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FINAL REPORT

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Table of Contents

Page

ABSTRACT 1

OBJECTIVES 6

1.0 THE STUDY DESIGN 6

2.0 SPECIES/STRAIN OF TEST ANIMAL 8

3.0 DOSING PERIOD 8

4.0 DEVELOPMENT OF THE REPRODUCTIVE SYSTEM AND THE THYROID 9
- 4.1 Sexual Differentiation 9
  - 4.1.1 Both Sexes 9
  - 4.1.2 Males 9
  - 4.1.3 Females 11
- 4.2 Thyroid 12

5.0 SELECTED ENDPOINTS 12
- 5.1 In-Life Evaluations 12
- 5.2 Organ Weights 14
- 5.3 Thyroid Hormones (TSH, T3, and T4) 15

6.0 PROTOCOL ISSUES THAT NEEDED RESOLUTION 15

7.0 TEST SUBSTANCE AND DOSES FOR THE PREVALIDATION STUDY 16
- 7.1 Chemical Selection 16
- 7.2 Dose Selection 17
  - 7.2.1 Males 18
  - 7.2.2 Females 20

8.0 MATERIALS AND METHODS 24
- 8.1 Test Materials and Dose Formulations 24
- 8.2 Animals and Husbandry 25
  - 8.2.1 F0 Females 27
  - 8.2.2 Progeny (F1) 28
- 8.3 F1 Weanling Female Uterotrophic Cohort 29
- 8.4 F1 Weanling Female Pubertal Cohort 29
- 8.5 F1 Weanling Male Pubertal Cohort 30
- 8.6 Necropsy of F1 Offspring 30
- 8.7 Histology and Pathology 35

9.0 STATISTICAL ANALYSES 36

10.0 ANALYTICAL REPORT AND PROTOCOL 37

11.0 STORAGE OF RECORDS 37

US EPA ARCHIVE DOCUMENT

Table of Contents (continued)

Page

12.0 COMPLIANCE 37

13.0 PERSONNEL 38

14.0 RESULTS 39
- 14.1 Dose Formulations 39
- 14.2 F0 Female Observations 39
- 14.3 F1 Preweaning Observations 41
- 14.4 F1 Female Uterotrophic Cohort 42
- 14.5 F1 Female Pubertal Cohort (Undosed) 43
- 14.6 F1 Female Pubertal Cohort (Dosed) 45
- 14.7 F1 Male Pubertal Cohort (Undosed) 47
- 14.8 F1 Male Pubertal Cohort (Dosed) 48

15.0 DISCUSSION AND CONCLUSIONS 51

16.0 REFERENCES 54

APPENDICES

I INDIVIDUAL TABLES

II PROTOCOL

III CHEMISTRY REPORT

IV HISTOPATHOLOGY REPORT

V LETTER FROM DR. R.W. TYL TO DR. D.P. HOUCHENS

VI E-MAIL FROM DR. L. E. GRAY

US EPA ARCHIVE DOCUMENT

List of Figures

Page

1. Study Design for Utero/Lactational Exposure Assay 7
2. Sexual Differentiation in Mammals.....10

List of Text Tables

Page

1. Study Schedule 25
2. Estradiol Recovery in Various Matrices 31
3. F0 Female CD Rat Serum 32
4. F1 Female CD Rat Serum 33
5. Female Uterotrophic CD Rat Serum.....33
6. F1 Male CD Rat Serum.....34

US EPA ARCHIVE DOCUMENT

List of Tables

1 Analyses of Dose Formulations of Methoxychlor in Corn Oil 62

2 Summary of the Fate of the F0 Females 64

3 Summary and Statistical Analysis of F0 Female Body Weights and Weight Change During Gestation 65

4 Summary and Statistical Analysis of F0 Female Feed Consumption During Gestation 68

5 Summary of the F0 Female Clinical Observations During Gestation 71

6 Summary and Statistical Analysis of F0 Female Body Weights and Weight Changes During Lactation 74

7 Summary and Statistical Analysis of F0 Female Feed Consumption During Lactation 76

8 Summary of the F0 Female Clinical Observations During Lactation 78

9 Summary and Statistical Analysis of F0 Reproductive and Lactational Indexes for the F1 Litters 84

10 Summary and Statistical Analysis of the F1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation 87

11 Summary of the F1 Pup Clinical Observations on Postnatal Days 0 Through 21 93

12 Summary of the F1 Pup Gross Necropsy Findings on Postnatal Days 0 Through 21 95

13 Summary and Statistical Analysis of the F0 Female Hormone Data at Necropsy 97

14 Summary of the F0 Female Necropsy Findings 98

15 Summary of the Fate of the F1 Uterotrophic Females 99

16 Summary and Statistical Analysis of the F1 Uterotrophic Female Body Weights and Weight Changes During the Post Wean Holding Period 100

17 Summary of the F1 Uterotrophic Female Clinical Observations During the Post Wean Holding Period 101

18 Summary and Statistical Analysis of the F1 Uterotrophic Female Necropsy Weights and Hormone Data 102

19 Summary of the F1 Uterotrophic Female Gross Necropsy Findings 104

US EPA ARCHIVE DOCUMENT

List of Tables (continued)

20 Summary of the Fate of the F1 Undosed Pubertal Females 105

21 Summary and Statistical Analysis of the F1 Undosed Pubertal Female Anogenital Distance, Body Weights and Body Weight Changes During the Post Wean Holding Period 106

22 Summary of the F1 Undosed Pubertal Female Clinical Observations During the Post Wean Period 110

23 Summary and Statistical Analysis of the F1 Undosed Pubertal Female Vaginal Opening and Vaginal Cytology Data 111

24 Summary and Statistical Analysis of the F1 Undosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data 114

25 Summary of the F1 Undosed Pubertal Female Gross Necropsy Findings 119

26 Summary of the Fate of the F1 Dosed Pubertal Females 120

27 Summary and Statistical Analysis of the F1 Dosed Pubertal Female Anogenital Distance, Body Weights and Body Weight Changes During the Post Wean Holding Period 121

28 Summary of the F1 Dosed Pubertal Female Clinical Observations During the Post Wean Period 125

29 Summary and Statistical Analysis of the F1 Dosed Pubertal Female Vaginal Opening and Vaginal Cytology Data 127

30 Summary and Statistical Analysis of the F1 Dosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data 130

31 Summary of the F1 Dosed Pubertal Female Gross Necropsy Findings 135

32 Summary of the Fate of the F1 Undosed Pubertal Males 136

33 Summary and Statistical Analysis of the F1 Undosed Pubertal Male Anogenital Distance, Body Weights and Body Weight Changes During the Post Wean Holding Period 137

34 Summary of the F1 Undosed Pubertal Male Clinical Observations During the Post Wean Period 145

35 Summary and Statistical Analysis of the F1 Undosed Pubertal Male Preputial Separation Data 146

US EPA ARCHIVE DOCUMENT

List of Tables (continued)

36 Summary and Statistical Analysis of the F1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data 147

37 Summary of the F1 Undosed Pubertal Male Gross Necropsy Findings 155

38 Summary of the Fate of the F1 Dosed Pubertal Males 156

39 Summary and Statistical Analysis of the F1 Dosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period 157

40 Summary of the F1 Dosed Pubertal Male Clinical Observations During the Post Wean Period..... 165

41 Summary and Statistical Analysis of the F1 Dosed Pubertal Male Preputial Separation Data 170

42 Summary and Statistical Analysis of the F1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis, and Hormone Data 171

43 Summary of the F1 Dosed Pubertal Male Gross Necropsy Findings 179

US EPA ARCHIVE DOCUMENT

RTI Project No.: 65U-08055.001.017
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FINAL REPORT

Validation of the In Utero/Lactational Exposure Screening Protocol with Methoxychlor

ABSTRACT

Sperm-positive female CD® (Sprague-Dawley) rats (the F0 generation) were administered methoxychlor (CAS No.72-43-5) orally by gavage from gestational day (gd) 6 (sperm detection = gd 0) to postnatal day (pnd) 21 (date of birth designated pnd 0), at 25, 50 or 100 mg/kg/day at a dose volume of 5 ml/kg in Mazola® corn oil. A vehicle control group dosed with corn oil was run concurrently. Dose analysis was done periodically throughout the study. Results indicated that actual concentrations of all in-life dose formulations were between 83 and 101% of target concentration indicating that F0 and F1 animals were exposed to methoxychlor accordingly. Fifteen sperm-positive F0 females were assigned to each treatment group. Body weight and feed consumption for the F0 females were recorded during gestation and lactation, and F1 offspring from birth through scheduled sacrifice. Clinical signs were recorded at least once daily for all animals, with twice daily observations during the treatment period. On the day of birth (pnd 0), individual anogenital distance (AGD) and body weights were recorded for all live F1 pups (n = 620) in all litters. F1 litters were standardized on pnd 4 to yield nine pups, with a ratio of 5:4 (female:male) if possible. Natural litters with ten or fewer pups were not adjusted. The culled F1 pups (n = 255) were weighed and euthanized. The remaining F1 pups were counted (and survival indices were calculated weekly) and sexed, and weighed throughout lactation to weaning (pnd 21). The presence or absence of retained nipples and areolae on the ventrum was recorded for all F1 males at approximately pnd 11-13. Males with one or more nipples or areolae were uniquely marked until weaning. At weaning on pnd 21, body weight was documented for all pups. One female from each litter was chosen for the uterotrophic cohort. Females were dosed subcutaneously (sc) from pnd 22-24 and evaluated on pnd 24. Clinical observations of F1 females assigned to the uterotrophic cohort were documented at least twice daily (at dosing and one to two hours postdosing) throughout the dosing period (pnd 22 through pnd 24). Beginning on pnd 22, each F1 female was dosed with the same dose level as her mother but via subcutaneous injection on pnd 22 through 24. Each animal was weighed every day prior to treatment and the body weight recorded. Each female was examined daily for vaginal patency on pnd 22 through 24. Females were necropsied six hours after the last dose on pnd 24. Body weight and paired ovary and uterus weight (wet) was determined. Blood was collected via cardiac puncture for determination of serum estradiol, thyroxine (T4), and thyroid-stimulating hormones (TSH). The uterus was evaluated histopathologically.

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The four remaining females from each litter were divided into dosed (n=2) and nondosed (n=2) groups per litter, and assigned to the pubertal cohort on pnd 21. AGD was measured. Methoxychlor or vehicle was administered via gavage from pnd 22-42, based on the most recent body weights for the dosed pubertal group. The dosed and undosed pubertal groups were weighed every other day. Clinical observations of F1 females assigned to the pubertal cohort were documented at least twice daily (at dosing and one to two hours postdosing) throughout the dosing period. Beginning on pnd 22, each F1 study female was examined daily for vaginal patency. Body weight at acquisition of complete vaginal patency was recorded. Beginning on the day of vaginal opening and continuing until pnd 42, daily vaginal smears were obtained from each F1 female, stained with Toluidine Blue, and evaluated under low- and high-power light microscopy for the presence of leukocytes, nucleated epithelial cells, or cornified epithelial cells to determine the age at the first complete vaginal cycle and/or any effects on estrous cyclicity. On pnd 42, all F1 females were shaved on the ventrum and examined for areolae/nipples at necropsy.

The four males from each litter were divided into dosed (n=2) and nondosed (n=2) groups per litter on pnd 21. At this time, AGD was measured. Methoxychlor or vehicle control was administered via gavage from pnd 23 to pnd 70+, based on the most recent body weights for the dosed pubertal group. The dosed and undosed pubertal groups were weighed every other day. Clinical observations of F1 males assigned to the pubertal cohort were documented at least twice daily throughout the dosing period (pnd 23 through pnd 70+). All F1 males were weighed in the morning on pnd 21 and every other day in the morning during the dosing period for adjustment of dosing volume, based on the most recent body weight. Beginning on pnd 23, each F1 study male was examined daily for preputial separation. Body weight at complete preputial separation was recorded.

This study showed:

<u>F1 preweanling observations (exposure to methoxychlor *in utero* and during lactation at doses up to 100 mg/kg/day)</u>:

- No significant dose-related effects on live litter size or absolute or adjusted AGD on pnd 0 or pnd 21 in male or female offspring.
- Minimal to no general toxicity.
- Neonatal morbidity/death primarily at the mid and high dose groups, that was, to a large extent, secondary to the morbidity of several dams in these groups.

<u>F1 female uterotrophic cohort (exposure to methoxychlor at doses up to 100 mg/kg/day during gestation, lactation, and after weaning on pnd 22-24)</u>:

- No persistent effect of treatment post weaning body weight (to pnd 24).

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- No acquisition of complete vaginal patency, although pinhole openings were observed in a few females at both the mid and high dose.

- Treatment effects for both absolute and adjusted paired ovarian weight (decrease) at the mid and high dose.

- No treatment effect on wet uterine weight (absolute or adjusted), or uterine histopathology. Comparison of the mean uterine weight for the control females in this study with historical control values for F1 female weanling uterine weight in this laboratory suggest that the control values in the present study are slightly higher than expected, suggesting the presence of endogenous estrogen. This may have masked the effect of the methoxychlor on uterine development.

F1 undosed female pubertal cohort (exposure to methoxychlor at doses up to 100 mg/kg/day during gestation and lactation; allowed to mature to pnd 42 without additional treatment after pnd 20):

- Significantly accelerated vaginal opening (absolute and adjusted for body weight on pnd 28), and younger age at first estrus at both the mid and high dose.

- Significant effects on the number of days from vaginal opening to first estrus or the end of the first cycle, average day of the start of the first cycle, and prolonged estrous.

- Decreased UVD and paired ovary weight (absolute, or adjusted for necropsy or pnd 21 weight).

- Increased uterine weight (absolute or adjusted; with or without fluid).

- Increased circulating T4, T3, and TSH levels.

F1 dosed female pubertal cohort (exposure to methoxychlor at doses up to 100 mg/kg/day during gestation and lactation, and continuing from pnd 22 to pnd 42):

- Significantly accelerated vaginal opening (absolute and adjusted for body weight on pnd 28), decreased age at first estrus, start, or end of the first cycle at all three doses of methoxychlor.

- Significantly prolonged period for the number of days from vaginal opening to the start or end of the first cycle at the high dose.

- Increase in the percent females with prolonged estrus at the mid and high dose.

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- Decreased UVD at both the mid and the high dose.
- Decreased paired ovary weight (absolute, or adjusted for necropsy or pnd 21 weight) at both the mid and the high dose.
- No effect on uterine weight (absolute or adjusted; with or without fluid).
- No effect on circulating T4, T3, and TSH levels.
- Treatment-related histopathological changes in both the ovaries and uterus at the mid and high dose.
- No treatment-related histopathology for the thyroid.

F1 undosed male pubertal cohort (exposure to methoxychlor at doses up to 100 mg/kg/day during gestation and lactation; allowed to mature to pnd 70+ without additional treatment after pnd 20);

- Slightly delayed preputial separation (absolute or adjusted for body weight on pnd 40) at the mid dose.
- Decreased absolute and adjusted (pnd 21 body weight) paired testis weight at the high dose, with a decreasing trend for paired adjusted (necropsy weight) testis weight.
- No effect or no consistent effect on the absolute or adjusted weight of other male reproductive organs.
- Increased spermatid head concentration and efficiency of daily sperm production at the high dose.
- No effect on circulating thyroid hormone levels.
- No treatment-related histopathology in the testis, epididymis, or thyroid.

F1 dosed male pubertal cohort (exposure to methoxychlor at doses up to 100 mg/kg/day during gestation and lactation, and then from pnd 22 to 70+; allowed to mature to pnd 70+;

- Delayed preputial separation (absolute or adjusted for body weight on pnd 40) at the mid and high dose.
- Reduced absolute and adjusted (pnd 21 body weight) weights for the male reproductive organs at either the mid and high dose, or all three doses.

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- Decreased epididymal sperm concentration and daily sperm production at the high dose.

- Increased circulating T4 levels at the mid dose, but no effect for T3 and TSH.

- No treatment-related histopathology for the testis, epididymis, or thyroid.

In conclusion, this study proves that the protocol can be technically conducted as written. In addition, most of the effects from exposure to methoxychlor were as expected. The exception was the uterotrophic portion of the study. No effect was seen on uterine weight or histopathology after treatment from pnd 22 to 24. If included in the protocol, the uterotrophic portion would need to be fine-tuned to ensure that a reliable response could be obtained. However, RTI, as the lead laboratory for this assay for the EDSP, is suggesting that if this protocol is implemented, the study design may be too complex for Tier 1. If used as a Tier 1, it should be simplified. Alternatively, it may be considered a Tier 2 test assay, preferably in place of the *in vitro* steroidogenesis and placental aromatase assays and the *in vivo* male Hershberger assay, the uterotrophic female assay, and either or both pubertal assays.

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OBJECTIVES

The objective of this assay was to detect reproductive and developmental effects in male and female rat offspring mediated by alterations in the estrogen, androgen, and thyroid (EAT) signaling pathways, resulting from exposure of the dam during gestation and lactation or from direct exposure of the offspring from weaning through puberty. It may be used to: (1) replace a number of protocols recommended by Endocrine Disruptor Tier I screening protocol (EDSTAC, 1998) for the Tier 1 screening battery, (2) serve as a follow-up test for certain chemicals for which a full multigeneration test had been run prior to the upgrading of the protocol in 1998, and/or (3) augment the current developmental toxicity testing protocol. The endpoints were selected for their potential to respond to EAT-induced alterations of development and include those that are both sensitive to disruption and can be easily detected in the offspring. The proposed protocol was identified by the U.S. Environmental Protection Agency (EPA) as the "*In Utero*/Lactational Exposure Screening Protocol" and was assigned for development under the Endocrine Disruptor Screening Program (EDSP).

