^e	Mid ^e	High
Incidence ^a	7/139 (5%)	2/3 (67%)	0/0	7/132 (5%)	--	--	--	--
Adjusted Rate ^b	11%	69%	--	15%	--	--	--	--
Terminal Sacrifice Rate ^c	1/16 (6%)	0/0	0/0	1/9 (11%)	--	--	--	--
First Incidence (Days)	439	661	--	31	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.358	--	--	--	--
Mean Lesion Severity Score	3.7	3.5	--	3.3	--	--	--	--
EPIDIDYMIDE (S); Sperm Granuloma								
Incidence ^a	3/139 (2%)	1/3 (33%)	0/0	0/132 (0%)	--	--	--	--
Adjusted Rate ^b	5%	47%	--	0%	--	--	--	--
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	--	--	--	--
First Incidence (Days)	93	813	--	--	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.193N	--	--	--	--
Mean Lesion Severity Score	2.7	4.0	--	--	--	--	--	--
HARDERIAN GLAND (S); Hyperplasia								
Incidence ^a	13/139 (9%)	0/0	0/0	9/132 (7%)	1/139 (1%)	0/0	0/0	1/134 (1%)
Adjusted Rate ^b	20%	--	--	20%	2%	--	--	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	2/9 (22%)	1/24 (4%)	0/0	0/0	0/17 (0%)
First Incidence (Days)	367	--	--	507	912	--	--	810
Poly 3 Test ^d	--	--	--	<i>P</i> =0.580	--	--	--	<i>P</i> =0.677
Mean Lesion Severity Score	1.9	--	--	2.4	4.0	--	--	4.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
HEART; Cardiomyopathy								
Incidence ^a	122/139 (88%)	115/141 (82%)	119/136 (88%)	111/132 (84%)	118/139 (85%)	115/142 (81%)	114/139 (82%)	109/134 (81%)
Adjusted Rate ^b	100%	98%	100%	99%	99%	99%	99%	98%
Terminal Sacrifice Rate ^c	16/16 (100%)	26/26 (100%)	18/18 (100%)	9/9 (100%)	24/24 (100%)	29/29 (100%)	17/17 (100%)	16/17 (94%)
First Incidence (Days)	30	31	31	25	30	30	32	30
Poly 3 Test ^d	P=0.677	P=0.289N	P=0.944N	P=0.398N	P=0.350N	P=0.645N	P=0.755N	P=0.288N
Mean Lesion Severity Score	1.9	2.0	1.9	1.8	1.8	1.8	1.7	1.8
KIDNEY (S); Hydronephrosis								
Incidence ^a	3/139 (2%)	1/141 (1%)	1/136 (1%)	4/132 (3%)	3/139 (2%)	1/142 (1%)	1/139 (1%)	2/134 (1%)
Adjusted Rate ^b	5%	1%	2%	9%	4%	1%	1%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	1/17 (6%)
First Incidence (Days)	366	94	94	93	522	354	422	788
Poly 3 Test ^d	P=0.408	P=0.503N	P=0.350N	P=0.323	P=0.469N	P=0.492N	P=0.311N	P=0.489N
Mean Lesion Severity Score	2.0	1.0	2.0	2.3	2.7	2.0	2.0	3.0
KIDNEY (S); Nephropathy								
Incidence ^a	87/139 (63%)	89/141 (63%)	96/136 (71%)	72/132 (55%)	95/139 (68%)	82/142 (58%)	89/139 (64%)	83/134 (62%)
Adjusted Rate ^b	91%	91%	95%	90%	93%	88%	91%	89%
Terminal Sacrifice Rate ^c	15/16 (94%)	24/26 (92%)	17/18 (94%)	8/9 (89%)	24/24 (100%)	28/29 (97%)	16/17 (94%)	15/17 (88%)
First Incidence (Days)	31	31	30	30	31	30	32	30
Poly 3 Test ^d	P=0.367	P=0.655	P=0.094	P=0.520N	P=0.212N	P=0.136N	P=0.368N	P=0.131N
Mean Lesion Severity Score	2.1	2.0	2.0	1.9	1.7	1.8	1.7	1.5

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
KIDNEY (S); PELVIS; Inflammation; Chronic								
Incidence ^a	56/139 (40%)	52/141 (37%)	58/136 (43%)	44/132 (33%)	22/139 (16%)	23/142 (16%)	21/139 (15%)	32/134 (24%)
Adjusted Rate ^b	64%	58%	67%	64%	29%	29%	28%	44%
Terminal Sacrifice Rate ^c	7/16 (44%)	8/26 (31%)	10/18 (56%)	2/9 (22%)	3/24 (13%)	2/29 (7%)	3/17 (18%)	11/17 (65%)
First Incidence (Days)	366	366	366	314	326	303	366	369
Poly 3 Test ^d	<i>P</i> =0.409	<i>P</i> =0.245N	<i>P</i> =0.415	<i>P</i> =0.498N	<i>P</i> =0.037 *	<i>P</i> =0.619N	<i>P</i> =0.512N	<i>P</i> =0.028 *
Mean Lesion Severity Score	1.9	2.0	1.9	2.0	1.7	1.6	1.8	1.8
LIVER; Basophilic Focus								
Incidence ^a	33/139 (24%)	25/141 (18%)	29/136 (21%)	23/132 (17%)	89/139 (64%)	91/142 (64%)	91/139 (65%)	89/134 (66%)
Adjusted Rate ^b	46%	34%	43%	44%	91%	89%	91%	93%
Terminal Sacrifice Rate ^c	6/16 (38%)	7/26 (27%)	9/18 (50%)	3/9 (33%)	24/24 (100%)	28/29 (97%)	15/17 (88%)	17/17 (100%)
First Incidence (Days)	438	384	481	384	366	318	366	367
Poly 3 Test ^d	<i>P</i> =0.543	<i>P</i> =0.107N	<i>P</i> =0.448N	<i>P</i> =0.467N	<i>P</i> =0.253	<i>P</i> =0.429N	<i>P</i> =0.575N	<i>P</i> =0.286
Mean Lesion Severity Score	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
LIVER; BILE DUCT; Cyst								
Incidence ^a	0/139 (0%)	0/141 (0%)	1/136 (1%)	0/132 (0%)	3/139 (2%)	0/142 (0%)	2/139 (1%)	4/134 (3%)
Adjusted Rate ^b	0%	0%	2%	0%	5%	0%	3%	6%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	--	--	809	--	731	--	662	529
Poly 3 Test ^d	<i>P</i> =0.676	--	<i>P</i> =0.563	--	<i>P</i> =0.307	<i>P</i> =0.281N	<i>P</i> =0.502N	<i>P</i> =0.426
Mean Lesion Severity Score	--	--	1.0	--	1.0	--	1.0	1.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
LIVER; BILE DUCT; Hyperplasia	Control	Low	Mid	High	Control	Low	Mid	High
Incidence ^a	22/139 (16%)	26/141 (18%)	23/136 (17%)	21/132 (16%)	53/139 (38%)	56/142 (39%)	51/139 (37%)	47/134 (35%)
Adjusted Rate ^b	33%	36%	36%	41%	63%	65%	60%	61%
Terminal Sacrifice Rate ^c	4/16 (25%)	6/26 (23%)	7/18 (39%)	4/9 (44%)	12/24 (50%)	16/29 (55%)	7/17 (41%)	12/17 (71%)
First Incidence (Days)	367	494	594	369	438	367	608	474
Poly 3 Test ^d	P=0.225	P=0.490	P=0.390	P=0.213	P=0.337N	P=0.523	P=0.369N	P=0.423N
Mean Lesion Severity Score	1.9	1.9	2.0	1.7	1.9	1.7	1.8	1.8
LIVER; Centrilobular; Fatty Change								
Incidence ^a	0/139 (0%)	3/141 (2%)	1/136 (1%)	3/132 (2%)	2/139 (1%)	0/142 (0%)	1/139 (1%)	0/134 (0%)
Adjusted Rate ^b	0%	4%	2%	7%	3%	0%	1%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	--	494	604	424	494	--	310	--
Poly 3 Test ^d	P=0.165	P=0.366	P=0.563	P=0.068	P=0.245N	P=0.509N	P=0.506N	P=0.198N
Mean Lesion Severity Score	--	1.3	2.0	1.7	1.5	--	2.0	--
LIVER; Centrilobular; Necrosis								
Incidence ^a	1/139 (1%)	1/141 (1%)	1/136 (1%)	1/132 (1%)	1/139 (1%)	1/142 (1%)	3/139 (2%)	2/134 (1%)
Adjusted Rate ^b	2%	1%	2%	2%	2%	1%	4%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	795	511	771	617	724	882	866	323
Poly 3 Test ^d	P=0.646	P=0.933N	P=0.791	P=0.662	P=0.282	P=0.925N	P=0.316	P=0.410
Mean Lesion Severity Score	4.0	2.0	3.0	3.0	2.0	3.0	2.3	2.5

