

Summary of Observations From the Multigenerational Reproductive Toxicology Feed Study of Ethinyl Estradiol^a

Endpoint	Generation					
	F ₀ Exposed from PND 42 to PND 140	F ₁ Exposed from GD 0 to PND 140	F ₂ Exposed from GD 0 to PND 140	F ₃ Exposed from GD 0 to PND 21 (Terminated on PND 140)	F ₄ Not Exposed (Terminated on PND 140)	F ₅ Not Exposed (Terminated on PND 21)
Body Weight						
Female						
Prewaning	NA	↓ (50)	↓ (50)	↓ (50)	-	NA
Postweaning	↓ (10, 50)	↓ (50)	↓ (50)	-	-	NA
Male						
Prewaning	NA	↓ (50)	↓ (50)	↓ (50)	-	NA
Postweaning	↓ (50)	↓ (50)	↓ (2, 10, 50)	-	-	NA
Feed Consumption						
Female	↓ (2)	-	↓ (50)	↑ (10, 50)	-	NA
Male	↓ (2, 10)	↓ (2)	↓ (2, 10, 50)	-	-	NA
Water Consumption						
Female During Lactation	-	-	-	-	-	NA
Pregnancy Index	-	-	-	-	-	NA
Mating Index	-	-	-	-	-	NA
Fertility Index	-	-	-	-	-	NA
Mating Time	-	-	-	-	-	NA
Gestation Length	-	-	-	-	-	NA
Litter Size	NA	-	-	-	-	-
Pup Birth Weight						
Male	NA	-	-	-	-	-
Female	NA	-	-	-	-	-
Sex Ratio (M:F)	NA	-	-	-	-	-

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Stillbirths	NA	-	-	-	-	-
Anogenital Distance						
Male PND 2						
ANCOVA	NA	-	-	↓ (50)	-	-
Ratio	NA	-	-	-	-	-
Female PND 2						
ANCOVA	NA	-	↑ (50)	↓ (10, 50)	-	-
Ratio	NA	-	↑ (50)	↓ (50)	-	-
Vaginal Opening						
Age	NA	↓ (50)	↓ (50)	↓ (50)	-	NA
Body Weight	NA	↓ (10, 50)	↓ (50)	↓ (50)	-	NA
Preputial Separation						
Age	NA	-	↑ (50)	-	-	NA
Body Weight	NA	-	-	-	-	NA
Testicular Descent						
Age	NA	↑ (2)	-	-	↓ (2)	NA
Vaginal Cytology After Vaginal Opening						
% Time Estrus	NA	↓ (10) ↑ (50)	↑ (50)	-	-	NA
% Time Diestrus	NA	-	-	-	-	NA
% Time Proestrus	NA	↓ (50)	↓ (50)	-	-	NA
% Abnormal Cycles	NA	↑ (50)	↑ (50)	-	-	NA
Number Abnormal Cycles	NA	↑ (50)	↑ (50)	-	-	NA
Length of Cycle	NA	↑ (2, 10, 50)	↑ (50)	-	-	NA

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Vaginal Cytology Before Termination						
% Time Estrus	-	-	-	-	-	NA
% Time Diestrus	-	-	-	-	-	NA
% Time Proestrus	-	-	-	-	-	NA
% Abnormal Cycles	-	-	-	-	-	NA
Number Abnormal Cycles	-	-	-	-	-	NA
Length of Cycle	-	-	-	-	-	NA
Estrous Cycle Synchrony in Reproductive Organs at Necropsy	-	-	-	-	-	NA
Terminal Body Weight						
Male	↓ (50)	↓ (50)	↓ (2, 10, 50)	-	-	NA
Female	↓ (10, 50)	↓ (50)	↓ (50)	-	↑ (10)	NA
Male Organ Weights						
Adrenal Gland						
Absolute	-	-	-	-	-	NA
Relative	↑ (50)	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA

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Brain						
Absolute	-	-	-	-	-	NA
Relative	↑ (50)	↑ (50)	↑ (2, 10, 50)	-	-	NA
ANCOVA	↑ (2, 50)	-	↑ (2)	-	↑ (2)	NA
Epididymis						
Absolute	-	-	-	-	-	NA
Relative	-	-	↑ (50)	-	-	NA
ANCOVA	-	-	-	-	-	NA
Kidney						
Absolute	↓ (50)	↓ (50)	↓ (2, 10, 50)	-	-	NA
Relative	↑ (50)	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Liver						
Absolute	↓ (50)	-	↓ (2, 50)	-	-	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Pituitary Gland						
Absolute	-	↑ (10)	-	-	-	NA
Relative	↑ (50)	↑ (50)	↑ (50)	-	-	NA
ANCOVA	↑ (50)	↑ (50)	-	-	-	NA
Prostate Gland Dorsal Lobe						
Absolute	-	-	-	-	-	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Prostate Gland Lateral Lobe						
Absolute	-	-	-	-	↑ (10)	NA
Relative	-	-	↑ (50)	-	↑ (10)	NA
ANCOVA	-	-	-	-	↑ (10)	NA