As part of the validation process, a prevalidation study plan was developed to address the following issues:

- The study design
- The endpoints of interest in the study
- The protocol issues needing resolution
- Recommended test substances and doses to be used during the prevalidation process, and justification for each recommendation
- The detailed study protocol.

1.0 THE STUDY DESIGN

The study design chosen for the *In Utero*/Lactational Exposure Screening Assay contains elements of assays originally proposed by Drs. L. Earl Gray (EPA), Rochelle W. Tyl (RTI), and Robert A. Kavlock (EPA), as modified by Dr. Gray which is partly described in a Detailed Review Paper (George and Tyl, 2001) (Figure 1). The elements of the study design and endpoints of interest are presented below, with an explanation of their biological importance and justification for inclusion in the protocol.

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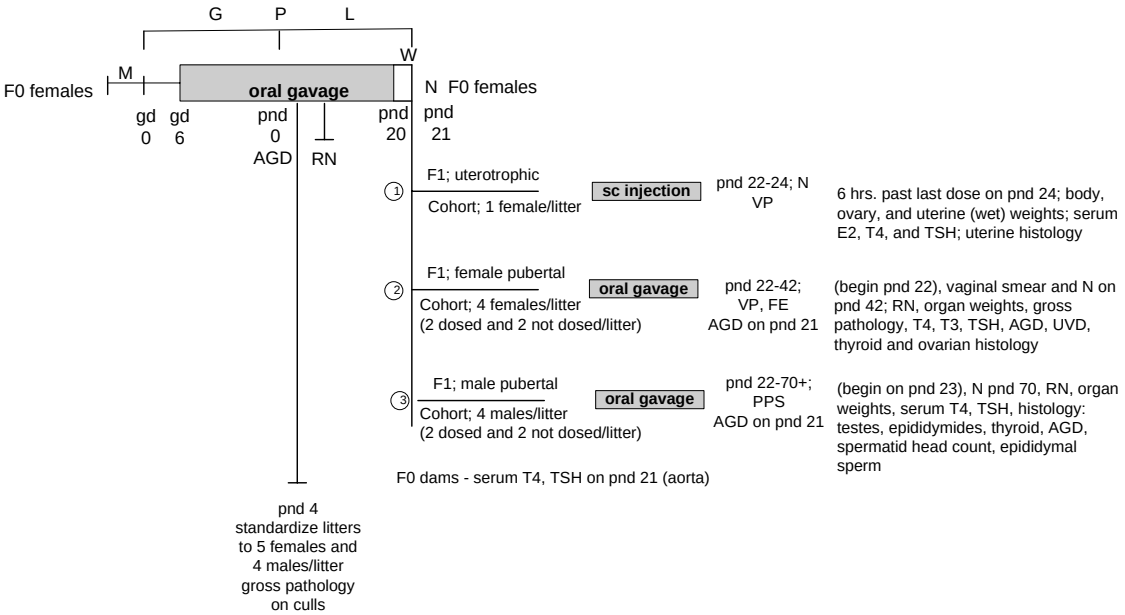

Key:

M = mating	RN = examination for retained nipples in F1 males on pnd 11-13
G = gestation	W = wean (pnd 21)
gd = gestational day	N = necropsy
P = parturition	VP = acquisition of vaginal patency (females)
pnd = postnatal day	PPS = acquisition of preputial separation (males)
AGD = anogenital distance	FE = first estrus
L = lactation	UVD = urethral vaginal distance

direct exposure to F0 dams and postweanling F1 offspring

Figure 1. Study Design for Utero/Lactational Exposure Assay.

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2.0 SPECIES/STRAIN OF TEST ANIMAL

The Sprague-Dawley rat was chosen for the test animal in the prevalidation phase for the following reasons:

- High fertility
- High fecundity
- Low incidence of spontaneous male reproductive tract lesions
- Large historical control data base for reproductive and developmental indices
- Larger pup size compared to other rat strains
- Sufficient litter size (~ 12 pups), compared to larger litters produced by other CD substrains (18-20 pups; unsupportable by the dam) or smaller litters produced by other strains (e.g., F344)

The Charles River CD® rat has been the subject of choice on reproductive and developmental toxicology contracts at RTI since 1976, and has been used for other reproductive toxicology studies with this test material. Large historical data bases for reproductive performance and prevalence of spontaneous malformations in control rats are available from studies conducted at RTI (currently based on over 300 control litters) as well as from the supplier (Charles River, 1988). This strain of rats has been proven to have robust fertility and fecundity, and did not present any unusual endocrinologic patterns. This study did not unnecessarily duplicate any previous study.

3.0 DOSING PERIOD

The maternal dosing period (gd 6 to pnd 20) provided exposure of the offspring to the test compound for the entire period of organogenesis (*in utero*) and preweaning development (lactation). During this dosing period, exposure of the offspring to the test compound occurred transplacentally or through the dam's milk. In addition, primary and secondary sex determinations and the thyroid, both relevant to the objective of this protocol, were developing in the rat pups during this period. Dosing of the F1 animal from weaning through pnd 42 (females) or pnd 70 (males directly exposed the animals during the period of the development of late secondary and tertiary sex characteristics.

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4.0 DEVELOPMENT OF THE REPRODUCTIVE SYSTEM AND THE THYROID

4.1 Sexual Differentiation

Primary sex determination concerns the determination of the gonads. In mammals, this determination is strictly chromosomal (established at fertilization). Secondary sex determination concerns the body phenotype outside the gonads, including accessory sex organs, sex-specific size, musculature, and vocal cartilage (the latter termed tertiary sex characteristics). These secondary (and tertiary) sex characteristics are determined by endocrine hormones secreted from the gonads (Gilbert, 1997; Quigley et al., 1995). The sequences for male and female sexual development are presented graphically in Figure 2, and further described below.

4.1.1 Both Sexes

Conception to ~gd 13-14. Mammalian embryos of both sexes develop identically. Both sexes are endowed with an initial urogenital ridge which converts to bipotential primordial gonadal tissue, and two sets of internal genital ducts, i.e., the Wolffian (mesonephric from the second stage kidney anlagen) and Müllerian (paramesonephric) ducts, and undifferentiated external genitalia. The bipotential primordial gonadal tissue consists of the primordial germ cells, and three bipotential somatic cell lines (Swain and Lovell-Badge, 1999). The supporting cell line gives rise to Sertoli cells in the testes, or follicular cells in the ovary. Sex hormones are produced by the steroidogenic cell line that differentiates into Leydig cells in the male, or theca cells in the female. The connective cell line forms the rest of the organs as a whole. Differentiation of these cell lines is under the control of various transcription factors, which act to produce either male or female phenotypes.

4.1.2 Males

Gd 14+, testis development. Primary sex determination (not androgen-dependent) is triggered by the activation of the testis-determining factor, SRY. SRY is thought to trigger differentiation of the supporting cell line into Sertoli cells. SRY is also thought to somehow trigger the production of another factor, perhaps SOX9, which maintains the Sertoli cell after differentiation.

Gd 13-15, inhibitory pathways. Regression of the Müllerian ducts and thus repression of the development of female internal genitalia from the duct (i.e., oviducts [fallopian tubes], uterus, and upper vagina) is mediated by anti-Müllerian hormone (AMH), a glycoprotein hormone, secreted by the Sertoli cells in the seminiferous tubules of the testis (Quigley et al., 1995; Swain and Lovell-Badge, 1999).

Gd 13-15, stimulatory pathways. Require high levels of androgens and a functional androgen receptor (AR). Stabilization of the Wolffian duct system to prevent its involution and to induce differentiation of the Wolffian ducts into the epididymides, vas deferens, and seminal

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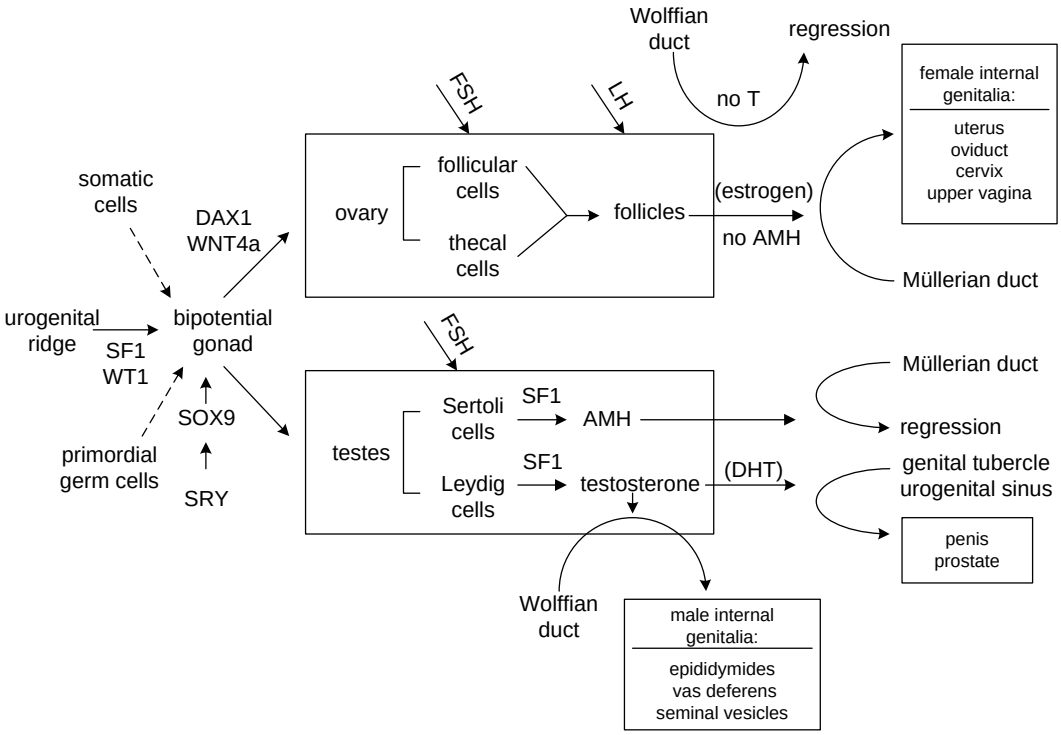
vesicles; induced by the action of testosterone itself, probably via a paracrine effect. The Müllerian ducts (characteristic of female development) regress as male sexual differentiation proceeds.

Gd 14-19. Testicular testosterone synthesis and secretion by fetal Leydig cells (located interstitially outside the seminiferous tubules within the testis). SRY is thought to downregulate another transcriptional factor, WNT-4a, to allow testosterone production in the male.



(figure modified from Gilbert, 1997, Chapter 20, Figure 20.2, per Swain and Lovell-Badge, 1999)

Figure 2. Sexual Differentiation in Mammals

Gd 14-19. Testicular testosterone synthesis and secretion by fetal Leydig cells (located interstitially outside the seminiferous tubules within the testis). SRY is thought to downregulate another transcriptional factor, WNT-4a, to allow testosterone production in the male.

Gd 17-20. Inhibition of the development of the breast primordia (Gilbert, 1997) regression of nipples in perinatal males by dihydrotestosterone (DHT, see below) produced in the fetal testis.

Gd 15-16. 5-alpha reductase first expressed, enabling conversion of testosterone to DHT.

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Gd 15+. Masculinization of external genitalia (T and AR dependent). DHT may act as signal amplifier for testosterone (Mahendroo et al., 2001).

Puberty. pnd 42[1]. The hypothalamic-pituitary-gonadal (hpg) axis begins functioning, leading to production and secretion of gonadotropin-releasing hormone (GnRH); stimulation of the pituitary by GnRH results in the production and release of the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH).

LH stimulates the interstitial cells of Leydig to trigger a burst of testosterone synthesis, inducing the formation of male secondary and tertiary sex characteristics and the onset of spermatogenesis.

FSH and prolactin (Prl) may up regulate the LH receptors in the Leydig cells to increase the response to LH stimulation. FSH stimulates the Sertoli cells (in the seminiferous tubules) to differentiate to become the "nurse cells" to the developing germ cells in the presence of high concentrations of testosterone.

4.1.3 Females

The cascade of molecular events that leads to the development of the female phenotypical genitalia is not yet as well defined as for the male. However, the steps appear to be parallel to those observed in the male.

Gd 14-19: The bipotential gonad, in the absence of SRY and AMH, and in the presence of products from other genes, including WNT-4a, WT-1, and DAX1 (Gilbert, 1997, p. 781; Swain and Lovell-Badge, 1999), follows the female pathway to make ovaries. Lacking AMH, the Müllerian duct remains intact and differentiates into the oviducts, uterus, cervix, and upper vagina (Parker and Schimmer, 1997; Sadovsky and Dorn, 2000). The Wolffian duct, deprived of testosterone, degenerates. Cells of the ovaries differentiate into follicular and thecal cells, which together synthesize estrogen and form follicles surrounding the female germ cells. Transcriptional factor DAX1 is thought to act in females as an antitestis substance.

Puberty, pnd 31[2]. The hpg axis plays a role, comparable to that of the male, in female puberty, whereby pituitary FSH stimulates the granulosa and thecal cells in the follicles of the ovary to trigger a burst of estrogen synthesis, and LH enhances receptivity of the follicles to estrogenic stimulation and triggers the continuation of oogenesis (no primary oocytes are formed postnatally) and the beginning of estrous cyclicity and ovulation.

[1] In control CD® (SD) rats in the authors' laboratory, the grand mean age at PPS is 41.9 days (based on 15 studies from 1996 to 2000).
[2] In control CD® (SD) rats in the authors' laboratory, the grand mean age at VP is 31.1 days (based on 15 studies from 1996 to 2000).

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4.2 Thyroid

Thyroid hormones are well known to play essential roles in vertebrate development (Dussault and Ruel, 1987; Porterfield and Hendrich, 1993; Porterfield and Stein, 1994; Timiras and Nzekwe, 1989). Experimental work focused on the effects of thyroid hormone on brain development in the neonatal rat supports the concept of a "critical period" during which thyroid hormone must be present to avoid irreversible damage (Timiras and Nzekwe, 1989). Though the duration of this critical period may be different for different thyroid hormone effects, the general view has developed that this is the period of maximal developmental sensitivity to thyroid hormone, and it occurs during the lactational period in the rat (Oppenheimer et al., 1994; Timiras and Nzekwe, 1989). The lactational period represents a stage of rapid expansion of the thyroid hormone receptors (Perez-Castillo et al., 1985) and an increase in the number of demonstrated effects of thyroid hormone on brain development.

5.0 SELECTED ENDPOINTS

5.1 In-Life Evaluations

Reproductive development involves both morphological and hormonal aspects, which operate together to result in correctly formed and responsive reproductive systems in both males and females. In mammals, gonadal origins begin early in embryonic development, prior to sexual differentiation (Schardein, 1999). Initial stages are the same for both male and female. Sexual differentiation and maturation are under hormonal control. Thus, both physical and hormonal indicators of reproductive development can be monitored to detect the presence of endocrine-disrupting activity.

AGD. AGD was measured on both male and female offspring at pnd 0, at weaning (pnd 21), and at necropsy (pnd 42 for female pubertal cohort; pnd 70+ for male pubertal cohort). The sex differences in AGD (measurement of distance from anus to genital papilla) at birth and beyond (male AGD is approximately twice as long as female AGD in rats and mice) are under androgen control, specifically DHT (Gray et al., 1998; Gray and Ostby, 1998) and do not appear to be affected by estrogens (Biegel et al., 1998a) but are affected by pup body weights (Ashby et al., 1997). Exposure to anti-androgens *in utero* results in shortened AGD in males, with no effects on female AGD (McIntyre et al., 2000; 2001; 2002). Exposure to androgens *in utero* results in increased AGD in females, but no effect on male AGD (Wolf et al., 2002). This parameter is very sensitive, although the biological significance and relevance of changes in AGD are unknown. Endocrine-mediated effects on AGD following *in utero* exposure have been shown to persist into adulthood. However, recent data suggest that although sensitive and easy to evaluate, this parameter may not be a reliable predictor of more serious morphological effects (McIntyre et al., 2001; 2002).

Retention of Areolae/Nipples. This was evaluated in males on pnd 12-13 and at necropsy (pnd 42/43 for female pubertal cohort; pnd 70+ for male pubertal cohort). Regression

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of nipples in male rats is DHT-mediated. Anti-testosterone effects *in utero* that promote nipple retention can persist into adulthood. This is a sensitive indicator of altered testosterone (T) and/or DHT levels (effects on synthesis, degradation, receptor binding, transcriptional activation, etc.). Male pups with retained nipples are more likely to exhibit reproductive system malformations, but the correlation is not perfect (i.e., some males with nipples exhibit no malformations, some males with no nipples do exhibit malformations; also see McIntyre et al., 2002). Retention of nipples is also a reasonable low-dose predictor of male reproductive malformations caused by perinatal exposures at similar or higher doses. In some instances, permanent nipples may qualify as a malformation (i.e., a permanent structural change that is rare in control animals (McIntyre et al., 2001).