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LIVER; Clear Cell Focus								
Incidence ^a	56/139 (40%)	58/141 (41%)	53/136 (39%)	44/132 (33%)	34/139 (24%)	32/142 (23%)	33/139 (24%)	23/134 (17%)
Adjusted Rate ^b	69%	70%	69%	71%	46%	41%	43%	34%
Terminal Sacrifice Rate ^c	14/16 (88%)	23/26 (88%)	16/18 (89%)	9/9 (100%)	18/24 (75%)	12/29 (41%)	9/17 (53%)	9/17 (53%)
First Incidence (Days)	366	366	367	366	466	530	367	366
Poly 3 Test ^d	<i>P</i> =0.492	<i>P</i> =0.592	<i>P</i> =0.528N	<i>P</i> =0.446	<i>P</i> =0.100N	<i>P</i> =0.375N	<i>P</i> =0.393N	<i>P</i> =0.068N
Mean Lesion Severity Score	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
LIVER; Eosinophilic Focus								
Incidence ^a	3/139 (2%)	6/141 (4%)	4/136 (3%)	3/132 (2%)	9/139 (6%)	10/142 (7%)	14/139 (10%)	7/134 (5%)
Adjusted Rate ^b	5%	9%	7%	7%	13%	14%	20%	11%
Terminal Sacrifice Rate ^c	0/16 (0%)	1/26 (4%)	1/18 (6%)	1/9 (11%)	2/24 (8%)	3/29 (10%)	3/17 (18%)	1/17 (6%)
First Incidence (Days)	509	630	515	292	566	325	624	521
Poly 3 Test ^d	<i>P</i> =0.496	<i>P</i> =0.448	<i>P</i> =0.500	<i>P</i> =0.477	<i>P</i> =0.533	<i>P</i> =0.645	<i>P</i> =0.193	<i>P</i> =0.429N
Mean Lesion Severity Score	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
LIVER; Extramedullary Hematopoiesis								
Incidence ^a	3/139 (2%)	2/141 (1%)	0/136 (0%)	0/132 (0%)	3/139 (2%)	0/142 (0%)	4/139 (3%)	0/134 (0%)
Adjusted Rate ^b	5%	3%	0%	0%	4%	0%	6%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	30	725	--	--	95	--	275	--
Poly 3 Test ^d	<i>P</i> =0.071N	<i>P</i> =0.679N	<i>P</i> =0.155N	<i>P</i> =0.197N	<i>P</i> =0.359N	<i>P</i> =0.283N	<i>P</i> =0.509	<i>P</i> =0.106N
Mean Lesion Severity Score	1.3	1.5	--	--	2.0	--	2.3	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LIVER; Fatty Change								
Incidence ^a	1/139 (1%)	3/141 (2%)	3/136 (2%)	1/132 (1%)	0/139 (0%)	0/142 (0%)	1/139 (1%)	2/134 (1%)
Adjusted Rate ^b	2%	4%	5%	2%	0%	0%	1%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	840	368	487	630	--	--	433	807
Poly 3 Test ^d	<i>P</i> =0.488	<i>P</i> =0.594	<i>P</i> =0.331	<i>P</i> =0.662	<i>P</i> =0.095	--	<i>P</i> =0.522	<i>P</i> =0.167
Mean Lesion Severity Score	2.0	1.3	1.7	2.0	--	--	2.0	2.5
LIVER; Mixed Cell Focus								
Incidence ^a	2/139 (1%)	5/141 (4%)	1/136 (1%)	0/132 (0%)	1/139 (1%)	1/142 (1%)	2/139 (1%)	0/134 (0%)
Adjusted Rate ^b	3%	7%	2%	0%	2%	1%	3%	0%
Terminal Sacrifice Rate ^c	1/16 (6%)	3/26 (12%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	713	630	747	--	884	487	540	--
Poly 3 Test ^d	<i>P</i> =0.218N	<i>P</i> =0.440	<i>P</i> =0.551N	<i>P</i> =0.310N	<i>P</i> =0.547N	<i>P</i> =0.923N	<i>P</i> =0.519	<i>P</i> =0.404N
Mean Lesion Severity Score	1.0	1.0	1.0	--	1.0	1.0	1.0	--
LIVER; Necrosis								
Incidence ^a	4/139 (3%)	5/141 (4%)	2/136 (1%)	2/132 (2%)	4/139 (3%)	3/142 (2%)	4/139 (3%)	5/134 (4%)
Adjusted Rate ^b	7%	7%	3%	5%	6%	4%	6%	8%
Terminal Sacrifice Rate ^c	0/16 (0%)	2/26 (8%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	2/17 (12%)
First Incidence (Days)	439	549	794	366	639	647	467	94
Poly 3 Test ^d	<i>P</i> =0.346N	<i>P</i> =0.713	<i>P</i> =0.390N	<i>P</i> =0.491N	<i>P</i> =0.376	<i>P</i> =0.636N	<i>P</i> =0.633N	<i>P</i> =0.418
Mean Lesion Severity Score	2.5	1.6	1.0	1.0	2.0	1.0	2.3	1.4

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LIVER; Periportal; Fatty Change								
Incidence ^a	11/139 (8%)	11/141 (8%)	12/136 (9%)	7/132 (5%)	21/139 (15%)	26/142 (18%)	19/139 (14%)	16/134 (12%)
Adjusted Rate ^b	18%	15%	20%	15%	28%	34%	26%	24%
Terminal Sacrifice Rate ^c	3/16 (19%)	0/26 (0%)	3/18 (17%)	1/9 (11%)	3/24 (13%)	8/29 (28%)	6/17 (35%)	4/17 (24%)
First Incidence (Days)	601	392	552	436	326	318	597	341
Poly 3 Test ^d	<i>P</i> =0.568	<i>P</i> =0.562N	<i>P</i> =0.476	<i>P</i> =0.470N	<i>P</i> =0.226N	<i>P</i> =0.331	<i>P</i> =0.453N	<i>P</i> =0.320N
Mean Lesion Severity Score	1.9	1.8	1.7	1.9	1.8	1.5	1.5	1.6
LIVER; Periportal; Infiltrate; Mixed Cell								
Incidence ^a	1/139 (1%)	3/141 (2%)	0/136 (0%)	1/132 (1%)	0/139 (0%)	2/142 (1%)	1/139 (1%)	2/134 (1%)
Adjusted Rate ^b	2%	4%	0%	2%	0%	3%	1%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	367	396	--	506	--	226	275	366
Poly 3 Test ^d	<i>P</i> =0.556N	<i>P</i> =0.587	<i>P</i> =0.576N	<i>P</i> =0.658	<i>P</i> =0.267	<i>P</i> =0.538	<i>P</i> =0.522	<i>P</i> =0.170
Mean Lesion Severity Score	1.0	1.7	--	2.0	--	1.0	2.0	2.0
LIVER; Pigment; Periportal								
Incidence ^a	4/139 (3%)	6/141 (4%)	8/136 (6%)	6/132 (5%)	22/139 (16%)	17/142 (12%)	19/139 (14%)	21/134 (16%)
Adjusted Rate ^b	7%	9%	13%	13%	28%	22%	25%	29%
Terminal Sacrifice Rate ^c	0/16 (0%)	1/26 (4%)	0/18 (0%)	1/9 (11%)	3/24 (13%)	2/29 (7%)	0/17 (0%)	1/17 (6%)
First Incidence (Days)	442	94	93	366	367	226	93	366
Poly 3 Test ^d	<i>P</i> =0.132	<i>P</i> =0.606	<i>P</i> =0.204	<i>P</i> =0.190	<i>P</i> =0.471	<i>P</i> =0.248N	<i>P</i> =0.348N	<i>P</i> =0.515
Mean Lesion Severity Score	2.3	1.8	2.0	2.2	1.9	1.7	1.9	1.9