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Seminal Vesicle/Coagulating Gland						
Absolute	-	-	↑ (10)	-	-	NA
Relative	↑ (50)	-	↑ (2, 10, 50)	-	-	NA
ANCOVA	-	-	↑ (10)	-	-	NA
Spleen						
Absolute	-	-	-	-	-	NA
Relative	↑ (50)	↑ (50)	↑ (50)	-	↑ (2)	NA
ANCOVA	-	↑ (2, 50)	-	-	↑ (2)	NA
Testis						
Absolute	-	-	-	-	-	NA
Relative	↑ (50)	-	↑ (50)	-	-	NA
ANCOVA	-	-	-	-	-	NA
Thymus						
Absolute	-	-	-	↑ (2)	-	NA
Relative	-	-	-	↑ (2)	-	NA
ANCOVA	-	-	-	↑ (2)	-	NA
Thyroid Gland						
Absolute	-	↓ (10, 50)	-	-	-	NA
Relative	-	↓ (10, 50)	-	-	-	NA
ANCOVA	-	↓ (10, 50)	-	-	-	NA
Ventral Prostate Gland						
Absolute	-	-	-	-	-	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA

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Female Organ Weights						
Adrenal Gland						
Absolute	-	-	-	-	-	NA
Relative	-	↑ (50)	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Brain						
Absolute	-	-	-	-	↑ (2)	NA
Relative	↑ (10, 50)	↑ (50)	↑ (50)	-	-	NA
ANCOVA	-	-	-	-	-	NA
Kidney						
Absolute	↓ (2, 10, 50)	↓ (50)	↓ (50)	-	↑ (10)	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Liver						
Absolute	↓ (50)	↓ (50)	↓ (50)	-	↑ (2, 10)	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Ovary						
Absolute	-	↓ (50)	-	-	-	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Pituitary Gland						
Absolute	-	-	-	-	-	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA

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Spleen						
Absolute	↓ (50)	↓ (50)	↑ (2)	-	-	NA
Relative	-	↑ (2)	↑ (2, 10, 50)	-	-	NA
ANCOVA	-	↑ (2)	↑ (2, 10)	-	-	NA
Thymus						
Absolute	-	-	-	-	↑ (2, 50)	NA
Relative	-	↑ (2, 50)	↑ (50)	-	↑ (50)	NA
ANCOVA	-	-	↑ (50)	-	↑ (2, 50)	NA
Thyroid Gland						
Absolute	↑ (10)	-	-	-	↑ (10)	NA
Relative	↑ (2, 10)	-	-	-	-	NA
ANCOVA	↑ (10)	-	-	-	-	NA
Uterus						
Absolute	-	-	-	-	-	NA
Relative	-	-	-	-	-	NA
ANCOVA	-	-	-	-	-	NA
Ovarian Follicle Counts						
Small	↑ (50)	-	-	-	-	NA
Growing	-	-	-	-	↓ (50)	NA
Antral	-	↑ (10)	↑ (10)	-	-	NA
Epididymal Sperm Count	-	-	↑ (10, 50)	-	-	NA
Testicular Spermatid Head Count	-	↓ (50)	-	-	-	NA
Sperm Motility	-	-	-	-	-	NA
Sperm Morphology	-	-	-	-	-	NA

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Histopathology						
Male						
Mammary Gland Alveolar/Ductal Hyperplasia	↑ (50)	↑ (2, 10, 50)	↑ (10, 50)	↑ (50)	-	NA
Renal Tubule Mineralization	-	↑ (50)	↑ (50)	-	-	NA
Female						
Mammary Gland Lobules, Hyperplasia	-	-	↑ (10, 50)	-	-	NA
Alveolar, Hyperplasia	-	-	-	-	-	NA
Renal Tubule Mineralization	-	↓ (50)	-	-	↓ (2, 50)	NA

^a GD=gestation day; NA=not applicable; PND=postnatal day; ANCOVA=analysis of covariance; ↑ or ↓, significant increase or decrease relative to controls at the exposure concentration indicated in parentheses; “-”, no exposed group significantly different from the control group in that generation in pairwise comparisons