Behavioral Assessments. Maternal and neonatal behaviors involving nesting and nursing are under the control of the endocrine system. Qualitative evaluation of these behaviors, as they affect viability and ability to thrive, provide another measure of possible endocrine disrupting activity of a test compound.

Puberty. Acquisition of puberty was determined in both females and males by a number of physical changes. For females, vaginal patency and age of first estrus was determined beginning on pnd 22 by means of daily examination and smears after vaginal opening. For males, preputial separation was monitored beginning on pnd 23. Statistically significant differences in age at acquisition of puberty may indicate endocrine-mediated effects, especially if the effects are different for the sexes (e.g., VP is delayed and PPS is accelerated or unchanged, VP is accelerated and PPS is delayed or unchanged, etc.; Chapin et al., 1999; Biegel et al., 1998a,b) and if the effects are profound (acceleration or delay of many days versus only a few days). However, acquisition of developmental landmarks is dependent on both age and weight (i.e., heavier animals acquire the landmark earlier, while lighter animals acquire the landmark later), but lighter animals do acquire the landmark (unless there is another cause for the delay) and, in many cases, acquire the landmark at a lighter weight than the heavier animals. This observation is consistent with the recognition by EPA (1996, p. 56295) that "body weight at puberty may provide a means to separate specific delays in puberty from those that are related to general delays in development." The significance (i.e., the consequence, if any) and "the biologic relevance of a change in these measures of a day or two is unknown" (EPA, 1996, p. 56295). Typically, pubertal delays of one to three days (in both sexes) are almost always accompanied by reduced body weights (e.g., Tyl et al., 1999, 2001, 2002). Since acquisition of puberty involves processes that, in part, become active after birth, exposure to putative endocrine disruptors during the postnatal period is likely to give a more complete indication of the effects of the compound. Extension of exposure into the postnatal period also provides the opportunity to affect endocrine-dependent processes that are maturational and do not result in frank malformations of the reproductive system, since malformations make evaluation of other ongoing processes problematic. Vaginal patency, first estrus, and preputial separation are discussed in more detail below:

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- ***Vaginal Patency in Females.*** In females, acquisition of puberty is indicated by vaginal opening or patency (VP). VP is dependent on 17ß-estradiol. In control CD® (SD) rats in the authors' laboratory, the grand mean age at VP is 31.1 days (based on 15 studies from 1996 to 2000). VP may be observed first as the appearance of a small "pin hole", but is typically recorded as acquired when vaginal opening is complete (with notation if a vaginal thread persists).

- ***Age of First Estrus in Females.*** Within a few days post-VP, the female exhibits her first estrus, so age at first estrus (absolute age and/or interval from VP to first estrus) is also useful. Late follicular growth of the first ovulatory cells is stimulated about the time of vaginal opening, although there is some variation in the initial release of oocytes. Following vaginal opening, daily vaginal smears are monitored to determine the age of first estrus or first vaginal cycle. Irregular estrous cycles are often seen in the immediate post-pubertal period (Goldman et al., 2000).

- ***Preputial Separation.*** Acquisition of puberty in males is indicated by preputial separation (PPS; balanopreputial separation) or separation of the foreskin of the penis from the glans. PPS is dependent on androgens (DHT induced apoptosis). PPS is a process that leads to the cleavage of the epithelium through cornification, forming the squamous lining of the prepuce of the penis (Stoker et al., 2000). As a sign of puberty and an essential prerequisite for further development of the ejaculatory process, PPS has been used as a reliable, noninvasive endpoint by which to monitor rodent pubertal development and perturbations of this process. This landmark of acquisition generally occurs during the peripubertal period (pnd 36-55 or 60; Goldman et al., 2000). In control CD® (SD) rats in the authors' laboratory, the grand mean age at PPS is 41.9 days (based on 15 studies from 1996 to 2000).

5.2 Organ Weights

Reproductive (including accessory sex organ weights). Reproductive organ weights were obtained at pnd 24 (female organs, uterotrophic cohort) and at necropsy (pnd 42 for female pubertal cohort; pnd 70+ for male pubertal cohort) and included: (a) ovaries and uterus for females, and (b) paired testes, epididymides (whole left and right separately), prostate (whole, dorsolateral and ventral lobes separately), seminal vesicles with coagulating glands, bulbourethral (Cowper's) glands, glans penis, and levator ani/bulbocavernosus (LABC) complex for males.

Thyroid. Thyroid hormones (triiodothyronine (T3) and T4) are necessary for normal growth, development, differentiation, and regulation in most organ systems (Goldman et al., 2000; Stoker et al., 2000). These changes would be evident in the weight of the thyroid gland, which was evaluated at necropsy for both males and females assigned to the pubertal cohorts.

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Systemic (liver, kidneys, etc). Systemic organ weight was obtained at necropsy in both sexes (pnd 42 for female pubertal cohort; pnd 70+ for male pubertal cohort), and included liver, kidneys, and adrenal glands for both males and females. Comparison of the effect of the test compound on these organ weights (absolute and relative) to effects on reproductive organ weights provided a more complete characterization of toxicity and suggested whether observed toxicity is more or less targeted to the endocrine system. In addition, since the adrenal glands are important endocrine organs and are a secondary source of steroid sex hormones, specifically T, alterations in the weight of these organs further characterized the toxicity of the compound.

Absolute and Relative to Body Weight. Organ weights (both reproductive and systemic) were presented as absolute and relative to terminal body weight. Relative weights correct for effects on body weights (i.e., systemic toxicity). An alteration in organ weights, in the presence of altered body weight, typically exhibits a significant change in absolute weight (usually reduced) and no change of and increased value for relative organ weight. These effects are most likely due to reduced body weight as the primary effect with secondary effects on organ weight.

5.3 Thyroid Hormones (TSH, T3, and T4)

There are a number of endpoints that are sensitive to thyroid hormone agonist/antagonists that may be of use in an *in utero*/lactational exposure study protocol. Growth, body weight, food consumption and efficiency, developmental abnormalities, perinatal mortality, testis size and daily sperm production, vaginal patency, and preputial separation, in addition to thyroid weight and histology, may reflect changes observed in T3 and T4 levels. Disruption of the feedback control of thyroid function may result in either a hypertrophic (goiter) or hypotrophic thyroid, depending on the mechanism of disruption. Evaluations of thyroid hormones were made for F0 females, F1 uterotrophic females, F1 undosed females and males, and F1 treated females and males.

6.0 PROTOCOL ISSUES THAT NEEDED RESOLUTION

The following issues were discussed during the development of the study protocol. The decision and accompanying rationale are provided:

- Weaning age for the litters. All litters were weaned on pnd 21, not on pnd 18. Pnd 21 is the most common day of weaning for rats, although weaning is sometimes done on a later postnatal day. The effects, if any, on premature weaning are unknown. RTI historical control data are all based on weaning on pnd 21. Also, no treatment of F1 offspring began before pnd 21, so it was deemed unnecessary, inappropriate, and would be a major confounder to wean the animals earlier than pnd 21.

- Fostering of pups. There was no fostering of pups from large litters into smaller litters on pnd 4. Since the dams were dosed since gd 6, the litter was the

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appropriate unit of analysis. Fostering pups into different litters (even within dose groups and even with the same birthdays) would have destroyed the ability to analyze the data by litters.

- Route of treatment administration for the uterotrophic cohort. The female uterotrophic cohort was exposed directly to methoxychlor by sc injection on pnd 22-24. The sc route was chosen in the EDSTAC and OECD uterotrophic protocols to: (1) detect weak estrogens, (2) detect those compounds where the parent compound is active and first-pass metabolism (in the liver from oral administration) renders them inactive, and (3) encompass organisms with varying metabolic capabilities (e.g., young rats, impaired animals, other vertebrates, and invertebrates).

- Sperm detection in the male pubertal cohort. Detection of sperm in the epididymides of F1 males on pnd 60, as originally planned, was problematic. At best, sperm is in the caput only, and not in the whole epididymis. The option of weighing, mincing, and evaluating the caput epididymis only was discussed. However, F1 males who had not yet achieved preputial separation (and therefore puberty) by pnd 60 would exhibit no sperm in the epididymis. This absence of sperm would not have been due to reduced sperm counts, per se, but to delays in puberty and in the onset of spermatogenesis. Therefore, evaluation of the male pubertal cohort on pnd 70+ instead of pnd 60, was discussed and agreed upon. Histopathological evaluation of the testes and epididymides was also recommended and agreed upon.

- Vaginal patency in the uterotrophic cohort. Examination of the F1 female uterotrophic cohort for acquisition of vaginal patency (beginning on pnd 22) was added since methoxychlor is known to accelerate puberty in offspring females, especially after developmental exposure.

- Testes descent in the male pubertal cohort. A less useful landmark of acquisition of puberty in males is testes descent (into the scrotal sacs from the abdominal cavity through the inguinal canal and ring), which occurs during lactation (pnd 15-20) and may be mediated by T and/or DHT. This parameter was not included in the current protocol, but it could be added in subsequent studies with little additional effort.

7.0 TEST SUBSTANCE AND DOSES FOR THE PREVALIDATION STUDY

7.1 Chemical Selection

The chemical selected for this first validation study of the *in utero*/lactational exposure screening protocol is methoxychlor. Methoxychlor is an organochlorine pesticide in use as a

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DDT substitute to control insects. It has known endocrine effects. The *in vivo* metabolite of methoxychlor, 2,2-bis(p-hydroxyphenol)-1,1,1-trichloroethane (HPTE), has selective agonist activity through the estrogen receptor (ER) alpha and antagonist activity through ER beta and the androgen receptor (AR) (e.g., Waters et al., 2000). Methoxychlor has been shown to inhibit androgen receptor-dependent transcriptional activity *in vitro* (Maness et al., 1998), so it also acts as an antiandrogen. In female mice and rats, methoxychlor is positive in the uterotrophic assay with ovariectomized adults or weanlings, causing increased uterine weights. It stimulates ER expression in the uteri of neonatal (days 1-4) and immature (days 10-14) mice after ip injection for four days of methoxychlor (Eroschenko et al., 1996). It also reduced the number of implants and newborns in a multigeneration study using dietary exposure (Aoyama et al., 2000). The day of vaginal opening was accelerated and body weight at acquisition was reduced by methoxychlor administered by ip injection to female rats on pnd 10-14 (Respess et al., 1999). In male mice and rats with *in utero* exposure, methoxychlor disrupted the morphology and growth of the developing testis (Cupp and Skinner, 2000). Perinatal and juvenile exposure to methoxychlor reduced testicular size and Sertoli cell numbers in adult rats (Johnson et al., 2000). Perinatal exposure to dams from gd 18 to parturition and directly to pups on pnd 1-5 resulted in increased lateral prostate lobe (but not ventral lobe) weight in adult male offspring (Stoker et al., 1999). Since methoxychlor (and its metabolite HPTE) has estrogenic, anti-estrogenic, and anti-androgenic properties, mediated through interactions with the ER" and β and the AR, because methoxychlor and HPTE can compete for binding to the ER (Cupp and Skinner, 2000), and because methoxychlor also affects circulating TSH and T4 levels (Gray et al., 1989), it was chosen as the first chemical for validation of this assay.

7.2 Dose Selection

Methoxychlor was dosed by oral gavage to F0 maternal animals from gd 6 through pnd 20 and by oral gavage to the F1 male and female pubertal cohorts (pnd 22-42 for females, pnd 22-70+ for males). It was also be administered by sc injection on pnd 22-24 to the F1 female uterotrophic cohort.

Based on a literature search and input from Dr. L. Earl Gray, Jr. (EPA NHEERL), the doses for the oral gavage dosing were 0, 25, 50, and 100 mg/kg/day methoxychlor in corn oil at a dosing volume of 5 ml/kg. The doses for the sc injection administration were set to the same levels (0, 25, 50, and 100 mg/kg/day) at the same dosing volume (5 ml/kg). For the uterotrophic cohort, with administration only on pnd 22-24, the F1 female pups were approximately 40-60 g body weight. Therefore, the volume administered by sc injection was approximately 0.2-0.3 ml/female. The justification for the doses and routes follows. The doses selected represent the mid range of gavage doses identified in the literature. Doses used and effects observed are discussed by sex, males first.

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7.2.1 Males

White et al. (2001) exposed Sprague-Dawley rats in a one-generation study design to methoxychlor in the diet at 10, 100, and 1000 ppm (with methoxychlor intakes calculated for this protocol of 0.7, 6.7, and 66.7 mg/kg/day), from gd 7 for F0 animals to pnd 77 for F1 offspring. The authors reported only increased splenic basal and stimulated lymphocyte proliferation response in F1 males (but not F1 females), especially following developmental exposure. Cupp and Skinner (2000, 2001) dosed pregnant rodents with methoxychlor at 50 mg/kg/day from gd 7 through gd 15. Embryonic gonads were collected on gd 16, pnd 4, and pnd 17 during testis development. Effects on the testis were observed only on pnd 17, with gross reduction in the testicular interstitium. They confirmed the methoxychlor effects with *in vitro* testis organ cultures, which exhibited inhibited/disrupted testicular cord formation and increased cell growth. Johnson et al. (2000) gavaged rat dams with methoxychlor at 0, 50, 50, or 150 mg/kg/day for the last week of gestation and the first week of lactation. Male pups were dosed directly from pnd 7 to 42. The offspring males in the two highest dose groups exhibited fewer testicular spermatids and reduced numbers of Sertoli cells as adults. Stoker et al. (1999) dosed rat dams by gavage to methoxychlor from gd 18 through pnd 5 at 50 mg/kg/day. Male offspring were examined on pnd 90. They exhibited increased prostate lateral lobe (but not ventral lobe) weight, with an increased incidence in the number and severity of inflammation in the lateral prostate. Chapin et al. (1996, 1997; Harris et al., 1996) exposed pregnant rats to methoxychlor at 0, 5, 50, and 150 mg/kg/day for the week before and after parturition (see above), with offspring pups dosed directly from pnd 7 to pnd 21 or pnd 42. In the male offspring, AGD was unaffected, but male preputial separation was delayed at 50 and 150 mg/kg/day by 8 and 34 days, respectively. Epididymal sperm counts were reduced at 150 mg/kg/day, and testes and epididymal weights were reduced at 50 and 150 mg/kg/day; seminal vesicle weights were reduced at all doses. The F1 animals (15/dose group) at adulthood were mated to untreated animals twice. Males at 150 mg/kg/day impregnated 3/30 untreated females versus 21/30 in controls; litter size was unaffected.

Anderson et al. (1994, 1995) evaluated methoxychlor in Long-Evans hooded rats under an alternative reproduction test (ART) protocol. It was administered by gavage at 0, 50, or 200 mg/kg/day to F0 males and females, starting at three weeks of age and continuing for 14 weeks in males or 18 weeks in females through gestation and lactation. For the F0 males as adults, ejaculated sperm counts, caudal epididymal sperm counts, and epididymal, ventral prostate, and seminal vesicle weights were all reduced at both doses. Methoxychlor suppressed both GnRH and hCG-stimulated testosterone levels; LH levels were significantly higher after GnRH challenge.

Gray et al. (1989) dosed rats at weaning through puberty, mating, and gestation to pnd 15 of lactation by gavage with methoxychlor at 0, 25, 50, 100, and 200 mg/kg/day. In the males, methoxychlor markedly reduced growth; seminal vesicle, cauda epididymis and pituitary weights; and cauda epididymal sperm content. Puberty was delayed at 100 and 200 mg/kg/day. Testicular spermatid measures were much less affected than cauda sperm measures. Testis

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weight and histology were slightly affected, and testicular sperm production and sperm morphology and motility were unaffected. Endocrine function of the testes and pituitary was altered by methoxychlor. Leydig cell testosterone production from hCG challenge was reduced, and pituitary levels of Prl, TSH, and FSH were altered (serum levels of Prl, FSH, and LH were unaffected). Serum TSH was reduced by 50% at 100 and 200 mg/kg/day, while pituitary levels were increased. In spite of these effects on males, the fertility of the treated males, mated with untreated females, was unaffected.

Gray et al. (1999) dosed weanling male Long-Evans hooded rats by gavage with methoxychlor at 0, 200, 300, or 400 mg/kg/day for ten months. The treated males were then mated to untreated females. Methoxychlor delayed puberty by as much as ten weeks at the top dose, and reduced fertility and copulatory plug formation in a dose-related manner at the initial mating. During mating, treated males exhibited shorter latencies to mount and ejaculate versus control males (with the number of intromissions prior to ejaculation unaffected), indicating that methoxychlor enhanced male arousal. Most methoxychlor-treated males mated, but time to pregnancy was lengthened. Very low sperm counts were associated with infertility, while prolonged delays in puberty were associated with reduced fecundity. Methoxychlor at 200-400 mg/kg/day did not mimic chronic effects of exposure to 17$-estradiol on testicular or pituitary hormone levels. Methoxychlor affected the CNS, epididymal sperm numbers, and accessory sex organs without affecting the secretion of LH, Prl, or testosterone. Therefore, methoxychlor did not alter pituitary endocrine function in either an estrogenic or anti-androgenic manner.