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LUNG (S); Accumulation; Macrophage								
Incidence ^a	0/139 (0%)	0/141 (0%)	0/136 (0%)	8/131 (6%)	0/139 (0%)	0/142 (0%)	0/139 (0%)	6/134 (4%)
Adjusted Rate ^b	0%	0%	0%	17%	0%	0%	0%	9%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	--	--	--	94	--	--	--	93
Poly 3 Test ^d	<i>P</i> <0.001 ***	--	--	<i>P</i> =0.001 **	<i>P</i> =0.001 **	--	--	<i>P</i> =0.013 *
Mean Lesion Severity Score	--	--	--	1.1	--	--	--	1.0
LUNG (S); Bronchiolization								
Incidence ^a	0/139 (0%)	0/141 (0%)	0/136 (0%)	38/131 (29%)	0/139 (0%)	0/142 (0%)	0/139 (0%)	30/134 (22%)
Adjusted Rate ^b	0%	0%	0%	58%	0%	0%	0%	41%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	4/9 (44%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	5/17 (29%)
First Incidence (Days)	--	--	--	346	--	--	--	367
Poly 3 Test ^d	<i>P</i> <0.001 ***	--	--	<i>P</i> <0.001 ***	<i>P</i> <0.001 ***	--	--	<i>P</i> <0.001 ***
Mean Lesion Severity Score	--	--	--	1.1	--	--	--	1.1
LUNG (S); Congestion								
Incidence ^a	2/139 (1%)	3/141 (2%)	5/136 (4%)	5/131 (4%)	1/139 (1%)	2/142 (1%)	4/139 (3%)	4/134 (3%)
Adjusted Rate ^b	3%	4%	8%	11%	2%	3%	6%	6%
Terminal Sacrifice Rate ^c	0/16 (0%)	1/26 (4%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	177	628	416	274	568	547	467	323
Poly 3 Test ^d	<i>P</i> =0.075	<i>P</i> =0.740	<i>P</i> =0.231	<i>P</i> =0.105	<i>P</i> =0.094	<i>P</i> =0.746	<i>P</i> =0.194	<i>P</i> =0.132
Mean Lesion Severity Score	4.0	4.0	3.0	2.8	4.0	3.5	3.3	3.5

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Table H.2 (Continued). Histopathologic Results (Non-neoplastic Lesions)								
Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LUNG (S); Fibrosis; Interstitial; Periacinar								
Incidence ^a	0/139 (0%)	0/141 (0%)	0/136 (0%)	93/131 (71%)	0/139 (0%)	0/142 (0%)	0/139 (0%)	101/134 (75%)
Adjusted Rate ^b	0%	0%	0%	91%	0%	0%	0%	91%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	6/9 (67%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	14/17 (82%)
First Incidence (Days)	--	--	--	83	--	--	--	93
Poly 3 Test ^d	<i>P</i> <0.001***	--	--	<i>P</i> <0.001***	<i>P</i> <0.001***	--	--	<i>P</i> <0.001***
Mean Lesion Severity Score	--	--	--	1.1	--	--	--	1.0
LUNG (S); Histiocytosis; Alveolar; Focal								
Incidence ^a	111/139 (80%)	116/141 (82%)	112/136 (82%)	93/131 (71%)	118/139 (85%)	115/142 (81%)	113/139 (81%)	92/134 (69%)
Adjusted Rate ^b	96%	96%	97%	93%	98%	97%	96%	90%
Terminal Sacrifice Rate ^c	14/16 (88%)	24/26 (92%)	18/18 (100%)	8/9 (89%)	23/24 (96%)	28/29 (97%)	17/17 (100%)	16/17 (94%)
First Incidence (Days)	30	31	30	31	30	30	30	30
Poly 3 Test ^d	<i>P</i> =0.342N	<i>P</i> =0.622	<i>P</i> =0.274	<i>P</i> =0.230N	<i>P</i> <0.001N***	<i>P</i> =0.589N	<i>P</i> =0.322N	<i>P</i> =0.001N**
Mean Lesion Severity Score	1.6	1.3	1.4	1.2	1.4	1.3	1.4	1.1
LUNG (S); Hyperplasia; Epithelium; Periacinar								
Incidence ^a	0/139 (0%)	0/141 (0%)	0/136 (0%)	117/131 (89%)	0/139 (0%)	0/142 (0%)	0/139 (0%)	116/134 (87%)
Adjusted Rate ^b	0%	0%	0%	99%	0%	0%	0%	97%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	9/9 (100%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	17/17 (100%)
First Incidence (Days)	--	--	--	83	--	--	--	93
Poly 3 Test ^d	<i>P</i> <0.001***	--	--	<i>P</i> <0.001***	<i>P</i> <0.001***	--	--	<i>P</i> <0.001***
Mean Lesion Severity Score	--	--	--	1.4	--	--	--	1.4

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LUNG (S); Infiltrate; Mixed Cell								
Incidence ^a	14/139 (10%)	9/141 (6%)	9/136 (7%)	8/131 (6%)	11/139 (8%)	11/142 (8%)	13/139 (9%)	12/134 (9%)
Adjusted Rate ^b	19%	12%	14%	16%	14%	14%	16%	17%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	30	93	31	30	30	93	93	30
Poly 3 Test ^d	<i>P</i> =0.342N	<i>P</i> =0.222N	<i>P</i> =0.251N	<i>P</i> =0.408N	<i>P</i> =0.358	<i>P</i> =0.619N	<i>P</i> =0.440	<i>P</i> =0.413
Mean Lesion Severity Score	1.0	1.1	1.0	1.0	1.1	1.0	1.0	1.0
LUNG (S); Metaplasia; Osseous								
Incidence ^a	2/139 (1%)	1/141 (1%)	3/136 (2%)	1/131 (1%)	0/139 (0%)	0/142 (0%)	0/139 (0%)	1/134 (1%)
Adjusted Rate ^b	3%	1%	5%	2%	0%	0%	0%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	580	429	93	415	--	--	--	30
Poly 3 Test ^d	<i>P</i> =0.588	<i>P</i> =0.731N	<i>P</i> =0.525	<i>P</i> =0.600N	<i>P</i> =0.343	--	--	<i>P</i> =0.375
Mean Lesion Severity Score	1.0	1.0	1.0	1.0	--	--	--	1.0
LUNG (S); Pigmentation; Focal								
Incidence ^a	0/139 (0%)	0/141 (0%)	0/136 (0%)	0/131 (0%)	0/139 (0%)	0/142 (0%)	0/139 (0%)	4/134 (3%)
Adjusted Rate ^b	0%	0%	0%	0%	0%	0%	0%	7%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	4/17 (24%)
First Incidence (Days)	--	--	--	--	--	--	--	912
Poly 3 Test ^d	--	--	--	--	<i>P</i> =0.011 *	--	--	<i>P</i> =0.039 *
Mean Lesion Severity Score	--	--	--	--	--	--	--	1.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
LYMPH NODE (S); TRACHEOBRONCHIAL; Pigmentation								
Incidence ^a	36/126 (29%)	24/111 (22%)	36/117 (31%)	28/115 (24%)	61/120 (51%)	63/128 (49%)	58/120 (48%)	63/121 (52%)
Adjusted Rate ^b	55%	45%	61%	61%	75%	74%	77%	79%
Terminal Sacrifice Rate ^c	4/11 (36%)	9/17 (53%)	8/15 (53%)	2/4 (50%)	14/23 (61%)	17/28 (61%)	13/16 (81%)	12/16 (75%)
First Incidence (Days)	535	458	524	558	296	303	275	369
Poly 3 Test ^d	<i>P</i> =0.168	<i>P</i> =0.198N	<i>P</i> =0.313	<i>P</i> =0.299	<i>P</i> =0.224	<i>P</i> =0.555N	<i>P</i> =0.409	<i>P</i> =0.268
Mean Lesion Severity Score	1.2	1.3	1.2	1.1	1.5	1.4	1.4	1.3
MAMMARY GLAND (S); Galactocele								
Incidence ^a	1/65 (2%)	0/0 ^e	0/2 (0%) ^e	1/61 (2%)	3/137 (2%)	2/46 (4%) ^e	3/47 (6%) ^e	3/127 (2%)
Adjusted Rate ^b	3%	--	0%	5%	4%	7%	10%	5%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	0/23 (0%)	0/13 (0%)	0/5 (0%)	1/17 (6%)
First Incidence (Days)	577	--	--	458	296	303	367	520
Poly 3 Test ^d	--	--	--	<i>P</i> =0.622	--	--	--	<i>P</i> =0.554
Mean Lesion Severity Score	1.0	--	--	2.0	3.7	2.5	2.3	1.7
MAMMARY GLAND (S); Hyperplasia								
Incidence ^a	0/65 (0%)	0/0 ^e	0/2 (0%) ^e	0/61 (0%)	32/137 (23%)	9/46 (20%) ^e	17/47 (36%) ^e	28/127 (22%)
Adjusted Rate ^b	0%	--	0%	0%	43%	26%	47%	39%
Terminal Sacrifice Rate ^c	0/9 (0%)	0/0	0/0	0/3 (0%)	8/23 (35%)	1/13 (8%)	3/5 (60%)	5/17 (29%)
First Incidence (Days)	--	--	--	--	568	318	310	369
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.377N
Mean Lesion Severity Score	--	--	--	--	2.3	2.6	2.4	2.2