Goldman et al. (1986) investigated the effects of methoxychlor on the pituitary and hypothalamic components of the male rat reproductive system at dose levels that did not affect the testis. Male Long-Evans rats were gavaged daily with methoxychlor at 0, 25, or 50 mg/kg/day, starting at 21 days of age for eight weeks. There were no effects on serum LH, FSH, or Prl levels, and no effects on pituitary concentrations of LH or FSH. Pituitary prolactin was elevated at both doses (and pituitary fragments *in vitro* released more prolactin than control fragments). The authors concluded that the reproductive effects of methoxychlor may be mediated, at least in part, through early increased prolactin concentration and release, which in turn affects hypothalamic levels of GnRH and subsequent pituitary and gonadal adverse responses.

When methoxychlor was administered by oral gavage to male rats at 70 days and to female rats at 14 days at 0, 100, or 200 mg/kg/day, methoxychlor inhibited spermatogenesis, with degenerative fatty changes in the Sertoli cells. Degeneration changes in spermatogonia and spermatocytes were also observed, with some seminiferous tubules devoid of all cellular elements except spermatogonia. The epithelium of the ductus epididymis also exhibited cytoplasmic vacuolation and distention of the lumen (Bal, 1984).

Sar et al. (2001) exposed pregnant SD rats to methoxychlor in the diet at 800 ppm (approximately 53 mg/kg/day). Inguinal mammary glands from F1 male offspring exhibited

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greater total glandular area and increased numbers of branch points, lateral buds, and terminal end buds than controls (F1 female offspring mammary glands were unaffected).

Welshons et al. (1999) have reported that fetal exposure (gd 11-17) of very low doses of methoxychlor (20 and 2000 g/kg) result in increased prostate weight in adult male offspring.

Therefore, the doses selected should result in effects on the male testis and accessory sex organs, in delay in preputial separation, effects on testicular spermatid and epididymal sperm counts, and serum hormone levels, including effects on TSH from the pituitary and T4 from the thyroid.

7.2.2 Females

The effects of methoxychlor on female reproduction have been more extensively researched and reported. Exposure of methoxychlor at 0, 10, 100, or 1000 ppm in the diet (0, 0.7, 6.7, or 66.7 mg/kg/day, respectively) to F0 SD rats did not produce increased splenic lymphocyte proliferation under either basal or stimulated conditions in F1 females (F1 males did respond with increased proliferation) (White et al., 2001). When Sar et al. (2001) exposed pregnant SD rats to 800 ppm methoxychlor in the diet (approximately 53 mg/kg/day), there was no effect on F1 female offspring inguinal mammary glands when evaluated for total glandular area and number of branch points, lateral buds, and terminal end buds (inguinal mammary glands for F1 male offspring were affected), but uterus weight and VO were affected.

Both rats and mice (either ovariectomized adult or intact immature females) respond to short-term daily dosing of methoxychlor by increased uterine weights (Aoyama et al., 2000 and Respess et al., 1999 in rats; Eroschenko et al., 1997 and Eroschenko et al., 2000 in mice). Female SD pups were administered methoxychlor on pnd 10-14 by ip injection of 0, 0.3, 3, or 300 mg/kg/day. Pups were sacrificed on pnd 15, 23, 31, and 70. Day of vaginal opening was accelerated by four days, and body weight at acquisition was reduced (by 25 g) at 300 mg/kg/day. Ovarian and uterine weights were increased at 300 mg/kg/day on pnd 15 (Respess et al., 1999).

One-day-old female mice (five to eight/group) were administered methoxychlor by ip injection for 14 days at 0.1, 0.5, or 1.0 mg methoxychlor (corresponding to 14-71, 68-357, or 135-714 mg/kg/day, respectively). Three months later, the females were paired with proven breeder, untreated males and checked daily for vaginal copulation plugs. Maternal females were necropsied 18 days after insemination. All mice from the three methoxychlor groups mated, with dose-related, decreased numbers of pregnant animals on gd 18. The mean number of live fetuses/litter was reduced at 0.5 and 1.0 mg methoxychlor. Ovarian corpora lutea were reduced only at 1.0 mg methoxychlor. No effects were observed at 0.1 mg methoxychlor. The authors concluded that methoxychlor did not affect mating but did affect initiation and/or maintenance of pregnancy. Therefore, the neonatal exposure to methoxychlor may affect the hypothalamic-pituitary-ovarian axis as well as the uterine environment (Swartz and Eroschenko, 1998).

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Methoxychlor was administered to pregnant mice on day 1, 2, 3, or 4 of pregnancy at 400 or 800 g/g body weight (400 or 800 mg/kg). At 400 mg/kg on day 1 or 2, methoxychlor-induced delays in implantation. At 800 mg/kg/day on day 1 or 2, only 50% of the females exhibited implanted conceptuses, and the number of embryos/female was significantly reduced. Administration of lower doses of methoxychlor or at later times did not affect implantation. However, embryonic development and transport were delayed at 400 and 800 mg/kg/day, administered on days 3 or 4. Reciprocal embryo transfers with embryos from methoxychlor-treated dams (800 mg/kg on day 1), transferred into untreated females, resulted in no implantations (control donor embryos exhibited a 79% implantation rate). The authors concluded that methoxychlor acts as an estrogen agonist in the uterus and oviduct but acts as an antiestrogen in the ovary. Methoxychlor also affects normal preimplantation embryonic development (Hall et al., 1997). Swartz and Vial (1996) have also reported that exposure to methoxychlor early in pregnancy disrupts implantation.

Cummings and Perreault (1990) also reported that methoxychlor administered by gavage to rats on days 1-3 of pregnancy (sperm positive = day 0) at 0, 100, 200, or 500 mg/kg/day resulted in accelerated embryo transport from the oviducts into the uterus on days 2 and 3 at 200 and 500 mg/kg/day. The top dose also reduced the total number of embryos recovered on the third day, 100 mg/kg/day also accelerated embryo transport, and 200 mg/kg/day reduced the number of total embryos recovered. This acceleration of embryonic transport appears to be the primary cause of methoxychlor-induced preimplantation embryonic loss when exposure to methoxychlor occurs after fertilization.

Gavage dosing of dams from gd 14 to pnd 7 (Chapin et al., 1996, 1997; Harris et al., 1996) to methoxychlor at 0, 5, 50, and 150 mg/kg/day resulted in dose-dependent amounts of methoxychlor and metabolites in milk and plasma of both dams and pups. Lactating mice were administered methoxychlor by ip injection for 14 days (pnd 1-14) at 0, 1.0, 2.0, or 5.0 mg of technical grade methoxychlor. At pnd 15, suckling female pups were necropsied. Stimulatory changes in the vagina and uterine horns indicated that methoxychlor was excreted in milk and remained biologically active in the suckling mice. Higher methoxychlor doses also caused “cellular atypia” in the uterine horns (Appel and Eroschenko, 1992).

Sexually mature CD-1 virgin female mice were administered technical grade methoxychlor by oral gavage at 0, 1.25, 2.5, or 5.0 mg for five days/week for two or four weeks (Martinez and Swartz, 1991) or to just 50 mg for five days/week for four weeks (Martinez and Swartz, 1992). Twenty-four hours after the last dose, the females were necropsied. Methoxychlor caused dose-dependent, persistent vaginal estrus and reduced ovarian weights. Ovaries from females at 2.5 and 5.0 mg exhibited an increased number of atretic large follicles (Martinez and Swartz, 1991) and increased lipid accumulation in interstitial and thecal cells at 5.0 mg methoxychlor (Martinez and Swartz, 1992). The authors concluded that methoxychlor appeared to mimic estrogen-induced effects on the female reproductive system, and that the exposed ovarian cells appeared to be unable to synthesize and secrete steroids.

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Mouse neonates were administered 14 daily ip injections of 0, 0.05, 0.1, 0.5, or 1.0 mg methoxychlor. Exposure to 0.5 or 1.0 mg Methoxychlor increased reproductive tract weights three-fold due to excessive fluid accumulation, induced vaginal cornification, and accelerated vaginal opening by ten days (similar to 10 :g 17$-estradiol). The surface alterations in the vagina and uterus induced by methoxychlor (cornified cells without complex surface microridges, uterine cells with dense microvilli growth, atypical morphology and separation) were different than those induced by estradiol (Eroschenko, 1991).

Cummings and Laskey (1992, 1993) administered methoxychlor to female rats at a range of doses during days 1-8 of pregnancy; the females were terminated on day 9. Ovaries were removed and incubated. Incubation medium and serum from the rats were analyzed for progesterone, estradiol, and testosterone ex vivo. *In vivo* methoxychlor treatment reduced serum progesterone but had no effect on ovarian secretion of progesterone *in vitro*. Conversely, methoxychlor had no effect on serum estradiol levels (testosterone was undetectable in serum) but induced a reduction in the rates of ovarian estradiol and testosterone secretion. Cummings and Gray (1989) have also shown that methoxychlor blocks pregnancy in female rats in a dose- and time-dependent pattern. Exposure on gd 1-3 (preimplantation) resulted in decreased implantations and uterine weight, while exposures on gd 4-8 (peri-implantation) increased resorptions to 100%, decreased uterine weight, and reduced serum progesterone without altering the number of implantations, ovarian weight, or corpora lutea (effect levels for both dosing regimens were >200-500 mg/kg/day). However, Cummings and Gray (1987) reported that methoxychlor affects the decidual cell response of the uterus but not other progestational parameters in the female rat.

Immature female rats were administered methoxychlor (or other compounds) by oral gavage at 250 mg/kg 24 hours prior to evaluation of uterine peroxidase activity (Cummings and Metcalf, 1994). Methoxychlor alone increased uterine peroxide activity by increasing RNA and protein synthesis, as did estradiol alone. Co-administration of progesterone or tamoxifen blocked this stimulation induced by both methoxychlor and estradiol. The same authors exposed immature female rats to methoxychlor (500 mg/kg) or estradiol (E2; 10 :g/rat), and uteri were evaluated for the presence of estrogen-induced protein (IP), also known as creatine kinase (Cummings and Metcalf, 1995a). Both methoxychlor and E2 stimulated IP. The induction of IP by methoxychlor was time- and dose-dependent. This induction by methoxychlor or E2 was blocked by actinomycin D (which blocks DNA-dependent RNA synthesis) or cycloheximide (which inhibits pattern synthesis), indicating the induction requires RNA and protein synthesis. Progesterone did not block the induction of IP by either E2 or methoxychlor. In fact, Cummings (1997) has proposed methoxychlor as a model for environmental estrogens. Interestingly, methoxychlor and E2 do not exhibit additivity or synergism in the reproductive tract of ovariectomized mice (Eroschenko et al., 2000).

Neonatal female mice received 14 days ip injections of 0, 0.05, 0.1, 0.5, or 1.0 mg (approximately 0, 7-35, 14-71, 68-357, or 135-714 mg/kg/day) of technical methoxychlor. At 3, 6, and 12 months, vaginal smears were collected and ovaries were examined (E2 at 10.0 :g, ip,

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was used as the positive control). All methoxychlor doses (and E2) increased the duration of vaginal cornification. Methoxychlor at 0.5 and 1.0 mg and E2 induced ovarian atrophy, relative ovarian weight depression, and depletion of corpora lutea. However, methoxychlor doses of 0.05 or 0.1 mg produced opposite effects: ovaries remained heavy, large, and filled with corpora lutea. At all methoxychlor doses, except 1.0 mg, follicular cysts were present. The authors concluded that the stimulatory effects of methoxychlor at low doses and the inhibiting effects of at high doses mimicked the effects of E2 at low and high doses and were probably due to alterations of the hypothalamic-hypophyseal (anterior pituitary) function (Eroschenko et al., 1995). Prenatal exposure to low doses (0.01 or 10 mg/kg) of methoxychlor in mice also alters the uterine response to estrogen as adults (Howdeshell et al., 1999).

Methoxychlor also affects endometriosis in rats. Endometriosis was surgically induced in sixty female rats on pnd 0. On pnd 21, all rats were ovariectomized and the size of fully-developed endometriotic implants measured. Also starting on pnd 21, these rats were treated daily for three weeks with vehicle; estrone, 1 microgram/rat, E; progesterone, 2 mg/rat, P; E + P, 1 microgram + 2mg; methoxychlor, 250 mg/kg; or methoxychlor + P, 250 mg/kg " 2 mg/rat. On day 42, the rats were terminated and the size of the endometriotic implants remeasured. Ovariectomy plus treatment altered the growth of endometriosis. Progesterone or vehicle produced full regression. Both E2 and methoxychlor increased the size of the endometriotic implants; exposure to methoxychlor or E2 + progesterone did not alter the growth (Cummings and Metcalf, 1995b).

Chapin et al. (1996, 1997; Harris et al., 1996; Johnson et al., 2000) dosed F0 maternal rats with methoxychlor by gavage from gd 14 to pnd 7 (starting one week before and ending one week after parturition) at 0, 5, 50, or 150 mg/kg/day. F1 offspring were directly dosed at the same dose levels as their dams from pnd 7 to pnd 21 (weaning) or to pnd 42. In the female offspring, AGD was unaffected, but vaginal opening was accelerated in all groups. Adult F1 female estrous cyclicity was disrupted at 50 and 150 mg/kg/day. Females in these groups also exhibited reduced rates of pregnancy and delivery. Uterine weights, corrected for pregnancy, were reduced in all treated pregnant females. All groups of treated females exhibited uterine dysplasia and less mammary gland alveolar development. Estrous levels of FSH were lower in all groups, and estrous progesterone levels were lower at 50 and 150 mg/kg/day, attributed to fewer corpora lutea secondary to ovulation defects. The author concluded that 5 mg/kg/day is not a NOEL or a NOAEL, and that effects on female puberty, ovarian weights, uterine weights, and female hormone data imply that the sites of methoxychlor action are both central and peripheral.

Shimizu et al. (2000) evaluated methoxychlor in teratogenicity studies in rats (Jcl:SD) and rabbits (Kbl:JW). Rats were dosed by gavage on gd 6 through 19 at 0, 1, 50, or 150 mg/kg/day, and rabbits were dosed by gavage on gd 6 through 27 at 0, 1, 15, or 45 mg/kg/day. At the two highest dose groups in both species, there was decreased maternal body weight gains and feed consumption during the dosing period. At 150 mg/kg/day in rats, gravid uterine weight was reduced, and resorptions and fetal deaths were increased, resulting in decreased number of

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live fetuses. Fetal body weights were reduced, but AGD was unaffected at 150 mg/kg/day; there were no treatment-related fetal rat abnormalities at any dose. In rabbit fetuses, fetal body weights were reduced at 45 mg/kg/day. Rabbit fetuses in the mid and high dose groups exhibited increased incidences of 13th rib pairs and of 27 presacral vertebrae (both designated as fetal skeletal variations in the presence of maternal toxicity). Therefore, methoxychlor was not teratogenic in either species but did result in *in utero* deaths at 150 mg/kg/day in rats.

It is clear that 150 mg/kg/day is too high, resulting in *in utero* deaths when administered to the dams starting on gd 6 (Shimizu et al., 2000) and as planned in this protocol, although it is well tolerated in dams and perinatal offspring when administered starting on pnd 14 (Chapin et al., 1996, 1997; Harris et al., 1996; Johnson et al., 2000). Therefore, the top dose for this study will be 100 mg/kg/day, an effective dose (Gray et al., 1989). The low dose chosen for this study will be 25 mg/kg/day, which resulted in demonstrable effects by Gray et al. (1989). The mid dose chosen, 50 mg/kg/day, has also been shown to produce adverse effects in the offspring (Gray et al., 1989; Goldman et al., 1986; Anderson et al., 1994, 1995; Johnson et al., 2000).

8.0 MATERIALS AND METHODS

8.1 Test Materials and Dose Formulations

Methoxychlor (CAS No. 72-43-5) was procured by the sponsor from Sigma, Inc. (Lot No. 49H1328). The chemical purity of the test compound determined by the manufacturer was 95.2%. GC-FID purity analysis by Battelle-Sequim indicated a purity of 89.7% [Chemistry Report for WA 2-23, Methoxychlor in Mazola Corn Oil, Battelle Marine Sciences Laboratory, final report November 17, 2005, Appendix III under signature cover]. However, the 95.2% purity provided by the manufacturer was used to adjust the weight of the methoxychlor during formulation calculations. At the request of the sponsor, Mazola® corn oil (expiration dates 6/12/03, 1/04/04, and 4/24/04) was purchased by Battelle-Sequim from retail outlets. Although the use of stripped corn oil (stripped of estrogenic compounds) as the vehicle was discussed, it was decided that regular corn oil would be used. Peroxide determination of the corn oil was less than 3 meq/kg, and was acceptable for use. The corn oil was stored frozen. Estrogen determinations were not made for the corn oil.

Dose formulations were mixed in corn oil for administration at 5 ml/kg. Stability analysis of dose formulations of methoxychlor in corn oil (5, 10, and 20 mg/ml) indicated that the formulations were stable for three weeks at 4°C. Formulations were stored at refrigerated temperatures, and were brought up to room temperature prior to administration. The formulations were stirred constantly throughout the time they were brought to room temperature, and during dosing. The formulations were used when they were visually homogeneous. Formulations assayed (triplicate average) between 87 and 108% of the target concentration (Table 1). The formulations used for subcutaneous injection for the uterotrophic portion of the study were mixed in the same corn oil as the gavage formulations (i.e., not sterilized). Sterilization of the corn oil was not deemed necessary since the dosing period (pnd 22-24) was so short.

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During the course of study, the mid and high doses formulated by the Battelle repository were inadvertently mislabeled at RTI. The error was discovered early in the study and confirmed by the repository by reanalysis of samples returned to Battelle. Dosing continued, based on the color codes, and the data were entered and analyzed based on the correct doses. When direct dosing of the F1 weanlings began, we continued with the same process so as not to confuse the technicians, but also entered the data based on the correct doses. See Appendix V for a more complete discussion.

8.2 Animals and Husbandry

One hundred (100) nulliparous female outbred albino CD® (Sprague-Dawley) rats (Crl:CD®[SD] IGS BR) were received from Charles River Breeding Laboratories (Raleigh, NC) on December 30, 2002 (Text Table 1). The females were 70 days old on arrival.

Text Table 1. Study Schedule

Event	Dates
Receive 100 Females	December 30, 2002
Quarantine	December 30, 2002– January 5, 2003
gd 0	January 7–9, 2003
Dosing Begins (gd 6)	January 13, 2003
pnd 0	January 29–February 1, 2003
pnd 21	February 19-21, 2003
Dosing Female Uterotropic Cohort (pnd 22-24)	February 20 –25, 2003
Dosing Female Pubertal Cohort (pnd 22 to 41)	February 20–March 15, 2003
Dosing Male Pubertal Cohort (pnd 22 to 70+)	February 20, 2003–April 18, 2003
Necropsy Female Uterotropic (pnd 24)	February 22–25, 2003
Necropsy Female Pubertal (pnd 42)	March 12–15 2003
Necropsy Male Pubertal (pnd 70+)	April 14–18, 2003
Hormone Data Complete	December 2, 2005
Histopathology Complete	December 2, 2005
Statistical Analysis of Study Data Complete	December 2, 2005
Draft Final Report to EPA	October 31, 2003
Approved Final Report to EPA	December 2, 2005

TBD = to be determined.

The animals were quarantined for one week, during which time they were examined by a veterinarian. Representative animals were subjected to fecal examination and serum viral antibody analysis. For serum viral antibody analysis, within one day after receipt, five female rats were arbitrarily chosen from the shipment of animals, sacrificed, and blood collected for assessment of viral antibody status. Heat-inactivated serum was sent to BioReliance (Rockville, MD) for their Level 1 Rat Antibody Screen. The viral screen consisted of evaluation for the

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presence of antibodies against the following: Toolan H-1 virus (H-1), Sendai virus, pneumonia virus of mice (PVM), rat coronavirus/sialodacryoadenitis (RCV/SDA), Kilham rat virus (KRV), CAR Bacillus (CARB), Mycoplasma pulmonis (M. Pul.) and parvo (PARVO). Results of the physical examination, serology, and parasitology were negative for signs of infectious disease. The animals were considered to be in good health and suitable for use in this study.

After mating was completed, four sperm-negative F0 female rats were randomly selected and designated as sentinels. They were singly housed in the study room(s) in polycarbonate solid-bottom cages with bedding and provided feed and water ad libitum (as described below for study animals). They were examined once daily by cage-side observation for morbidity or mortality at the same time as clinical observations or morbidity/mortality checks for the study animals. No sentinels exhibited any morbidity or mortality. At the time of necropsy of F0 females, the sentinels were terminated, blood samples collected, and serum samples prepared. Similarly, sentinels were chosen for the F1 female pubertal cohort, and for the F1 male pubertal cohort. F1 sentinels were terminated when their respective cohorts were terminated, and serum samples prepared for the viral antibody screen. All sentinel serum samples were submitted to BioReliance (Rockville, MD) for serological evaluation (see above). Analysis of serum (as described above) from sentinels sacrificed during the necropsy of the F0 female sentinels was negative, as was the analysis from serum taken from the F1 sentinel animals at necropsy.

F0 females were individually identified by eartag. One hundred ten (110) male rats of the same strain from the RTI breeding colony, originally from the same supplier, were used to generate timed-mated females. For breeding, individual females were placed in the home cage of singly-housed males (i.e., one male and one female). On the following morning and each morning thereafter, the females were examined for the presence of vaginal sperm or a vaginal copulation plug (Hafez, 1970). The day on which vaginal sperm or plugs were found was designated as gd 0. These females were presumed pregnant. The sperm-positive females (dams), designated the F0 generation, were housed individually or with their litters until scheduled sacrifice. Sperm-negative females were retained in the same male's cage and checked for sperm or vaginal plug on successive mornings until insemination occurred or the treatment groups were filled. When all treatment groups were filled, the remaining sperm-negative females were sacrificed by asphyxiation with CO2. The fate of all animals was fully documented.

A total of 15 timed-mated females per group were assigned to this study. Confirmed-mated females were assigned to treatment groups by stratified randomization for body weight on gd 0, so that mean body weight on gd 0 did not differ among treatment groups. Selected F1 weanlings were identified by eartag, and F1 pups prior to weaning were not uniquely identified. The method and numbers for identification were documented in the study records.

All adult animals were euthanized by CO2 asphyxiation. F1 pups culled on pnd 4 were sacrificed by decapitation. Records were kept documenting the fate of all animals received for the study.

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The experiment was carried out under standard laboratory conditions. The animals were individually housed during the quarantine period and upon the initiation of the treatment period in solid-bottom polycarbonate cages with stainless-steel wire lids (Laboratory Products, Rochelle Park, NJ) with Sani-Chip® cage litter (P.J. Murphy Forest Products Corp., Montville, NJ). F0 females were housed in monogamous breeding pairs during the mating period. Females were caged separately and individually once they were successfully mated (or at the end of the mating period). F0 females were housed with their F1 litters during lactation. Postwean, retained F1 males were housed singly until necropsy. All animals were housed in the RTI Animal Research Facility for the duration of the study. All animal rooms were on a 14:10 hour (light:dark) light cycle per day and were air-conditioned; temperature and relative humidity (RH) were continuously monitored, controlled, and recorded using an automatic system (Siebe/Barber-Colman Network 8000 System, Sentinel Software, Version 4.4.1, Loves Park, IL).

Purina Certified Rodent Chow (No. 5002, PMI Feeds, Inc., St. Louis, MO; batch numbers documented in the study records) was available ad libitum. All animals in all groups received the same batch/lot (Lot #DEC 02 02 2B) of Purina Certified Rodent Chow at all times. The analyses of each feed batch for nutrient levels and possible contaminants were performed by the supplier, examined by the Study Director, and maintained in the study records. The feed was also analyzed at the manufacturer for the phytoestrogens daidzein, genistein, and glycitein. Analysis indicated that the total phytoestrogens (as aglycones) in this lot of feed ranged from 129 to 303 ppm). Deionized water (generated in-house from tap water; source: City of Durham, Department of Water Resources, Durham, NC) was available ad libitum by polycarbonate water bottles with butyl rubber stoppers and stainless-steel sipper tubes. Contaminant levels of the Durham City water were measured at regular intervals by the supplier per EPA specifications. The deionized water was analyzed by Balazs Analytical Laboratories, Inc. (Sunnyvale, CA). There were no known contaminants that may have affected the outcome of this study. The phytoestrogen content in the rodent chow was low, and at a level that would not have any effect on the study results. The cages and water bottles were polycarbonate, a polymer of bisphenol A, and were in good condition. Studies by Hunt et al. (2003) indicate that unless the cages and/or water bottles are damaged or crazed, there is no leaching of estrogenic compounds.

8.2.1 F0 Females

Exposure began for F0 females on gd 6 beginning on January 13, 2003, when they were approximately 12 weeks old. The doses were chosen based on results in the literature. F0 females were assigned to the different groups by means of randomization stratified by body weight, such that the body weights of all groups were homogeneous at study initiation. The weight range for all F0 females on gd 0 was 216.3 to 257.4 g. F0 females were dosed with vehicle control, 25, 50 or 100 mg/kg of methoxychlor in Mazola® corn oil at 5 ml/kg, adjusted with respect to the most recent body weight. Dosing was done once daily by oral gavage with an appropriate-sized syringe fitted with a 16 g two-inch stainless-steel curved dosing needle (Perfektum®, Popper and Sons, New Hyde Park, NY). F0 females were dosed daily, from gd 6 through pnd 20, and necropsied after weaning of their litters.

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Observations for mortality were made twice daily (a.m. and p.m.), and the general condition of all animals was checked daily. Clinical examinations were conducted and recorded daily throughout the course of the study. This record included the degree and duration of symptoms. These cage-side observations included, but were not limited to, changes in: skin and fur, eyes, mucous membranes, respiratory and circulatory system, autonomic and central nervous system, somatomotor activity, and behavioral pattern.

The body weights of the F0 female rats were determined and recorded upon assignment to dose groups. During gestation, F0 females were weighed daily from gd 6 through gd 20. Dams producing litters were weighed daily during lactational (pnd 0 through pnd 21), and body weight gains were computed.

During pregnancy of F0 females, feed weight was recorded for gd 0, 6, 9, 12, 15, 18, and 20. During lactation of the F1 litters, maternal feed weight was recorded for pnd 0, 4, 7, 14, and 21, although maternal feed consumption after pnd 14 was confounded by the contribution from the pups since the pups were self-feeding by this time. (The contribution of self-feeding pups on "maternal" feed consumption during the last week of lactation has been estimated at 30-40%, e.g., Hanley and Watanabe, 1985; Tyl et al., 2002).

Beginning on gd 20, each female was observed twice daily (a.m. and p.m.) for evidence of littering. On the day of birth (pnd 0), AGD was measured and body weight recorded for all live F1 pups in all litters. Body weight was recorded for all live pups on pnd 4 prior to culling and euthanasia. F0 females that had not delivered by gd 26 were euthanized and examined internally for pregnancy status. The F0 dams with litters were allowed to rear their young to pnd 21. On pnd 21, each litter was weaned. All F0 females in all groups were subjected to a complete gross necropsy on pnd 21. No tissues were weighed or retained.

8.2.2 Progeny (F1)

All F1 pups were counted, sexed, weighed, and examined as soon as possible after birth (date of birth designated pnd 0) to determine the number of viable and stillborn pups from each litter. Thereafter, litters were evaluated for survival on pnd 4, 7, 14, and at weaning (pnd 21). Individual AGD and body weight were recorded on pnd 0 for all F1 offspring.

On pnd 4, the size of each litter was adjusted to nine pups (five females and four males). F1 pups culled to standardize litters on pnd 4 were weighed and euthanized, and subjected to a gross examination.

All live pups were counted, sexed, weighed individually, and examined grossly at birth (pnd 0), pnd 2, 10, 17 and at weaning (pnd 21). The body weights and sexes were recorded on an individual basis, with male pups with areolae/nipples uniquely identified on pnd 11-13. AGD was recorded with the individual pup weight on pnd 0 for all F1 pups, and the presence or absence of retained nipples and areolae on the ventrum was recorded for F1 male offspring at

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approximately pnd 11-13. All pups were examined for physical abnormalities at birth and throughout the preweaning and postwean period. All litters were weaned on pnd 21.

8.3 F1 Weanling Female Uterotrophic Cohort

On pnd 21, one female from each standardized litter was chosen for the uterotrophic cohort. Clinical observations of F1 females assigned to the uterotrophic cohort were documented at least twice daily throughout the dosing period (pnd 22 through pnd 24). Beginning on pnd 22, each F1 female was dosed with the same dose level as her mother, but via subcutaneous (sc) injection, through 24. The body weight for each animal was recorded every day prior to treatment, and each female was examined for vaginal patency on pnd 21 through 24. Treatments were administered sc daily using an 22-gauge needle and a 1 cc glass (disposable) tuberculin syringe for each treatment. The treatments were administered on a mg/kg body weight basis, adjusted based on the most recent body weight, and the volume of the dose administered was recorded each day. Injections were made interscapularly. No reaction was noted at the injection site. Females assigned to the uterotrophic cohort were necropsied six hours after the last dose on pnd 24.

8.4 F1 Weanling Female Pubertal Cohort

The four remaining females from each litter were divided into dosed (n=2) and nondosed (n=2) groups per litter on pnd 21. Thus, one group of F1 females (undosed) was evaluated for effects occurring after *in utero*/lactational exposure, whereas the other group of F1 females (dosed) was evaluated for effects after exposure both *in utero*/lactational and postweaning. At this time, AGD was measured using a Vernier calipers (precision to 0.1 mm), and recorded with the individual pup weight. Methoxychlor or corn oil was administered to the animals in the dosed group via gavage from pnd 22 to 42, based on daily body weights. Clinical observations of F1 females assigned to the pubertal cohort were documented at least twice daily throughout the dosing period. All F1 females were weighed in the morning on pnd 21 and every other day in the morning during the dosing period on pnd 22 through pnd 42 for adjustment of dosing volume, based on the most recent body weight. F1 female weight gains were calculated for pnd 21-22, 22-24, 24-26, 26-28, 28-30, 30-32, 32-34, 34-36, 36-38, 38-40, 40-42, and 21-42. F1 female body weights were also recorded on the day of acquisition of vaginal patency.

Beginning on pnd 22, each F1 study female was examined daily for vaginal patency. Body weight at acquisition of complete vaginal patency was recorded. Beginning on the day of vaginal opening and continuing until pnd 42, daily vaginal smears were obtained from each F1 female, and evaluated for the presence of leukocytes, nucleated epithelial cells, or cornified epithelial cells to determine the age at the first complete vaginal cycle and/or any effects on estrous cyclicity. On pnd 42, all F1 females were shaved on the ventrum and examined for areolae/nipples at necropsy.

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8.5 F1 Weanling Male Pubertal Cohort

The four males from each standardized litter were divided into dosed (n=2) and nondosed (n=2) groups per litter on pnd 21. As noted above, these two groups were used to distinguish between effects after *in utero*/lactational exposure alone, and exposure continuing into the postweaning period. At this time, AGD was measured using an eyepiece grid and platform micrometer, and recorded with the individual pup weight. Methoxychlor or vehicle was administered to the dosed groups via gavage from pnd 22to pnd 70+, based on daily body weights. Clinical observations of F1 males assigned to the pubertal cohort were documented at least twice daily throughout the dosing period (pnd 22 through pnd 70+). All F1 males were weighed in the morning on pnd 21, pnd 22, and every other day in the morning during the dosing period on pnd 22 through pnd 70+ for adjustment of dosing volume, based on the most recent body weight, and these data were used to calculate body weight gain. F1 male body weights were also recorded on the day of acquisition of preputial separation.

Beginning on pnd 23, each F1 study male was examined daily for preputial separation. Body weight at complete preputial separation was recorded.

8.6 Necropsy of F1 Offspring

Terminal Blood Collection. At scheduled necropsy of the F1 females (on pnd 24 or 42) and males (on pnd 70+), after terminal anesthesia (CO2 asphyxiation), the animals were weighed and the maximum amount of blood was taken by external cardiac puncture and placed in a labeled tube. The blood was allowed to clot and was centrifuged under refrigeration at approximately 1400 x g for approximately 10 minutes. The resulting serum was frozen at approximately -20°C for subsequent analysis of E2 (uterotrophic cohort samples only), T4, T3, and TSH.

Gross Necropsy and Organ Weights. Once each F1 animal was bled, it was necropsied and internal thoracic and abdominal organs and cavities examined. Observed abnormalities were documented.

For F1 females assigned to the uterotrophic cohort, paired ovary and uterus weight (wet) were determined. The uterus was processed for microscopic evaluation.

F1 females assigned to the female pubertal cohort were examined externally for the number of nipples, AGD, and urethral-vaginal distance (UVD). The liver, kidneys (paired), adrenal glands (paired), ovaries (paired), uterus (see below), pituitary, and fixed thyroid (with attached portion of trachea removed) were dissected and weighed. The uterus and cervix were separated from the vagina and the weight of the uterus with fluid, and without fluid, was recorded. The thyroid and ovaries were processed for microscopic evaluation.

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F1 males were shaved on the ventrum and examined externally for retained nipples. F1 male AGD inadvertently was not measured at necropsy. The thoracic and abdominal organs and cavities were examined and any abnormalities documented. Paired testis and epididymis (whole, left and right separately), prostate (intact and separated into ventral and dorsolateral lobes), seminal vesicles with coagulating glands (and fluid), Cowper's glands, glans penis, levator ani plus bulbcavernosus muscle complex, liver, adrenal glands (paired), kidneys (paired), pituitary, and fixed thyroid (with attached portion of trachea removed) were dissected and weighed. In addition, one cauda epididymis from each F1 male was immediately removed, weighed, and seminal fluid from the cauda was assessed for sperm number. Sperm number was assessed using an HTM-IVOS (Version 10.8 S) automated sperm analysis system (Hamilton-Thorne Research, Beverly, MA). The testis, epididymides, pituitary, and thyroid were processed for microscopic evaluation

Estradiol Radioimmunoassay Procedure The estradiol radioimmunoassay (RIA) used was a no-extraction, double antibody ^{125}I RIA (Diagnostic Systems Laboratories [DSL], Webster, Texas) which utilized estradiol antibody, ^{125}I-estradiol, estradiol calibrators as the standard curve, and a precipitating solution consisting of goat anti-rabbit gamma globulin combined with dilute polyethylene glycol. Normal control serum from the same species/strain/sex as unknown samples was assayed. From the control values, the intra- and interassay coefficient of variation, percent recovery, and index of parallelism for the assays was determined (see Text Table 2).