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
NERVE (S); SCIATIC; Degeneration	Control	Low	Mid	High	Control	Low	Mid	High
Incidence ^a	85/135 (63%)	0/0 ^e	0/0 ^e	62/126 (49%)	78/135 (58%)	0/0 ^e	0/0 ^e	71/134 (53%)
Adjusted Rate ^b	89%	--	--	87%	86%	--	--	78%
Terminal Sacrifice Rate ^c	13/14 (93%)	0/0	0/0	7/9 (78%)	23/24 (96%)	0/0	0/0	14/17 (82%)
First Incidence (Days)	177	--	--	366	296	--	--	323
Poly 3 Test ^d	--	--	--	<i>P</i> =0.368N	--	--	--	<i>P</i> =0.066N
Mean Lesion Severity Score	1.1	--	--	1.0	1.1	--	--	1.0
NOSE/TURBINATE 1; Epithelium; Lateral Wall; Hyperplasia								
Incidence ^a	21/138 (15%)	36/139 (26%)	29/136 (21%)	30/132 (23%)	30/139 (22%)	31/140 (22%)	42/139 (30%)	31/134 (23%)
Adjusted Rate ^b	33%	49%	45%	54%	41%	40%	52%	45%
Terminal Sacrifice Rate ^c	7/16 (44%)	14/25 (56%)	11/18 (61%)	7/9 (78%)	11/24 (46%)	12/29 (41%)	8/17 (47%)	11/17 (65%)
First Incidence (Days)	520	436	395	369	458	513	506	511
Poly 3 Test ^d	<i>P</i> =0.021 *	<i>P</i> =0.043 *	<i>P</i> =0.091	<i>P</i> =0.008 **	<i>P</i> =0.164	<i>P</i> =0.611N	<i>P</i> =0.094	<i>P</i> =0.327
Mean Lesion Severity Score	1.5	1.4	1.6	1.5	1.2	1.3	1.4	1.5
NOSE/TURBINATE 1; Epithelium; Lateral Wall; Necrosis								
Incidence ^a	1/138 (1%)	0/139 (0%)	0/136 (0%)	0/132 (0%)	3/139 (2%)	0/140 (0%)	0/139 (0%)	0/134 (0%)
Adjusted Rate ^b	2%	0%	0%	0%	4%	0%	0%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/25 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	650	--	--	--	611	--	--	--
Poly 3 Test ^d	<i>P</i> =0.454N	<i>P</i> =0.884N	<i>P</i> =0.574N	<i>P</i> =0.546N	<i>P</i> =0.039N*	<i>P</i> =0.284N	<i>P</i> =0.129N	<i>P</i> =0.106N
Mean Lesion Severity Score	2.0	--	--	--	2.3	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
NOSE/TURBINATE 1; Inflammation Suppurative								
Incidence ^a	25/138 (18%)	24/139 (17%)	21/136 (15%)	30/132 (23%)	32/139 (23%)	21/140 (15%)	30/139 (22%)	42/134 (31%)
Adjusted Rate ^b	37%	34%	32%	52%	40%	28%	37%	52%
Terminal Sacrifice Rate ^c	3/16 (19%)	9/25 (36%)	4/18 (22%)	2/9 (22%)	1/24 (4%)	3/29 (10%)	3/17 (18%)	3/17 (18%)
First Incidence (Days)	509	462	305	384	590	318	326	30
Poly 3 Test ^d	<i>P</i> =0.085	<i>P</i> =0.541N	<i>P</i> =0.350N	<i>P</i> =0.038 *	<i>P</i> =0.026 *	<i>P</i> =0.089N	<i>P</i> =0.441N	<i>P</i> =0.060
Mean Lesion Severity Score	2.1	1.6	1.9	1.7	2.0	1.4	1.5	2.0
NOSE/TURBINATE 1; Metaplasia Squamous Respiratory Epithelium								
Incidence ^a	6/138 (4%)	4/139 (3%)	4/136 (3%)	4/132 (3%)	12/139 (9%)	8/140 (6%)	2/139 (1%)	8/134 (6%)
Adjusted Rate ^b	10%	6%	7%	9%	17%	11%	3%	12%
Terminal Sacrifice Rate ^c	2/16 (13%)	1/25 (4%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	514	701	422	513	611	618	724	625
Poly 3 Test ^d	<i>P</i> =0.513N	<i>P</i> =0.483N	<i>P</i> =0.401N	<i>P</i> =0.568N	<i>P</i> =0.118N	<i>P</i> =0.306N	<i>P</i> =0.007N**	<i>P</i> =0.289N
Mean Lesion Severity Score	2.2	2.0	2.3	2.5	2.2	2.0	2.0	2.4
NOSE/TURBINATE 1; Metaplasia; Squamous; Lateral Wall								
Incidence ^a	45/138 (33%)	25/139 (18%)	29/136 (21%)	44/132 (33%)	41/139 (29%)	27/140 (19%)	31/139 (22%)	55/134 (41%)
Adjusted Rate ^b	56%	33%	40%	64%	47%	34%	39%	61%
Terminal Sacrifice Rate ^c	5/16 (31%)	4/25 (16%)	4/18 (22%)	2/9 (22%)	1/24 (4%)	0/29 (0%)	4/17 (24%)	4/17 (24%)
First Incidence (Days)	30	32	32	31	94	31	32	30
Poly 3 Test ^d	<i>P</i> =0.204	<i>P</i> =0.003N**	<i>P</i> =0.028N*	<i>P</i> =0.168	<i>P</i> =0.013 *	<i>P</i> =0.054N	<i>P</i> =0.155N	<i>P</i> =0.028 *
Mean Lesion Severity Score	2.3	1.9	2.3	2.2	2.5	2.3	2.2	2.4

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Table H.2 (Continued). Histopathologic Results (Non-neoplastic Lesions)								
Organ/Tissue and Finding	Males				Females			
NOSE/TURBINATE 1; Respiratory Epithelium; Hyperplasia	Control	Low	Mid	High	Control	Low	Mid	High
Incidence ^a	14/138 (10%)	10/139 (7%)	16/136 (12%)	12/132 (9%)	17/139 (12%)	9/140 (6%)	19/139 (14%)	25/134 (19%)
Adjusted Rate ^b	21%	15%	26%	26%	23%	13%	25%	35%
Terminal Sacrifice Rate ^c	0/16 (0%)	4/25 (16%)	3/18 (17%)	2/9 (22%)	1/24 (4%)	1/29 (3%)	0/17 (0%)	1/17 (6%)
First Incidence (Days)	632	625	562	562	590	730	618	594
Poly 3 Test ^d	<i>P</i> =0.221	<i>P</i> =0.314N	<i>P</i> =0.368	<i>P</i> =0.355	<i>P</i> =0.020 *	<i>P</i> =0.102N	<i>P</i> =0.459	<i>P</i> =0.067
Mean Lesion Severity Score	2.0	1.7	1.6	1.9	1.4	1.7	1.4	1.6
NOSE/TURBINATE 1; Lateral Wall Hyperplasia or Metaplasia; Squamous								
Incidence ^a	66/138 (48%)	60/139 (43%)	58/136 (43%)	73/132 (55%)	71/139 (51%)	58/140 (41%)	73/139 (53%)	86/134 (64%)
Adjusted Rate ^b	77%	72%	73%	89%	75%	65%	77%	88%
Terminal Sacrifice Rate ^c	12/16 (75%)	18/25 (72%)	15/18 (83%)	9/9 (100%)	12/24 (50%)	12/29 (41%)	12/17 (71%)	15/17 (88%)
First Incidence (Days)	30	32	32	31	94	31	32	30
Poly 3 Test ^d	<i>P</i> =0.019 *	<i>P</i> =0.284N	<i>P</i> =0.315N	<i>P</i> =0.009 **	<i>P</i> =0.002 **	<i>P</i> =0.101N	<i>P</i> =0.403	<i>P</i> =0.005 **
Mean Lesion Severity Score	2.0	1.6	2.0	1.9	2.0	1.8	1.7	2.1
NOSE/TURBINATE 1; Respiratory Epithelium Hyperplasia or Metaplasia								
Incidence ^a	20/138 (14%)	14/139 (10%)	19/136 (14%)	16/132 (12%)	29/139 (21%)	17/140 (12%)	21/139 (15%)	33/134 (25%)
Adjusted Rate ^b	30%	21%	30%	33%	36%	23%	27%	44%
Terminal Sacrifice Rate ^c	2/16 (13%)	5/25 (20%)	3/18 (17%)	2/9 (22%)	1/24 (4%)	1/29 (3%)	0/17 (0%)	1/17 (6%)
First Incidence (Days)	514	625	422	513	590	618	618	594
Poly 3 Test ^d	<i>P</i> =0.345	<i>P</i> =0.208N	<i>P</i> =0.573N	<i>P</i> =0.419	<i>P</i> =0.160	<i>P</i> =0.054N	<i>P</i> =0.139N	<i>P</i> =0.190
Mean Lesion Severity Score	2.1	1.8	1.7	2.1	1.7	1.8	1.5	1.8

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
NOSE/TURBINATE 2; Degeneration; Olfactory Epithelium								
Incidence ^a	12/137 (9%)	14/140 (10%)	12/134 (9%)	23/131 (18%)	12/137 (9%)	23/138 (17%)	29/136 (21%)	27/132 (20%)
Adjusted Rate ^b	19%	20%	19%	40%	17%	30%	36%	36%
Terminal Sacrifice Rate ^c	2/16 (13%)	4/26 (15%)	2/18 (11%)	0/9 (0%)	1/24 (4%)	7/29 (24%)	3/17 (18%)	1/17 (6%)
First Incidence (Days)	177	94	366	31	650	31	326	31
Poly 3 Test ^d	<i>P</i> =0.009 **	<i>P</i> =0.625	<i>P</i> =0.588	<i>P</i> =0.005 **	<i>P</i> =0.008 **	<i>P</i> =0.070	<i>P</i> =0.007 **	<i>P</i> =0.007 **
Mean Lesion Severity Score	1.3	1.5	1.7	1.6	1.8	1.5	1.5	1.5
NOSE/TURBINATE 2; Inflammation Suppurative								
Incidence ^a	5/137 (4%)	3/140 (2%)	4/134 (3%)	3/131 (2%)	2/137 (1%)	4/138 (3%)	1/136 (1%)	5/132 (4%)
Adjusted Rate ^b	8%	5%	7%	7%	3%	6%	2%	8%
Terminal Sacrifice Rate ^c	1/16 (6%)	2/26 (8%)	1/18 (6%)	0/9 (0%)	0/24 (0%)	2/29 (7%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	569	701	501	544	823	731	699	625
Poly 3 Test ^d	<i>P</i> =0.562N	<i>P</i> =0.477N	<i>P</i> =0.542N	<i>P</i> =0.538N	<i>P</i> =0.281	<i>P</i> =0.529	<i>P</i> =0.511N	<i>P</i> =0.169
Mean Lesion Severity Score	1.2	1.7	1.8	2.3	2.0	1.3	2.0	1.2
NOSE/TURBINATE 2; Metaplasia; Squamous; Olfactory Epithelium								
Incidence ^a	1/137 (1%)	5/140 (4%)	1/134 (1%)	2/131 (2%)	2/137 (1%)	7/138 (5%)	4/136 (3%)	2/132 (2%)
Adjusted Rate ^b	2%	7%	2%	5%	3%	10%	6%	3%
Terminal Sacrifice Rate ^c	1/16 (6%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	4/29 (14%)	0/17 (0%)	1/17 (6%)
First Incidence (Days)	845	30	524	366	654	487	32	646
Poly 3 Test ^d	<i>P</i> =0.595	<i>P</i> =0.290	<i>P</i> =0.792	<i>P</i> =0.374	<i>P</i> =0.506N	<i>P</i> =0.167	<i>P</i> =0.355	<i>P</i> =0.608
Mean Lesion Severity Score	1.0	1.0	1.0	2.0	1.5	1.1	1.0	1.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
NOSE/TURBINATE 2; Respiratory Metaplasia; Olfactory Epithelium	Control	Low	Mid	High	Control	Low	Mid	High
Incidence ^a	0/137 (0%)	1/140 (1%)	1/134 (1%)	4/131 (3%)	0/137 (0%)	1/138 (1%)	0/136 (0%)	1/132 (1%)
Adjusted Rate ^b	0%	2%	2%	9%	0%	1%	0%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	--	703	366	366	--	530	--	366
Poly 3 Test ^d	<i>P</i> =0.030 *	<i>P</i> =0.902	<i>P</i> =0.562	<i>P</i> =0.030 *	<i>P</i> =0.506	<i>P</i> =0.862	--	<i>P</i> =0.374
Mean Lesion Severity Score	--	1.0	1.0	1.3	--	1.0	--	1.0
NOSE/TURBINATE 3; Degeneration; Olfactory Epithelium								
Incidence ^a	2/139 (1%)	7/138 (5%)	4/134 (3%)	11/132 (8%)	4/137 (3%)	14/137 (10%)	13/134 (10%)	15/134 (11%)
Adjusted Rate ^b	3%	10%	7%	22%	6%	19%	18%	21%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/25 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	1/29 (3%)	1/16 (6%)	0/17 (0%)
First Incidence (Days)	391	367	416	31	326	303	30	341
Poly 3 Test ^d	<i>P</i> =0.007 **	<i>P</i> =0.208	<i>P</i> =0.341	<i>P</i> =0.002 **	<i>P</i> =0.020 *	<i>P</i> =0.032 *	<i>P</i> =0.022 *	<i>P</i> =0.007 **
Mean Lesion Severity Score	1.5	1.4	2.0	1.5	1.5	1.2	1.2	1.4
NOSE/TURBINATE 3; Foreign Material								
Incidence ^a	0/139 (0%)	0/138 (0%)	1/134 (1%)	3/132 (2%)	0/137 (0%)	0/137 (0%)	2/134 (1%)	1/134 (1%)
Adjusted Rate ^b	0%	0%	2%	7%	0%	0%	3%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/25 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/16 (0%)	0/17 (0%)
First Incidence (Days)	--	--	597	541	--	--	699	732
Poly 3 Test ^d	<i>P</i> =0.038 *	--	<i>P</i> =0.560	<i>P</i> =0.068	<i>P</i> =0.212	--	<i>P</i> =0.247	<i>P</i> =0.379
Mean Lesion Severity Score	--	--	1.0	1.0	--	--	1.0	1.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
NOSE/TURBINATE 3; Inflammation Suppurative	Control	Low	Mid	High	Control	Low	Mid	High
Incidence ^a	0/139 (0%)	1/138 (1%)	3/134 (2%)	5/132 (4%)	1/137 (1%)	3/137 (2%)	2/134 (1%)	2/134 (1%)
Adjusted Rate ^b	0%	2%	5%	11%	2%	4%	3%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/25 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	2/29 (7%)	0/16 (0%)	0/17 (0%)
First Incidence (Days)	--	701	597	541	897	325	699	696
Poly 3 Test ^d	<i>P</i> =0.007 **	<i>P</i> =0.901	<i>P</i> =0.134	<i>P</i> =0.013 *	<i>P</i> =0.486	<i>P</i> =0.534	<i>P</i> =0.507	<i>P</i> =0.419
Mean Lesion Severity Score	--	2.0	1.3	1.8	2.0	1.7	2.0	2.0
NOSE/TURBINATE 4; Degeneration; Olfactory Epithelium								
Incidence ^a	1/138 (1%)	1/135 (1%)	1/131 (1%)	2/131 (2%)	3/134 (2%)	4/137 (3%)	2/133 (2%)	0/131 (0%)
Adjusted Rate ^b	2%	2%	2%	5%	5%	6%	3%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/24 (0%)	0/17 (0%)	0/9 (0%)	1/24 (4%)	1/29 (3%)	0/17 (0%)	0/16 (0%)
First Incidence (Days)	367	701	31	562	326	303	376	--
Poly 3 Test ^d	<i>P</i> =0.390	<i>P</i> =0.937N	<i>P</i> =0.778	<i>P</i> =0.364	<i>P</i> =0.108N	<i>P</i> =0.685	<i>P</i> =0.505N	<i>P</i> =0.103N
Mean Lesion Severity Score	1.0	2.0	1.0	2.5	1.7	1.8	1.5	--
OVARY (IES); Atrophy								
Incidence ^a	--	--	--	--	19/139 (14%)	25/141 (18%)	30/136 (22%)	31/133 (23%)
Adjusted Rate ^b	--	--	--	--	26%	32%	39%	42%
Terminal Sacrifice Rate ^c	--	--	--	--	1/24 (4%)	4/29 (14%)	2/17 (12%)	3/17 (18%)
First Incidence (Days)	--	--	--	--	590	496	534	520
Poly 3 Test ^d	--	--	--	--	<i>P</i> =0.012 *	<i>P</i> =0.309	<i>P</i> =0.046 *	<i>P</i> =0.020 *
Mean Lesion Severity Score	--	--	--	--	2.0	2.0	2.1	2.1