Text Table 2. Estradiol Recovery in Various Matrices

Parameter	Uterotropic	Adult CD Female	Adult CD Male	Saline
Units	(pg/mL)	(pg/mL)	(pg/mL)	(pg/mL)
Intra-assay Variation[a]				
Blank matrix	4.0%	%	%	%
Mass added	25/4.9% 75/4.1%	25/3.5% 75/2.9%	25/% 75/%	25/4.2% 75/4.1%
Inter-assay Variation[a]				
No. of assays	1	1	1	1
Blank matrix	N/A[c]	N/A	N/A	N/A
Mass added	N/A	N/A	N/A	N/A
% recovery of added mass[b]	25/10.2% 75/12.8%	25/76.9% 75/101.4%	25/77.9% 75/114.7%	25/80.6% 75/124.0%

[a] Numbers are mass added/percentage variation.

[b] Numbers are mass added/percentage recovered.

[c] N/A = not applicable

The sensitivity of the assay was 0.6 pg/mL as reported by DSL. All samples read within curve range of 1.5 to 150 pg/mL. For the RIA procedure, the sample (200 µL) was pipetted into a

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glass culture tube and the estradiol antiserum was added. The tubes were vortexed and incubated at 4°C for 4 hours. The ^{125}I-estradiol was added, and the tubes were vortexed and incubated at 4°C for 21 hours. After overnight incubation, cold precipitating solution was added and the tubes vortexed. The tubes were centrifuged, the supernatant was decanted and the tubes containing pellets were counted in a gamma counter. Results were reported as pg/mL.

Rat Thyroid Stimulating Hormone Radioimmunoassay Procedure. The rat thyroid stimulating hormone (rTSH) RIA used was a no-extraction, double antibody ^{125}I RIA (Amersham Biosciences, Piscataway, NJ) which utilized rTSH antibody, ^{125}I-rTSH, rTSH calibrators as the standard curve, and a precipitating solution consisting of donkey anti-rabbit serum coated onto magnetizable polymer particles. Normal control serum from the same species/strain/sex as unknown samples was assayed. From the standards values, the intra- and interassay coefficient of variation, percent recovery, and index of parallelism for the assays was determined (see Text Tables 3, 4, 5, and 6).

Text Table 3. F_0 Female CD Rat Serum (Pooled Female Rat Serum Designated RTI-Lot 129)

Parameter	TSH	T4
Units	(ng/mL)	(μg/dL)
Intra-assay Variation[a]		
Blank matrix	8.1%	7.8%
Mass added	8/3.1% 32/5.9%	2/5.3% 10/3.8%
Inter-assay Variation[a]		
No. of assays	2	1
Blank matrix	7.4%	N/A
Mass added	8/3.4% 32/1.4%	N/A
% recovery of added mass[b]	8/101.8%-109.6% 32/115.0%-124.1%	2/79.8%-92.5% 10/97.8%-105.7%
Index of parallelism[c]	0/123.3% 8/103.5% 32/97.1%	2/105.1% 10/101.4%

[a] Numbers are mass added/percentage variation. Intra-assay data is from validation assay. Inter-assay data does not include validation.

[b] Numbers are mass added/percentage recovered (range of all assays, including validation assay).

[c] Index of parallelism = concentration of low volume ÷ concentration of high volume x 100.

NA = Not Applicable.

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Text Table 4. F_1 Female CD Rat Serum (Pooled Female Rat Serum Designated RTI-Lot 126)

Parameter	TSH	T4	T3
Units	(ng/mL)	(μg/dL)	(ng/dL)
Intra-assay Variation[a]			
Blank matrix	10.5%	5.7%	6.3%
Mass added	8/5.1% 32/3.6%	2/3.5% 10/2.9%	40/4.2% 160/4.1%
Inter-assay Variation[a]			
No. of assays	2	3	4
Blank matrix	0.79%	6.0%	10.7%
Mass added	8/4.8% 32/7.2%	2/5.0% 10/5.5%	40/11.6% 160/4.7%
% recovery of added mass[b]	8/102.6%-115.3% 32/102.7%-130.6%	2/85.5%-94.0% 10/85.6%-95.4%	40/62.6%-92.7% 160/81.2%-91.3%
Index of parallelism[c]	0/120.3% 8/100.4% 32/101.1%	2/99.7% 10/104.4%	40/105.1% 160/105.0%

[a] Numbers are mass added/percentage variation. Intra-assay data is from validation assay. Inter-assay data does not include validation.
[b] Numbers are mass added/percentage recovered (range of all assays, including validation assay).
[c] Index of parallelism = concentration of low volume ÷ concentration of high volume x 100.

Text Table 5. Female Uterotrophic CD Rat Serum (Pooled Female Rat Serum Designated RTI-Lot 130)

Parameter	TSH	T4
Units	(ng/mL)	(μg/dL)
Intra-assay Variation[a]		
Blank matrix	9.8%	8.2%
Mass added	8/2.6% 32/6.4%	2/5.9% 10/3.8%
Inter-assay Variation[a]		
No. of assays	1	1
Blank matrix	N/A	N/A
Mass added	N/A	N/A
% recovery of added mass[b]	8/103.3% 32/110.0%	2/81.5%-130.5% 10/81.9%-100.6%
Index of parallelism[c]	N/A	2/92.0% 10/102.3%

[a] Numbers are mass added/percentage variation. Intra-assay data is from validation assay. Inter-assay data does not include validation.
[b] Numbers are mass added/percentage recovered (range of all assays, including validation assay).
[c] Index of parallelism = concentration of low volume ÷ concentration of high volume x 100.
NA = Not Applicable.

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Text Table 6. F_1 Male CD Rat Serum (Pooled Male Rat Serum Designated RTI-Lot 127)

Parameter	TSH	T4	T3
Units	(ng/mL)	(μg/dL)	(ng/dL)
Intra-assay Variation[a]			
Blank matrix	5.3%	3.8%	7.7%
Mass added	8/3.5% 32/6.1%	2/3.3% 10/2.8%	40/6.5% 160/5.1%
Inter-assay Variation[a]			
No. of assays	2	2	4
Blank matrix	5.0%	4.7%	10.3%
Mass added	8/2.2% 32/5.8%	2/1.6% 10/0.2%	40/3.1% 160/6.1%
% recovery of added mass[b]	8/96.8%-121.9% 32/114.9%-126.7%	2/57.0%-91.3% 10/83.0%-86.9%	40/84.0%-122.2% 160/82.7%-114.6%
Index of parallelism[c]	0/110.2% 8/106.2% 32/94.0%	2/100.5% 10/103.1%	40/103.7% 160/106.1%

[a] Numbers are mass added/percentage variation. Intra-assay data is from validation assay. Inter-assay data does not include validation.

[b] Numbers are mass added/percentage recovered (range of all assays, including validation assay).

[c] Index of parallelism = concentration of low volume ÷ concentration of high volume x 100.

The sensitivity of the assay was 0.5 ng/mL as reported by Amersham Biosciences. All samples read within curve range of 1 to 64 ng/mL. For the RIA procedure, the sample (100 μL) was pipetted into a glass culture tube, the rTSH antiserum was added, followed by the ^{125}I-rTSH, and the tubes were vortexed and incubated at room temperature for approximately 21 hours. After overnight incubation, cold precipitating solution was added and the tubes vortexed. The tubes were centrifuged, the supernatant was decanted, and the tubes containing pellets were counted in a gamma counter. Results were reported as ng/mL.

Total Triiodothyronine Radioimmunoassay Procedure. The total triiodothytonine (T3) RIA used was a no-extraction, solid-phase ^{125}I RIA which utilized T3-specific antibody-coated tubes and ^{125}I-T3 (DPC, Los Angeles, CA). The T3 (Sigma, St. Louis, MO) standard curve was prepared in charcoal stripped serum. T3 controls in serum were prepared in the same species/strain/sex as unknown samples by adding known concentrations of T3 to the appropriate matrix. From the control values, the intra- and interassay coefficient of variation, percent recovery, and index of parallelism for the assays was determined (see Text Tables 4 and 6). The sensitivity of the assay was 7 ng/dL as reported by DPC. All samples read within curve range of 6.25 to 800 μg/dL. For the RIA procedure, the sample (100 μL) was pipetted into the antibody-coated tube and the ^{125}I-T3 was added. The tubes were vortexed and incubated in a 37°C water bath for two hours. After incubation, the supernatant was aspirated and the tubes were counted in a gamma counter. Results were reported as ng/dL.

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Total Thyroxine Radioimmunoassay Procedure. The total thyroxine (T4) RIA used was a no-extraction, solid-phase ^{125}I RIA which utilized T4-specific antibody-coated tubes and ^{125}I-T4 (DPC, Los Angeles, CA). The T4 (Sigma, St. Louis, MO) standard curve was prepared in RIA Buffer I (0.01 M sodium phosphate plus 0.85% [w/v] sodium chloride with 0.1% [w/v] sodium azide and 1% [w/v] bovine serum albumin, pH 7.6). T4 standards in serum were prepared in the same species/strain/sex as unknown samples by adding known concentrations of T4 to the appropriate matrix. From the control values, the intra- and interassay coefficient of variation, percent recovery, and index of parallelism for the assays was determined (see Text Tables 3, 4, 5, and 6). The sensitivity of the assay was 0.25 µg/dL as reported by DPC. All samples read within curve range of 0.63 to 40 µg/dL. For the RIA procedure, the sample (25 µL) was pipetted into the antibody-coated tube and the ^{125}I-T4 was added. The tubes were vortexed and incubated in a 37°C water bath for one hour. After incubation, the supernatant was aspirated and the tubes were counted in a gamma counter. Results were reported as µg/dL.

8.7 Histology and Pathology

All protocol-specified tissues in every dose group were evaluated histopathologically. All tissue sections were read blind for dose.

For F1 females assigned to the uterotrophic cohort, stained sections of the uterus were evaluated by a Board Certified veterinary pathologist for pathologic abnormalities and potential treatment-related effects.

For F1 females assigned to the pubertal cohort, the pituitary, ovaries, uterus, and thyroid with attached portion of trachea were dissected out, the ovaries, uterus, and pituitary weighed, and the tissues placed in Bouin's fixative for 24 hours, after which they were rinsed and stored in 70% alcohol. Once the tissues were fixed, they were transferred to Experimental Pathology Laboratories (EPL), where the trachea was carefully removed from the fixed thyroid (to retain glandular integrity) and weighed. The tissues were then embedded in paraffin, sectioned at 3-5 microns, and stained with hematoxylin and eosin (H and E) for subsequent histological evaluations. Optional tissues for histopathology including the vagina, liver, paired kidneys, and paired adrenal glands were not selected for evaluation. Stained sections of the protocol-specified tissues, including the ovaries, uterus, pituitary, and thyroid, were evaluated by a Board Certified veterinary pathologist for pathologic abnormalities and potential treatment-related effects.

For F1 males assigned to the pubertal cohort, one testis, one epididymis, the pituitary, and the thyroid with attached portion of trachea were dissected out, the testis, epididymis, and pituitary weighed, and the tissues placed in Bouin's fixative for 24 hours, after which they were rinsed and stored in 70% alcohol. The tissues were then transferred to EPL and processed and evaluated as described above. The other testis was weighed and frozen, then subsequently used to enumerate homogenization-resistant spermatid heads for calculation of daily sperm production (DSP) and efficiency of DSP (Robb et al., 1978; Sharpe et al., 1995). The other epididymis was also weighed, and used for sperm counts. Optional tissues for histopathology including the liver,

US EPA ARCHIVE DOCUMENT

paired kidneys, and paired adrenal glands (paired) were not chosen for evaluation. The fixed testis and epididymis was evaluated for spermatogenesis, spermiogenesis, status of seminiferous tubules in the testis, and sperm in the epididymis, as well as the structural integrity of these organs. Stained sections of the protocol-specified tissues, including the testis, epididymides, pituitary, and thyroid, were evaluated by a Board Certified veterinary pathologist for pathologic abnormalities and potential treatment-related effects.

9.0 STATISTICAL ANALYSES

The unit of comparison was the pregnant female, the litter, or the retained F1 offspring, as appropriate. Treatment groups were compared to the concurrent control group using either parametric ANOVA under the standard assumptions or robust regression method (Zeger and Liang, 1986; Royall, 1986; Huber, 1967), which does not assume homogeneity of variance or normality. The homogeneity of variance assumption was examined via Levene's test (Levene, 1960), which is more robust to the underlying distribution of the data than the traditional Bartlett's test. When Levene's test indicated lack of homogeneity of variance ($p<0.05$), robust regression methods were used to test all treatment effects. The robust regression methods use variance estimators that make no assumptions regarding homogeneity of variance or normality of the data. They were used to test for overall treatment group differences, followed by individual tests for exposed vs. control group comparisons (via Wald Chi-square tests), if the overall treatment effect was significant. The presence of linear trends was analyzed by GLM procedures in SAS® Release 8 for homogenous data or by robust regression methods for nonhomogenous data (SAS Institute Inc., 1999a, b, c, d, e, 2000). Standard ANOVA methods, as well as Levene's test, are available in the GLM procedure of SAS® Release 8, and the robust regression methods are available in the REGRESS procedure of SUDAAN® Release 8.0 (RTI, 2001).

When Levene's test did not reject the hypothesis of homogeneous variances, standard ANOVA techniques were applied for comparing the treatment groups. The GLM procedure in SAS® 8.0 was used to evaluate the overall effect of treatment and, when a significant treatment effect was present, to compare each exposed group to control via Dunnett's Test (Dunnett, 1955, 1964). For the litter-derived percentage data (e.g., periodic pup survival indices), the ANOVA was weighted according to litter size. A one-tailed test (i.e., Dunnett's test) was used for all pairwise comparisons to the vehicle control group, except that a two-tailed test was used for parental and pup body weight and organ weight parameters, feed consumption, percent males per litter, and AGD.

Frequency data such as offspring survival indices were not transformed. All indices were analyzed by the chi-square test for independence for differences among treatment groups (Snedecor and Cochran, 1967) and by the Cochran-Armitage test for linear trend on proportions (Cochran, 1954; Armitage, 1955; Agresti et al., 1990). When chi-square revealed significant ($p<0.05$) differences among groups, then a Fisher's exact probability test, with appropriate adjustments for multiple comparisons, was used for pairwise comparisons between each

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treatment group and the control group. For correlated data (e.g., body and organ weights at necropsy, with more than one pup/sex/litter), SUDAAN® software (RTI, 2001) was used for analysis of overall significance, presence of trend, and pairwise comparisons to the control group values. Organ weights were analyzed by Analysis of Covariance (ANCOVA) using the initial (assignment to group) body weight and body weight at necropsy as the covariate, when there was a significant effect on body weight. When statistically significant effects were observed, treatment means were examined further using LSMeans.

For the male sperm parameters, where only the control and high dose groups were analyzed, a Student's t-Test with a Folded F test to determine homogeneity of variances was used.

A test for statistical outliers (SAS® Release 8) was performed on F0 maternal body weights, feed consumption (in g/day), and retained F1 male or female body and organ weights. When examination of pertinent study data did not provide a plausible biologically sound reason for inclusion of the data flagged as "outlier," the data was excluded from summarization and analysis and was designated as outliers. When feed consumption data for a given animal for a given observational interval (e.g., pnd 0-7 or 7-14 during the lactational exposure period) were designated outliers or unrealistic, then summarized data for this animal encompassing this period (e.g., pnd 0-21 for the lactational exposure period) also did not include this value. For all statistical tests, p # 0.05 (one- or two-tailed) was used as the criterion for significance.

10.0 ANALYTICAL REPORT AND PROTOCOL

The bulk chemical and dose formulation analytical report was prepared and signed by the author(s) and included as Appendix III of this report. The protocol detailing the design and conduct of the study are presented in Appendix II of this report.

11.0 STORAGE OF RECORDS

All original data sheets and records collected during the present study will be stored in the RTI Archives, under the control of the RTI Chemistry and Life Sciences Archivist, and remain the responsibility of RTI. Worksheets and computer printouts, which were generated in the statistical analysis of data, are stored in the RTI Archives. Copies of this report are filed with the RTI Archives and with Battelle. All remaining dose formulations were shipped back to the sponsor. Records and samples from this study in RTI Archives may be released to the Sponsor upon written request.

12.0 COMPLIANCE

All records, data, biological specimens, and reports will be maintained in storage for the time period specified by the contract or for as long as the quality of the preparation affords evaluation, whichever is less. Quality control (QC) and quality assurance (QA) procedures

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followed those outlined in the Quality Assurance Project Plan (QAPP) prepared for this study, and in accordance with the Quality Management Plan (QMP) for this project. The RTI Animal Research Facility is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), International. At all times, animals were housed, handled, and used according to the NRC Guide (NRC, 1996).