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
OVARY (IES); Cyst								
Incidence ^a	--	--	--	--	8/139 (6%)	5/141 (4%)	5/136 (4%)	4/133 (3%)
Adjusted Rate ^b	--	--	--	--	12%	7%	8%	7%
Terminal Sacrifice Rate ^c	--	--	--	--	4/24 (17%)	2/29 (7%)	2/17 (12%)	1/17 (6%)
First Incidence (Days)	--	--	--	--	368	803	633	667
Poly 3 Test ^d	--	--	--	--	<i>P</i> =0.212N	<i>P</i> =0.370N	<i>P</i> =0.301N	<i>P</i> =0.208N
Mean Lesion Severity Score	--	--	--	--	1.0	1.0	1.0	1.0
OVARY (IES); Granulosa Cell; Hyperplasia								
Incidence ^a	--	--	--	--	3/139 (2%)	10/141 (7%)	6/136 (4%)	6/133 (5%)
Adjusted Rate ^b	--	--	--	--	4%	14%	9%	10%
Terminal Sacrifice Rate ^c	--	--	--	--	0/24 (0%)	6/29 (21%)	1/17 (6%)	0/17 (0%)
First Incidence (Days)	--	--	--	--	566	731	705	696
Poly 3 Test ^d	--	--	--	--	<i>P</i> =0.327	<i>P</i> =0.085	<i>P</i> =0.237	<i>P</i> =0.179
Mean Lesion Severity Score	--	--	--	--	2.3	2.2	2.7	2.0
OVARY (IES); Interstitial Cell; Hyperplasia								
Incidence ^a	--	--	--	--	8/139 (6%)	6/141 (4%)	13/136 (10%)	4/133 (3%)
Adjusted Rate ^b	--	--	--	--	12%	8%	19%	6%
Terminal Sacrifice Rate ^c	--	--	--	--	2/24 (8%)	1/29 (3%)	4/17 (24%)	1/17 (6%)
First Incidence (Days)	--	--	--	--	731	730	534	635
Poly 3 Test ^d	--	--	--	--	<i>P</i> =0.501N	<i>P</i> =0.467N	<i>P</i> =0.164	<i>P</i> =0.199N
Mean Lesion Severity Score	--	--	--	--	2.0	2.3	2.2	2.3

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
PANCREAS; Islet Cell; Hyperplasia	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
Incidence ^a	4/138 (3%)	0/2 (0%)	0/1 (0%)	2/131 (2%)	0/139 (0%)	0/3 (0%)	0/3 (0%)	3/134 (2%)
Adjusted Rate ^b	7%	0%	0%	5%	0%	0%	0%	5%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	0/24 (0%)	0/2 (0%)	0/0	1/17 (6%)
First Incidence (Days)	731	--	--	710	--	--	--	704
Poly 3 Test ^d	--	--	--	<i>P</i> =0.491N	--	--	--	<i>P</i> =0.081
Mean Lesion Severity Score	2.0	--	--	1.5	--	--	--	2.7
PARATHYROID GLAND (S); Hyperplasia								
Incidence ^a	2/128 (2%)	0/0	0/0	3/119 (3%)	1/128 (1%)	0/0	0/0	1/125 (1%)
Adjusted Rate ^b	4%	--	--	8%	2%	--	--	2%
Terminal Sacrifice Rate ^c	0/11 (0%)	0/0	0/0	0/4 (0%)	0/20 (0%)	0/0	0/0	0/16 (0%)
First Incidence (Days)	766	--	--	544	839	--	--	367
Poly 3 Test ^d	--	--	--	<i>P</i> =0.332	--	--	--	<i>P</i> =0.693
Mean Lesion Severity Score	3.5	--	--	2.3	2.0	--	--	1.0
PITUITARY GLAND; PARS DISTALIS; Angiectasis								
Incidence ^a	0/134 (0%)	0/28 (0%)	3/28 (11%)	0/131 (0%)	1/136 (1%)	0/61 (0%)	0/58 (0%)	0/133 (0%)
Adjusted Rate ^b	0%	0%	17%	0%	2%	0%	0%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/9 (0%)	0/4 (0%)	0/9 (0%)	0/23 (0%)	0/15 (0%)	0/9 (0%)	0/17 (0%)
First Incidence (Days)	--	--	625	--	731	--	--	--
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.401N
Mean Lesion Severity Score	--	--	3.7	--	3.0	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females	Females	Females	Females
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
PITUITARY GLAND; PARS DISTALIS; Hyperplasia								
Incidence ^a	30/134 (22%)	0/28 (0%)	3/28 (11%)	23/131 (18%)	22/136 (16%)	1/61 (2%)	2/58 (3%)	27/133 (20%)
Adjusted Rate ^b	43%	0%	17%	43%	29%	3%	5%	38%
Terminal Sacrifice Rate ^c	6/16 (38%)	0/9 (0%)	1/4 (25%)	3/9 (33%)	1/23 (4%)	1/15 (7%)	1/9 (11%)	5/17 (29%)
First Incidence (Days)	367	--	625	314	366	912	745	366
Poly 3 Test ^d	--	--	--	<i>P</i> =0.550	--	--	--	<i>P</i> =0.149
Mean Lesion Severity Score	2.1	--	2.3	2.0	2.2	3.0	2.0	2.0
PITUITARY GLAND; PARS INTERMEDIA; Hyperplasia								
Incidence ^a	4/134 (3%)	0/28 (0%)	2/28 (7%)	3/131 (2%)	2/136 (1%)	0/61 (0%)	0/58 (0%)	2/133 (2%)
Adjusted Rate ^b	7%	0%	12%	7%	3%	0%	0%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/9 (0%)	1/4 (25%)	0/9 (0%)	0/23 (0%)	0/15 (0%)	0/9 (0%)	0/17 (0%)
First Incidence (Days)	509	--	639	367	732	--	--	731
Poly 3 Test ^d	--	--	--	<i>P</i> =0.630N	--	--	--	<i>P</i> =0.628
Mean Lesion Severity Score	2.5	--	3.0	2.3	2.5	--	--	2.0
PREPUTIAL GLAND (S); Duct; Cyst								
Incidence ^a	1/135 (1%)	1/3 (33%)	3/6 (50%)	1/129 (1%)	0/0	0/0	0/0	0/0
Adjusted Rate ^b	2%	35%	58%	2%	--	--	--	--
Terminal Sacrifice Rate ^c	0/15 (0%)	1/2 (50%)	0/1 (0%)	0/9 (0%)	0/0	0/0	0/0	0/0
First Incidence (Days)	710	845	500	549	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.659	--	--	--	--
Mean Lesion Severity Score	1.0	1.0	1.0	1.0	--	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
PREPUTIAL GLAND (S); Inflammation Suppurative								
Incidence ^a	3/135 (2%)	0/3 (0%)	2/6 (33%)	1/129 (1%)	--	--	--	--
Adjusted Rate ^b	5%	0%	51%	2%	--	--	--	--
Terminal Sacrifice Rate ^c	0/15 (0%)	0/2 (0%)	1/1 (100%)	0/9 (0%)	--	--	--	--
First Incidence (Days)	654	--	552	732	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.431N	--	--	--	--
Mean Lesion Severity Score	3.3	--	4.0	4.0	--	--	--	--
PROSTATE GLAND; Epithelium; Hyperplasia								
Incidence ^a	17/139 (12%)	1/7 (14%)	0/1 (0%)	6/132 (5%)	--	--	--	--
Adjusted Rate ^b	26%	22%	0%	14%	--	--	--	--
Terminal Sacrifice Rate ^c	2/16 (13%)	0/1 (0%)	0/0	2/9 (22%)	--	--	--	--
First Incidence (Days)	520	698	--	520	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.097N	--	--	--	--
Mean Lesion Severity Score	1.8	2.0	--	2.2	--	--	--	--
PROSTATE GLAND; Inflammation; Chronic-active								
Incidence ^a	44/139 (32%)	3/7 (43%)	0/1 (0%)	40/132 (30%)	--	--	--	--
Adjusted Rate ^b	57%	60%	0%	63%	--	--	--	--
Terminal Sacrifice Rate ^c	8/16 (50%)	1/1 (100%)	0/0	5/9 (56%)	--	--	--	--
First Incidence (Days)	367	661	--	274	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.253	--	--	--	--
Mean Lesion Severity Score	2.1	2.0	--	1.9	--	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
PROSTATE GLAND; Inflammation; Suppurative	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
Incidence ^a	5/139 (4%)	1/7 (14%)	0/1 (0%)	2/132 (2%)	--	--	--	--
Adjusted Rate ^b	8%	24%	0%	5%	--	--	--	--
Terminal Sacrifice Rate ^c	0/16 (0%)	0/1 (0%)	0/0	0/9 (0%)	--	--	--	--
First Incidence (Days)	494	813	--	520	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.378N	--	--	--	--
Mean Lesion Severity Score	1.2	4.0	--	1.5	--	--	--	--
SALIVARY GLAND (S); Inflammation; Chronic; Active								
Incidence ^a	9/137 (7%)	0/0	0/1 (0%)	2/132 (2%)	6/138 (4%)	0/2 (0%)	1/2 (50%)	6/133 (5%)
Adjusted Rate ^b	14%	--	0%	5%	9%	0%	50%	9%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	0/24 (0%)	0/1 (0%)	0/0	0/17 (0%)
First Incidence (Days)	542	--	--	475	493	--	597	537
Poly 3 Test ^d	--	--	--	<i>P</i> =0.098N	--	--	--	<i>P</i> =0.533
Mean Lesion Severity Score	2.4	--	--	2.5	2.0	--	4.0	2.0
SEMINAL VESICLE (S); Inflammation; Chronic-active								
Incidence ^a	2/138 (1%)	0/10 (0%)	0/7 (0%)	3/132 (2%)	--	--	--	--
Adjusted Rate ^b	3%	0%	0%	7%	--	--	--	--
Terminal Sacrifice Rate ^c	0/16 (0%)	0/1 (0%)	0/0	0/9 (0%)	--	--	--	--
First Incidence (Days)	366	--	--	274	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.338	--	--	--	--
Mean Lesion Severity Score	1.0	--	--	2.0	--	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
SEMINAL VESICLE (S); Inflammation; Suppurative	Control	Low ^e	Mid ^e	High	Control	Low ^e	Mid ^e	High
Incidence ^a	1/138 (1%)	1/10 (10%)	0/7 (0%)	3/132 (2%)	--	--	--	--
Adjusted Rate ^b	2%	19%	0%	7%	--	--	--	--
Terminal Sacrifice Rate ^c	0/16 (0%)	0/1 (0%)	0/0	0/9 (0%)	--	--	--	--
First Incidence (Days)	830	813	--	628	--	--	--	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.191	--	--	--	--
Mean Lesion Severity Score	2.0	2.0	--	2.3	--	--	--	--
SKELETAL MUSCLE; Degeneration								
Incidence ^a	15/139 (11%)	0/1 (0%)	0/0	15/132 (11%)	29/139 (21%)	0/0	0/1 (0%)	22/134 (16%)
Adjusted Rate ^b	25%	0%	--	32%	39%	--	0%	33%
Terminal Sacrifice Rate ^c	9/16 (56%)	0/0	0/0	4/9 (44%)	8/24 (33%)	0/0	0/0	10/17 (59%)
First Incidence (Days)	678	--	--	25	529	--	--	369
Poly 3 Test ^d	--	--	--	<i>P</i> =0.244	--	--	--	<i>P</i> =0.249N
Mean Lesion Severity Score	1.4	--	--	1.5	1.1	--	--	1.0
SKIN; Ulceration								
Incidence ^a	1/138 (1%)	0/7 (0%)	0/7 (0%)	2/133 (2%)	0/139 (0%)	4/11 (36%)	2/11 (18%)	0/134 (0%)
Adjusted Rate ^b	2%	0%	0%	5%	0%	49%	25%	0%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/4 (0%)	0/0	0/9 (0%)	0/24 (0%)	0/1 (0%)	0/2 (0%)	0/17 (0%)
First Incidence (Days)	670	--	--	326	--	344	366	--
Poly 3 Test ^d	--	--	--	<i>P</i> =0.376	--	--	--	--
Mean Lesion Severity Score	4.0	--	--	3.0	--	2.8	2.5	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low ^e	Mid ^e	High	Control	Low ^e	Mid ^e	High
SPLEEN; Extramedullary Hematopoiesis								
Incidence ^a	15/139 (11%)	2/3 (67%)	3/6 (50%)	7/131 (5%)	16/139 (12%)	4/8 (50%)	8/8 (100%)	15/134 (11%)
Adjusted Rate ^b	22%	70%	66%	16%	22%	56%	100%	22%
Terminal Sacrifice Rate ^c	1/16 (6%)	0/0	0/0	0/9 (0%)	2/24 (8%)	0/1 (0%)	0/0	0/17 (0%)
First Incidence (Days)	30	511	377	513	529	660	422	323
Poly 3 Test ^d	--	--	--	<i>P</i> =0.247N	--	--	--	<i>P</i> =0.527N
Mean Lesion Severity Score	2.3	3.0	2.7	2.4	2.1	3.5	3.4	2.7
STOMACH; FORESTOMACH; Hyperplasia								
Incidence ^a	7/139 (5%)	0/1 (0%)	0/1 (0%)	4/132 (3%)	2/139 (1%)	0/3 (0%)	1/3 (33%)	1/134 (1%)
Adjusted Rate ^b	11%	0%	0%	9%	3%	0%	39%	2%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	0/24 (0%)	0/1 (0%)	0/0	0/17 (0%)
First Incidence (Days)	601	--	--	479	689	--	422	341
Poly 3 Test ^d	--	--	--	<i>P</i> =0.461N	--	--	--	<i>P</i> =0.458N
Mean Lesion Severity Score	2.7	--	--	3.0	2.5	--	3.0	3.0
STOMACH; FORESTOMACH; Ulceration								
Incidence ^a	7/139 (5%)	0/1 (0%)	0/1 (0%)	4/132 (3%)	1/139 (1%)	0/3 (0%)	1/3 (33%)	2/134 (1%)
Adjusted Rate ^b	11%	0%	0%	9%	2%	0%	39%	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	0/24 (0%)	0/1 (0%)	0/0	0/17 (0%)
First Incidence (Days)	514	--	--	479	689	--	422	323
Poly 3 Test ^d	--	--	--	<i>P</i> =0.463N	--	--	--	<i>P</i> =0.413
Mean Lesion Severity Score	2.3	--	--	3.3	2.0	--	3.0	2.0