13.0 PERSONNEL

This study was conducted at RTI International, Research Triangle Park, NC, under contract to Battelle, Columbus, OH. Dr. David P. Houchens, EDSP Program Manager, was the Sponsor's Representative. Dr. R. W. Tyl served as Project Toxicologist. Dr. Julia D. George served as Study Director. Reproductive and Developmental Toxicology personnel included Ms. M.C. Marr (Laboratory Supervisor), Ms. C.B. Myers (Reproductive Toxicity Study Supervisor and Data Analyst), Mr. W.P. Ross, Ms. M.C. Rieth, Ms. V.I. Wilson, Ms. L.B Pelletier, Ms. M.P. Gower, Ms. N.M. Kuney, Ms. R.T. Krebs, Ms. S.W. Pearce, Ms. K.D. Vick, Ms. L. McDonald, Ms. A.J. Parham, Mr. M.D. Crews, Mr. C.G. Leach, Mr. J.E. Gray, Ms. A. Goodman, and Mr. T.W. Wiley. Bulk chemical analysis and handling, dose formulation, and dose formulation analysis were provided by the sponsor through Dr. E.A. Crecelius, PNNL, Battelle Marine Sciences Laboratory, Sequim, WA. Mr. M.M. Veselica (Supervisor, RTI Materials Handling Facility), Mr. D.L. Hubbard, and Mr. R.A. Price provided receipt and disbursement of dose formulations at RTI. Animal care was provided by Dr. D.B. Feldman, DVM, ACLAM, Veterinarian, and Mr. F.N. Ali, Manager of RTI Animal Research Facility. RTI Quality Assurance personnel were Ms. D. A. Drissel, Ms. M.D. Phillips, Ms. C.A. Ingalls, and Ms. Michelle Oh. Ms. Kathleen A. Andrews, QA Consultant, audited the hormone data.

The final report was prepared by Dr. J.D. George, with assistance from Dr. R.W. Tyl, Ms. B.T. Hamby, Ms. M.C. Marr, and Ms. C.B. Myers. Ms. C.B. Myers was responsible for data compilation and statistical analyses, and Mr. T.W. Wiley was responsible for data entry. Ms. M. C. Marr was responsible for all activities concerning organization and custody of the study records, and archiving the study records. Ms. D.B. Bynum and Ms. K.L. Kehagias provided secretarial assistance.

US EPA ARCHIVE DOCUMENT

14.0 RESULTS

14.1 Dose Formulations

Formulations of methoxychlor in corn oil were prepared at Battelle, PNNL, Battelle Marine Sciences Laboratory, Sequim, WA, at five different times. Replicates 1 and 2 were prepared and shipped to RTI together at the start of the study. Subsequently, Replicates 3 through 6 were each prepared approximately two weeks apart and shipped to RTI separately. Predosing analysis of methoxychlor in corn oil indicated that the formulations were between 87 and 108% of the target concentrations (Table 1). At RTI, the formulations were stirred until visually homogenous before use. Aliquots of the dosing solutions and the control formulation were taken on the first day of dosing (first gd 6), and on the first pnd 0, 7, 14, and 21. In addition, the dosing bottles, with the remainder of the dosing solutions from Replicates 2 and 3, were saved after dosing was completed. These first-day aliquots and postdosing samples in the dosing bottles were shipped back to the sponsor and were analyzed for test chemical concentration. In-life samples ranged from 83 to 101% of the nominal concentration (Table 1). Postdosing samples from Replicates 1 and 3 assayed at 82-99% of the nominal concentration (Table 1). Additional analytical data are presented in Appendix III to the Final Report.

14.2 F0 Female Observations

Fate of F0 Females. Fifteen sperm-positive F0 females were assigned to each treatment group (Table 2). Two, four, and one F0 females in the vehicle control, 25 mg/kg/day, and 100 mg/kg/day groups, respectively, were removed from the study due to a misdirected dose. One animal in the 25 mg/kg/day group, and one animal in the 100 mg/kg/day group were removed from the study because the correct postnatal day 0 could not be established. One F0 female in the 100 mg/kg/day dose group died during delivery on gd 23, and one, one, and two females in the vehicle control, 25 mg/kg/day, and 100 mg/kg/day groups, respectively, were not pregnant. In addition, two females in the 50 mg/kg/day group and one female in the 100 mg/kg/day group were found moribund and were euthanized within the first three days after delivery of their litters. Thus, 12, 9, 13, and 9 females in the vehicle control, 25, 50, and 100 mg/kg/day dose groups, respectively, were necropsied at scheduled sacrifice on pnd 21 (Table 2).

F0 Female Gestation. Maternal body weight was equivalent across treatment groups on gd 0 and gd 6 (Table 3). Beginning on gd 9, and continuing through gd 20, maternal body weight exhibited a decreasing trend, with the high dose group value significantly less than the control group value. The 50 mg/kg/day dose group value was significantly decreased compared to the control value for gd 12 through 20, whereas the 25 mg/kg/day dose group exhibited a significant decrease compared to the control group for gd 12 through 18. Maternal body weight change exhibited a decreasing trend for all time intervals except gd 0 to 6 and 18 to 20. Methoxychlor-treated animals either gained less weight or lost weight, compared to the vehicle control animals, on gd 6 to 9 and 9 to 12. In addition, the high dose group gained less weight

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than the control group for gd 0 to 6 and 12 to 15. Body weight change for the treatment period (gd 6 to 20), or for gd 0 to 20 exhibited a decreasing trend, and was significantly decreased at the mid and high dose level of methoxychlor, compared to the vehicle control group.

F0 female absolute feed consumption (g/day) was equivalent across treatment groups for gd 0 to 6 (Table 4). However, during the period spanning the first three gavage doses of methoxychlor (gd 6 to 9), all three treatment groups ate significantly less than the vehicle control animals, likely due to initiation of dosing with the test chemical. Thereafter, absolute feed consumption values for the high dose group were most often affected, and were reduced compared to the vehicle control group values for gd 9 to 12, 12 to 15, 15 to 18, 6 to 20, and 0 to 20. The mid dose group was similarly affected with the exception of gd 9 to 12 and 18 to 20, which exhibited no significant difference compare to the vehicle control value. Absolute maternal feed consumption was unaffected at the low dose after gd 9. When maternal feed consumption was calculated relative to body weight, no difference was observed across the treatment groups for gd 0 to 6, or 18 to 20, or for the 25 mg/kg/day dose group at the other measured intervals. Both the 50 and the 100 mg/kg/day dose groups consumed less feed per kg body weight than did the vehicle control group on gd 6 to 9, 12 to 15, 6 to 20, and 0 to 20. In addition, the high dose group was significantly reduced compared to the vehicle control group on gd 9 to 12 and 15 to 18 (Table 4).

Clinical signs observed in F0 females during gestational treatment included one animal in each treatment group with alopecia, efflux of the dosing solution in two vehicle control, six low dose, and one mid dose animal(s), piloerection in one, seven, and one animal(s) in the control, mid, and high dose group, respectively, and one control animal with audible respiration (Table 5). One and three animal(s) in the mid and high dose groups, respectively, exhibited rooting behavior, and 5, 6, 13, and 10 animals in the control, low, mid and high dose groups, respectively, exhibited weight loss.

F0 Female Lactation. F0 maternal lactational body weights in the methoxychlor-treated animals exhibited a dose-related decreasing trend from pnd 0 through 21 (Table 6). Maternal body weight was significantly decreased in all three methoxychlor-treated groups compared to the vehicle control group on pnd 0, 4, and 7. In addition, the high dose group value was significantly decreased compared to the control group on pnd 14 and 21. Body weight change was increased at the mid and high doses of methoxychlor, compared to the control group value, for pnd 7 to 14, and in the low and high dose group for pnd 0 to 21. For pnd 0 to 21, the mid dose group value was also greater than the control value, but did not reach statistical significance. Examination of the data suggests that this increased weight change was a rebound effect, since, for example, the high dose group was 19.5% less than the control group value on pnd 0, but only 7.65% less than the control value on pnd 21. F0 maternal lactational feed consumption, expressed as g/day and g/kg/day, was unaffected by methoxychlor treatment (Table 7). Maternal clinical observations in the vehicle control group during lactation (Table 8) included alopecia, efflux of the dosing solution, and soft feces in two females each, and mass under right front leg, piloerection, audible respiration, and rooting in one female each. Females in the 25 mg/kg/day dose group exhibited alopecia (four), and chromodachryorrhea, efflux of the

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dosing solution, rooting, and sore(s) (one each). The 50 mg/kg/day dose group exhibited alopecia in six females, piloerection in 5 females, salivation in three females, efflux of the dosing solution, moribundity, rooting, and rough coat in two females each, and soft feces, hunched posture, and deficient nursing behavior in one female each. The 100 mg/kg/day dose group exhibited alopecia and piloerection in three females each, efflux of the dosing solution in two females, and moribundity, soft feces, struggling during dosing, vaginal bleeding, and clear vaginal discharge in one female each.

F0 Female Reproductive and F1 Lactational Indices. Pregnancy was confirmed in 12, 10, 15, and 12 F0 females in the 0, 25, 50, and 100 mg/kg/day methoxychlor groups, respectively (Table 9). F0 females exhibited a fertility index of 85.7 - 100 %, whereas the gestational index was 100% for each treatment group. The number of females producing live litters (pnd 0) was 12, 10, 15, and 11 in the control, low, mid, and high dose groups. Gestational length exhibited an increasing trend, but no significant pairwise comparisons to the control group. Exposure to methoxychlor did not affect the number of live or dead pups, or total number of pups, stillbirth index, or live birth index on pnd 0. Neither was there any effect on indices of survival for pnd 4, 7, 14, 21, or for the period of pnd 4 to 21.

F0 Female Necropsy and Hormone Levels. Circulating T4 and TSH, assayed in serum taken from F0 females at scheduled sacrifice on pnd 21, were not affected by methoxychlor treatment (Table 13). Necropsy findings for F0 females at scheduled sacrifice were minimal and consisted of alopecia on different parts of the body, occurring in one to three animals in the vehicle control, low, or mid dose groups (Table 14). For the one high dose animal that was necropsied during gestation, chromodacryorrhea was observed; seven pups were found in each uterine horn, in addition to one pup in the vagina. The one high dose animal necropsied during lactation exhibited anogenital fur stained with blood, rust colored fur on limbs and nose, and 5 resorptions in the uterus.

14.3 F1 Preweaning Observations

Fate of F1 Animals During Lactation. There were 12, 9, 15, and 10 live litters on pnd 0 at 0, 25, 50, and 100 mg/kg/day methoxychlor, respectively (Table 10). As a result of two moribund dams in the 50 mg/kg/day dose group and one moribund dam in the 100 mg/kg/day dose group, there were 12, 9, 13, and 9 F1 litters at 0, 25, 50, and 100 mg/kg/day, respectively, on pnd 21 (Table 10).

Observations of F1 Pups During Lactation. Treatment with methoxychlor had no effect on the average number of pups per litter on pnd 0, 4, 7, 14, or 21, average male pup AGD per litter on pnd 0 (absolute or adjusted for body weight at acquisition), average adjusted female AGD per litter on pnd 0, average pup body weight per litter (male, female, or sexes combined) on pnd 0, 4, 7, 10, 14, 17, or 21, average pup body weight per litter for the males or sexes combined on pnd 2, the average number of nipples or areolae per male, or the average number of male pups with one or more nipples or areolae (Table 10). Slight treatment effects were noted

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for average absolute female AGD per litter (low dose group value significantly less than the control group value), average female body weight per litter on pnd 2 (high dose value significantly less than the control value), the percent male pups per litter on pnd 0 (increasing trend), and the percent male pups per litter on pnd 4 (low dose value greater than the control value). Clinical signs observed for pnd 0 through 21, other than dead or missing (presumed dead) pups, were minimal and included a bite mark on the left side, umbilical hernia, and a sore on the back (1) in the vehicle control group, alopecia (8) in the 25 mg/kg/day dose group, anal atresia and string-like tail (1), and no milk band (13) in the 50 mg/kg/day dose group, and no milk band (5) in the 100 mg/kg/day group (Table 11).

Unscheduled F1 Pup Necropsy During Lactation. Necropsy findings of F1 pups found dead or euthanized moribund on pnd 0-21 included the usual findings: pups that died on pnd 0 or 1 exhibited open (fetal state) or closed ductus arteriosus (postnatal state), no air (fetal state) or air (postnatal state) in lungs, no or little milk in stomach, and autolysis of abdominal organs (Table 12). Pups that died after pnd 2 had no milk band, autolysis of the abdominal organs, or bite marks.

14.4 F1 Female Uterotrophic Cohort

Fate of F1 Females in the Uterotrophic Cohort. At weaning, 13, eight, eight, and ten F1 females from the vehicle control, 25, 50, and 100 mg/kg/day dose groups, respectively, were assigned to the uterotrophic cohort (Table 15). One, two, and one female(s) in the vehicle control, low, and high dose groups, respectively, were subsequently removed from the study, when examination of the data collected from their dams resulted in the removal of the dams from the study (see Table 2). Thus, 12, 6, 8, and 9 females were evaluated at scheduled sacrifice on pnd 24 for the control, 25, 50, and 100 mg/kg/day dose groups, respectively.

F1 Female Uterotrophic Cohort Observations. There was no effect of exposure to methoxychlor on the body weight of the F1 females assigned to the uterotrophic cohort, either after gestational and lactational exposure (body weight on pnd 21), or with continued exposure (subcutaneously at the same dose level) on pnd 22, 23, and 24 (Table 16). Differences in body weight change were minimal. A decreasing trend was observed for body weight change from pnd 21 to 22, 22 to 23, and 21 to 24. The high dose animals gained significantly less weight than the vehicle control animals for pnd 21 to 22.

Clinical observations of females assigned to the uterotrophic cohort included three to six females in the 50 mg/kg/day dose group, and two females in the 100 mg/kg/dose group with a pinhole opening in the vagina (Table 17). Acquisition of completed vaginal opening was not observed in any animal.

Scheduled Necropsy of F1 Females in the Uterotropic Cohort. At necropsy on pnd 24, the average body weight of the F1 females was equivalent across treatment groups (Table 18). The absolute paired ovary weight was significantly decreased compared to the control value at

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50 and 100 mg/kg/day methoxychlor. Absolute uterine weight (with fluid) was not affected. When paired ovary or uterine weight were adjusted for body weight at sacrifice or on pnd 21, adjusted paired ovary weight was still significantly decreased at the mid and high dose, whereas adjusted uterine weight exhibited no treatment effect.

Circulating estradiol and T4 levels were not affected by methoxychlor treatment (Table 18). However, circulating TSH levels were significantly increased at all treatment levels. There were no gross observations at scheduled necropsy (Table 19). Histopathological findings for the uterus were unremarkable.

14.5 F1 Female Pubertal Cohort (Undosed)

Fate of Undosed F1 Females. Twenty to 25 F1 females were assigned to the untreated group of the female pubertal cohort (Table 20). These animals remained in groups identified by the dose level of methoxychlor received by their dams, but received no further treatment. No animals died during the pubertal evaluation, but two to five animals were removed from the groups born of the vehicle control, low, or high dose dams, because their dams were removed from the study. At scheduled necropsy, 23, 18, 23, and 16 undosed F1 females were evaluated for the control, 25, 50, and 100 mg/kg/day dose groups, respectively.

AGD on pnd 21 (absolute or adjusted for pnd 21 body weight) was not affected by methoxychlor treatment prior to weaning (Table 21). In addition, body weight for intervals from pnd 21 to pnd 42 exhibited no treatment effects. Body weight change for pnd 21 to 22 exhibited a decreasing trend, but no other dose related changes were noted. On pnd 34 to 36 and 38 to 40, the low dose group value was significantly less than the control group value, although no other changes were noted. Clinical observations of the undosed F1 females during the post wean holding period (pnd 21 to 42) were few, and consisted of chromodacryorrhea in one animal in the 25 mg/kg/day dose group, umbilical hernia in one animal in the vehicle control group, a pin hole opening in the vagina of four, three, eight, and six animals in the control, low, mid, and high dose groups, and a vaginal thread in one animal in the 25 mg/kg/day dose group (Table 22).

Vaginal opening was significantly accelerated in the both the mid and high dose groups, compared to the control group (Table 23). Control animals acquired vaginal opening at a mean age of 32.6 days, whereas mid and high dose animals exhibited vaginal opening at 23.5 and 29.5 days, respectively. Acquisition of vaginal opening was slightly accelerated at the low dose (31.3 days vs. 32.6 days for the control group), although this difference was not statistically significant. Average body weight on the day of acquisition was decreased at both the mid and the high dose, compared to the control group, likely a reflection of the younger age of these animals. When the day of acquisition of vaginal opening was adjusted for body weight on pnd 28, the mid and high dose groups were still significantly accelerated compared to the control group. The average number of days from vaginal opening until first estrus exhibited an increasing trend. However, only the mid dose group value was significantly different from the control group value. The average postnatal day of estrus occurred significantly sooner for the

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mid and high dose groups (30.8 and 31.1 days, respectively) compared to the control group (33.5 days).

The percent of females cycling was 87, 100, 91, and 81% for the control, low, mid, and high dose groups, respectively (Table 23). The average number of days from vaginal opening until the start of the first cycle was significantly longer in the mid dose group compared to the control group, but there was no treatment effect in the other two exposed groups. The average postnatal day of the start of the first cycle exhibited a decreasing trend, and was significantly accelerated at the mid dose compared to the control group. The low and high dose groups also exhibited slightly acceleration of the start of the first cycle compared to the control group, although these differences were not statistically significant. The average number of days from vaginal opening to the end of the first cycle exhibited an increasing trend, and was significantly longer at the mid dose, but not at the low or high dose, compared to the control group. No effect of methoxychlor exposure was observed on the average postnatal day of the end of the first cycle. The percent of females with prolonged estrus exhibited an increasing trend, with 0, 11, 74, and 19% of the females in the control, low, mid, and high dose groups exhibiting prolonged estrus. Only the mid dose group value reached statistical significance. The percent of females exhibiting prolonged diestrus also exhibited an increasing trend, although no significant pairwise comparisons were observed.