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low	Mid	High
TESTIS (ES); Atrophy; Seminiferous Tubule								
Incidence ^a	26/139 (19%)	33/141 (23%)	17/136 (13%)	22/132 (17%)	--	--	--	--
Adjusted Rate ^b	38%	42%	26%	42%	--	--	--	--
Terminal Sacrifice Rate ^c	7/16 (44%)	9/26 (35%)	5/18 (28%)	4/9 (44%)	--	--	--	--
First Incidence (Days)	439	30	94	30	--	--	--	--
Poly 3 Test ^d	<i>P</i> =0.348N	<i>P</i> =0.429	<i>P</i> =0.084N	<i>P</i> =0.401	--	--	--	--
Mean Lesion Severity Score	2.1	2.0	2.0	2.0	--	--	--	--
TESTIS (ES); Polyarteritis								
Incidence ^a	4/139 (3%)	6/141 (4%)	4/136 (3%)	4/132 (3%)	--	--	--	--
Adjusted Rate ^b	7%	9%	7%	9%	--	--	--	--
Terminal Sacrifice Rate ^c	0/16 (0%)	3/26 (12%)	0/18 (0%)	1/9 (11%)	--	--	--	--
First Incidence (Days)	766	657	604	706	--	--	--	--
Poly 3 Test ^d	<i>P</i> =0.511	<i>P</i> =0.598	<i>P</i> =0.658	<i>P</i> =0.435	--	--	--	--
Mean Lesion Severity Score	2.8	2.5	2.5	2.5	--	--	--	--
THYMUS; Atrophy								
Incidence ^a	12/122 (10%)	0/3 (0%) ^e	0/3 (0%) ^e	15/120 (13%)	7/129 (5%)	0/9 (0%) ^e	0/18 (0%) ^e	4/122 (3%)
Adjusted Rate ^b	22%	0%	0%	31%	11%	0%	0%	7%
Terminal Sacrifice Rate ^c	2/12 (17%)	0/1 (0%)	0/1 (0%)	0/9 (0%)	0/22 (0%)	0/4 (0%)	0/3 (0%)	0/17 (0%)
First Incidence (Days)	439	--	--	25	296	--	--	351
Poly 3 Test ^d	--	--	--	<i>P</i> =0.203	--	--	--	<i>P</i> =0.287N
Mean Lesion Severity Score	2.6	--	--	2.9	2.7	--	--	2.8

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
THYROID GLAND (S); C-Cell; Hyperplasia	Control	Low	Mid	High	Control	Low	Mid	High
Incidence ^a	45/134 (34%)	45/89 (51%) ^e	50/86 (58%) ^e	33/131 (25%)	66/138 (48%)	59/94 (63%) ^e	63/93 (68%) ^e	62/132 (47%)
Adjusted Rate ^b	58%	66%	72%	55%	73%	72%	81%	75%
Terminal Sacrifice Rate ^c	6/14 (43%)	13/23 (57%)	7/14 (50%)	2/9 (22%)	16/24 (67%)	15/28 (54%)	14/16 (88%)	12/17 (71%)
First Incidence (Days)	366	326	377	366	367	226	433	474
Poly 3 Test ^d	P=0.343	P=0.201	P=0.029 *	P=0.415N	P=0.219	P=0.555N	P=0.097	P=0.405
Mean Lesion Severity Score	1.6	1.6	1.8	1.7	1.5	1.9	2.0	1.7
THYROID GLAND (S); Follicular Cell; Hyperplasia								
Incidence ^a	2/134 (1%)	9/89 (10%) ^e	8/86 (9%) ^e	5/131 (4%)	7/138 (5%)	7/94 (7%) ^e	4/93 (4%) ^e	4/132 (3%)
Adjusted Rate ^b	3%	17%	17%	12%	10%	12%	7%	7%
Terminal Sacrifice Rate ^c	0/14 (0%)	3/23 (13%)	0/14 (0%)	3/9 (33%)	1/24 (4%)	4/28 (14%)	0/16 (0%)	0/17 (0%)
First Incidence (Days)	442	384	508	630	640	731	655	754
Poly 3 Test ^d	P=0.096	P=0.030 *	P=0.016 *	P=0.105	P=0.218N	P=0.601	P=0.354N	P=0.298N
Mean Lesion Severity Score	1.5	2.9	2.4	2.2	1.6	2.3	2.0	2.5
TRACHEA; Inflammation								
Incidence ^a	3/138 (2%)	0/139 (0%)	0/134 (0%)	2/131 (2%)	2/138 (1%)	0/141 (0%)	0/139 (0%)	0/134 (0%)
Adjusted Rate ^b	5%	0%	0%	5%	3%	0%	0%	0%
Terminal Sacrifice Rate ^c	2/16 (13%)	0/26 (0%)	0/18 (0%)	0/9 (0%)	0/24 (0%)	0/29 (0%)	0/17 (0%)	0/17 (0%)
First Incidence (Days)	93	--	--	94	493	--	--	--
Poly 3 Test ^d	P=0.488N	P=0.296N	P=0.154N	P=0.629N	P=0.112N	P=0.507N	P=0.248N	P=0.197N
Mean Lesion Severity Score	1.3	--	--	1.0	2.0	--	--	--

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Thyroid glands from low- and mid-exposure animals in 1-, 3-, 12-, and 24-month interim sacrifice groups were not examined microscopically (see text Results). Reported rates and *P* values reflect exclusion of these animals from statistical analysis.

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
URINARY BLADDER; Epithelium; Hyperplasia	Control	Low ^c	Mid ^c	High	Control	Low ^c	Mid ^c	High
Incidence ^a	3/139 (2%)	1/3 (33%)	0/0	3/131 (2%)	1/136 (1%)	0/0	0/0	2/132 (2%)
Adjusted Rate ^b	5%	69%	--	7%	2%	--	--	3%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	0/23 (0%)	0/0	0/0	0/16 (0%)
First Incidence (Days)	686	810	--	706	817	--	--	732
Poly 3 Test ^d	--	--	--	<i>P</i> =0.484	--	--	--	<i>P</i> =0.408
Mean Lesion Severity Score	4.0	3.0	--	2.7	2.0	--	--	2.0
URINARY BLADDER; Inflammation								
Incidence ^a	0/139 (0%)	0/3 (0%)	0/0	2/131 (2%)	1/136 (1%)	0/0	0/0	3/132 (2%)
Adjusted Rate ^b	0%	0%	--	5%	2%	--	--	5%
Terminal Sacrifice Rate ^c	0/16 (0%)	0/0	0/0	0/9 (0%)	0/23 (0%)	0/0	0/0	0/16 (0%)
First Incidence (Days)	--	--	--	449	817	--	--	732
Poly 3 Test ^d	--	--	--	<i>P</i> =0.159	--	--	--	<i>P</i> =0.233
Mean Lesion Severity Score	--	--	--	3.0	2.0	--	--	1.7
UTERUS; Dilatation								
Incidence ^a	--	--	--	--	3/138 (2%)	4/20 (20%)	2/18 (11%)	5/134 (4%)
Adjusted Rate ^b	--	--	--	--	5%	25%	16%	8%
Terminal Sacrifice Rate ^c	--	--	--	--	1/24 (4%)	1/8 (13%)	0/3 (0%)	0/17 (0%)
First Incidence (Days)	--	--	--	--	720	94	633	594
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.301
Mean Lesion Severity Score	--	--	--	--	2.3	2.5	4.0	2.8

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.

Organ/Tissue and Finding	Males				Females			
	Control	Low	Mid	High	Control	Low ^e	Mid ^e	High
UTERUS; Hyperplasia; Endometrial								
Incidence ^a	--	--	--	--	8/138 (6%)	5/20 (25%)	5/18 (28%)	14/134 (10%)
Adjusted Rate ^b	--	--	--	--	12%	36%	40%	21%
Terminal Sacrifice Rate ^c	--	--	--	--	4/24 (17%)	4/8 (50%)	1/3 (33%)	2/17 (12%)
First Incidence (Days)	--	--	--	--	749	731	699	366
Poly 3 Test ^d	--	--	--	--	--	--	--	<i>P</i> =0.105
Mean Lesion Severity Score	--	--	--	--	1.6	2.6	2.0	2.2

^a Number of lesion-bearing animals/number of animals examined.

^b Poly-3 estimated lesion incidence after adjustment for intercurrent mortality.

^c Observed incidence at terminal sacrifice.

^d The *P* value in the control column is associated with the trend test across control and treated groups; *P* values in exposure group columns correspond to pairwise comparisons between the control and exposed groups. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice.

^e Numbers of animals examined limited to those that exhibited gross lesions. No statistical comparisons reported because of examination bias (see Methods).

* *P* < 0.05, ** *P* < 0.01, ****P* < 0.001. "N" indicates negative trend.