Scheduled Necropsy of the Undosed F1 Pubertal Females. At scheduled sacrifice, there was no significant difference between the treatment groups for body weight, or absolute or adjusted AGD (Table 24). In addition, the number of areolae or nipples per female was not affected by *in utero*/lactational exposure to methoxychlor. However, urethral-vaginal distance (UVD) was significantly shortened in animals exposed to the mid or high dose of methoxychlor (2.17 mm or 2.30 mm, respectively) compared to the control group (2.68 mm). The low dose group also exhibited a shortened UVD (2.38 mm), although this value was not statistically different from the control value. Pituitary, thyroid, liver, paired adrenal, and paired kidney weight (absolute, or adjusted for necropsy weight, or pnd 21 body weight) were unaffected by *in utero*/lactational exposure to methoxychlor. However, paired ovary weight (absolute, adjusted for necropsy weight, or adjusted for pnd 21 body weight) exhibited a significant treatment effect, with the mid dose value significantly less than the control value. Uterine weight (with or without fluid) exhibited an increasing trend, with only the mid dose group value significantly greater than the control group value. Circulating T4 levels exhibited a significant treatment effect, with the mid dose group significantly greater than the control group. Circulating T3 levels exhibited an increasing trend, but no pairwise differences between the treated group values and the control group values. Circulating TSH levels exhibited an increasing trend, a treatment effect, and a significant increase at the mid dose compared to the control group.

Observations at necropsy were minimal, and included one animal in the control group with either a hole in the abdominal wall at the umbilicus (no herniated viscera) or enlarge thymus (Table 25). Two animals in the low dose group exhibited hydronephrosis and one and six animals in the mid dose group exhibited hydronephrosis and fluid in the uterus, respectively. In

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the high dose group, one animal had hydronephrosis, and three animals had fluid in the uterus. No treatment-related histopathological changes were noted in the thyroid. Administration of methoxychlor at 50 and 100 mg/kg/day was associated with ovarian hypoplasia, characterized by a reduction or absence of corpora lutea and a reduction or absence of large pre-ovulatory follicles (Graffian follicles). Uterine hyperplasia was also noted at the 50 and 100 mg/kg/day dose levels.

14.6 F1 Female Pubertal Cohort (Dosed)

Fate of Dosed F1 Pubertal Females. Twenty to 25 F1 females were assigned to the treated groups of the female pubertal cohort (Table 26). These animals continued treatment at the same dose level of methoxychlor as their dams, beginning on pnd 22 and continuing until scheduled necropsy on pnd 42 . One animal in the mid dose group was found dead on pnd 34 from a misdirected gavage dose, and two to five animals were removed from the vehicle control, low, or high dose, because their dams were removed from the study. At scheduled necropsy, 23, 18, 22, and 16 F1 females were evaluated in the control, 25, 50, and 100 mg methoxychlor/kg/day groups, respectively.

Observations of Dosed F1 Pubertal Females. AGD on pnd 21 (absolute or adjusted for pnd 21 body weight) was not affected by methoxychlor treatment prior to weaning (Table 27). Body weight from pnd 24 through pnd 42, and body weight change for intervals from pnd 22 to 24, 26 to 28, and 21 to 42, exhibited a decreasing linear trend with the high dose group significantly below the control group. Body weight change for pnd 28 to 30, 36 to 38, and 38 to 40 exhibited a significant treatment effect ($p<0.05$). On pnd 28 to 30, the mid dose group was greater than the control group, on pnd 36 to 38, the mid and high dose groups were less than the control groups, and on pnd 38 to 40, the high dose group was less than the control group. Clinical observations of the dosed F1 pubertal females during the post wean treatment period (pnd 21 to 42) consisted of efflux of the dosing solution and a pin-hole vaginal opening in three and ten animals, respectively, in the control group; efflux of the dosing solution, rooting post dosing, salivation prior to dosing, and pin-hole vaginal opening in two, one, one, and nine animals, respectively, at 25 mg/kg/day; efflux of the dosing solution, post dosing lethargy, post dosing rooting, salivation prior to dosing, and pin hole vaginal opening in eight, one, three, one, and 18 animals, respectively, at 50 mg/kg/day; and efflux of dosing solution, post dosing rooting, salivation prior to dosing, and pin hole vaginal opening in four, seven, six, and four animals, respectively, at 100 mg/kg/day (Table 28).

The day of vaginal opening was significantly accelerated in a dose-related manner at all three doses of methoxychlor, compared to the control group (Table 29). The control animals acquired vaginal opening at a mean age of 33.0 days, whereas the low, mid, and high dose animals exhibited vaginal opening at 30.1, 27.9, and 25.9 days, respectively. Average body weight on the day of acquisition was decreased in a dose-related manner at all three dose levels as well, compared to the control group, likely a reflection of the younger age of these animals. When the day of acquisition of vaginal opening was adjusted for body weight on pnd 28, all three methoxychlor-treated groups were still significantly accelerated compared to the control

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group. The average number of days from vaginal opening until first estrus tended to increase slightly, although this change was not significant (Table 29). The average postnatal day of first estrus occurred significantly sooner with increasing dose for all three methoxychlor-treated groups (31.5, 29.8, and 28.0 days, respectively, in the low, mid, and high dose groups) compared to the control group (34.3 days).

The percent of females cycling was 91, 83, 64, and 94% for the control, low, mid, and high dose groups, respectively (Table 29). The average number of days from vaginal opening until the start of the first cycle was significantly longer in the high dose group compared to the control group, but there was no treatment effect in the other two exposed groups. The average postnatal day of the start of the first cycle exhibited a dose-related decreasing trend, and was significantly accelerated at all three doses compared to the control group. The average number of days from vaginal opening to the end of the first cycle exhibited a dose-related increasing trend, and was significantly longer at the high dose, but not at the low or high dose, compared to the control group. Methoxychlor exposure was associated with a significant decrease in the age at which the first cycle ended at each dose level. The percent of females with prolonged estrus exhibited an increasing trend, with 0, 0, 77, and 44% of the females in the control, low, mid, and high dose groups exhibiting prolonged estrus. The mid and high dose group values for this parameter reached statistical significance. The percent of females exhibiting prolonged diestrus did not exhibit a statistically significant change.

Scheduled Necropsy of the Dosed F1 Pubertal Females. At scheduled sacrifice, body weight was significantly lower in the high dose group than the control group (Table 30). There was no significant difference between the treatment groups for absolute AGD. The number of areolae or nipples per female was not affected by *in utero*/lactational and pubertal exposure to methoxychlor. However, urethral-vaginal distance (UVD) was significantly shortened in animals exposed to the mid or high dose of methoxychlor (2.17 mm or 2.21 mm, respectively) compared to the control group (2.68 mm). The low dose group also exhibited a shortened UVD (2.51 mm), although this value was not statistically different from the control value. Absolute pituitary, liver, paired kidney weight, and paired ovary weight each exhibited a decreasing trend. Significant pairwise differences from the control group were observed in the high dose for liver and paired kidney weight, and in both the mid and high dose for paired ovary weight. Thyroid weight at the mid dose was increased over the control value. When organ weight was adjusted for body weight at necropsy, the effects on the pituitary, thyroid, and paired ovary weights were the same as observed for the absolute weights; no other effects of treatment were noted. When organ weights were adjusted for pnd 21 body weight, the effects mirrored those observed for the absolute organ weights. Circulating T4 levels exhibited a treatment effect, but no significant pairwise differences from the control value. Circulating T3 and TSH levels were unaffected by *in utero*/lactational and pubertal exposure to methoxychlor.

Observations at necropsy were minimal, and included one animal in the control group and the mid dose group with a fluid-filled uterus, and one animal in the low dose group and three animals in the mid dose group with hydronephrosis (Table 31). There were no treatment-related

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histopathological changes in the thyroid. Histopathological examination revealed ovarian hypoplasia and some follicular cysts in the ovaries of the mid and high dose animals. In addition, uterine epithelial hyperplasia and evidence of epithelial degeneration and squamous cell metaplasia were noted in the uteri of the mid and high dose animals

14.7 F1 Male Pubertal Cohort (Undosed)

Fate of Undosed F1 Pubertal Males. Nineteen to 25 F1 males were assigned to the untreated group of the male pubertal cohort (Table 32). These animals remained in groups identified by the dose level of methoxychlor received by their dams, but received no further treatment . No animals died during the pubertal evaluation, but one to five animals were removed from the groups born of the vehicle control, low or high dose dams, because their dams were removed from the study. At scheduled necropsy on postnatal day 75-77; 23, 17, 24, and 18 undosed F1 males were evaluated for the control, 25, 50, and 100 mg/kg/day dose groups, respectively.

Observations of Undosed F1 Pubertal Males. AGD on pnd 21 (absolute or adjusted for pnd 21 body weight) was not affected by methoxychlor treatment prior to weaning (Table 33). In addition, body weight for intervals from pnd 21 to pnd 36 exhibited no treatment effects (Table 33). A decreasing trend was noted for all body weights from pnd 38 to pnd 74 (the last day all the animals were weighed). No pairwise differences from the control values were noted. Body weight change for pnd 22 to 24, 34 to 36, 36 to 38, 40 to 42, 54 to 56, and 21 to 74 exhibited a decreasing trend. The mid and high dose group values were significantly less the control values for pnd 36 to 38, and 40 to 42. Clinical observations of the undosed F1 males during the post wean holding period (pnd 21 to 75) consisted of alopecia in one, one, and three animals in the control, low, and high dose groups, respectively (Table 34).

The day of preputial separation exhibited a significant effect for dose (Table 35). However, there was no trend, and the only significant pairwise difference was a delay in the mid-dose group. Preputial separation adjusted for body weight at pnd 40 exhibited the same pattern.

Scheduled Necropsy of the Undosed F1 Pubertal Males. At scheduled sacrifice, body weight exhibited a decreasing trend (Table 36). There was no significant difference between the treatment groups for the number of nipples per male. Absolute paired testes weight exhibited a decreasing trend, with the high dose group significantly less than the control group, but no other treatment effects were noted for absolute organ weight, including pituitary, thyroid, liver, paired adrenal, paired kidney, glans penis, right or left epididymis, seminal vesicles with coagulating glands, prostate (ventral, dorsolateral, or whole), LABC, or Cowper's glands. When organ weights were adjusted for necropsy weight, adjusted thyroid weight was significantly increased at both the low and mid doses, but showed no overall trend. Adjusted LABC weight exhibited an increasing trend, with the mid and high dose group values significantly greater than the control value. Adjusted paired testis weight exhibited a decreasing trend. When organ weights

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were adjusted for pnd 21 body weight, adjusted paired testis weight exhibited a decreasing trend, with the high dose significantly decreased compared to the control group.

Sperm parameters were evaluated for the control and high-dose exposed animals (Table 36). There was no effect of *in utero*/lactational exposure to 100 mg/kg/day methoxychlor on the percent motile sperm, percent progressively motile sperm, epididymal sperm concentration, or daily sperm production per testis. The spermatid head concentration and the efficiency of daily sperm production were significantly increased (each by 20%) compared to the control value.

Circulating T4, T3, and TSH levels, determined for all animals at necropsy, were not affected by *in utero*/lactational exposure to methoxychlor (Table 36). Observations at necropsy were minimal, and included alopecia in one animal in the high dose group, a cyst on the right kidney of one animal in the high dose group, gas-filled caecum in one animal at the mid dose, missing right Cowper's glands in one low dose and one mid dose animal, hydronephrosis in seven control, two low dose, four mid dose, and four high dose animals, and air-filled large intestines in one animal at the low and high dose (Table 37). Histopathological examination of the testes, epididymis, and thyroid was unremarkable.

14.8 F1 Male Pubertal Cohort (Dosed)

Fate of Dosed F1 Males. Nineteen to 25 F1 males were assigned to the treated group of the male pubertal cohort (Table 36). These animals received the same treatment as their dams, beginning on pnd 22 and continuing until necropsy on pnd 75, 76, or 77. One animal in the control group was found dead on pnd 24. One to five animals were removed from the vehicle control, low, or high dose groups because their dams were removed from the study. In addition, one animal was removed from the mid dose group due to death after a misdirected dose. At scheduled necropsy on postnatal day 75-77; 22, 17, 23, and 18 dosed F1 males were evaluated in the control, low, mid, and high dose groups, respectively.

Observations of Dosed F1 Pubertal Males. AGD on pnd 21 (absolute or adjusted for pnd 21 body weight) was not affected by exposure to methoxychlor during the *in utero*/lactational period and postweaning period (Table 39). In addition, body weight for intervals from pnd 21 to pnd 26 exhibited no treatment effects (Table 39). A decreasing trend was noted for all body weights from pnd 28 to pnd 74 (the last day all the animals were weighed). The effects of methoxychlor treatment were progressive with time, with the high, mid, and low dose groups weighing significantly less than the control group beginning on pnd 30, pnd 40, and pnd 46, respectively. Body weight change exhibited a similar but less consistent pattern. No effect of treatment was noted for body weight change for pnd 21 to 22 and 22 to 24. For pnd 24 to 26, a treatment effect was noted, with the high dose group significantly below the control value, but there was no significant trend. Beginning with the interval of pnd 26 to 28, a decreasing trend was noted for all intervals up to pnd 72 to 74. In general, and with few exceptions, the high dose group was significantly less than the control group beginning on

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pnd 26 to 28, and the mid dose group was significantly decreased beginning on pnd 36 to 38. The low dose group exhibited a less consistent effect, and was intermittently decreased compared to the control group throughout the postweaning period.

Body weight change for the period of pnd 21 to 74 was significantly depressed in a dose-related manner at all three treatment levels, compared to the control value. Clinical observations of the dosed F1 males during the post wean holding period (pnd 21 to 75) consisted of the following: alopecia (one at 25 mg/kg/day), ataxia (one at 0 mg/kg/day), chromodachryorrhea (two animals each at 0, 25, or 50 mg/kg/day), efflux of the dosing solution (3,1,8, and 8 animals at 0, 25, 50, or 100 mg/kg/day, respectively), lethargy (one at 50 mg/kg/day), bleeding mouth after dosing (one at 0 mg/kg/day), swollen front right metatarsal (one at 100 mg/kg/day), piloerection (3 at 50 mg/kg/day and 1 at 100 mg/kg/day), audible respiration (one at 50 mg/kg/day), rooting post dosing (five, eight, 13 and 14 at 0, 25, 50, or 100 mg/kg/day, respectively), salivation prior to dosing (five, seven, eight, or 12 at 0, 25, 50, or 100 mg/kg/day), scab(s) (one at 25 mg/kg/day) and blood in urine (one at 0 mg/kg/day) (Table 40).

The day of preputial separation (absolute or adjusted with respect to body weight at pnd 40), exhibited a significant delay at both the mid and high dose (Table 41). The absolute mean day of acquisition of PPS was 40.4 for the control group, compared to 44.0 and 44.6 for the mid and high dose groups.

Scheduled Necropsy of the Dosed F1 Pubertal Males. At scheduled sacrifice, body weight exhibited a dose-related decreasing trend, with all three treated groups significantly less than the control group (Table 42). There was no significant difference between the treatment groups for the number of nipples per male (0 for all groups). The following absolute organ weights exhibited a dose-related decreasing trend that was significant at all three dose levels: liver, paired kidney, paired testis, seminal vesicles with coagulating glands, dorsolateral prostate, and whole prostate. Significant decreases in absolute organ weight were observed at the mid and high dose groups for right epididymis, left epididymis, ventral prostate, LABC, and Cowper's glands, whereas only the high dose group was significantly decreased for the pituitary. Absolute paired adrenal gland weight exhibited an increasing trend, but no pairwise differences from the control group. When organ weights were adjusted for necropsy weight, liver, paired adrenal gland, and paired kidney weight all exhibited an increasing trend, with either all the treatment groups (paired kidney) or the mid and high dose groups (adjusted liver and paired adrenal glands) increased significantly compared to the control group. Adjusted pituitary, thyroid, glans penis, paired testis, right and left epididymis, seminal vesicles, and dorsolateral prostate weight showed no treatment effect. Adjusted (pnd 21) paired adrenal weight exhibited an increasing trend. All other adjusted (pnd 21) weights exhibited a decreasing trend with the high dose (pituitary), the mid and high dose (right or left epididymis; ventral or whole prostate; LABC; Cowper's glands), or all the doses (liver, paired kidney, paired testis, seminal vesicles with coagulating glands, and dorsolateral prostate) significantly below the control value.

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Sperm parameters were evaluated for the control and high-dose exposed animals (Table 42). There was no effect of *in utero*/lactational and postweaning exposure to 100 mg/kg/day methoxychlor on the percent motile sperm, percent progressively motile sperm, spermatid head concentration, or efficiency of daily sperm production. Epididymal sperm concentration and daily sperm production per testis were significantly decreased (by 13 and 20%, respectively) compared to the control value.

Circulating T3, and TSH levels, determined for all animals at necropsy, were not affected by *in utero*/lactational and postweaning exposure to methoxychlor (Table 42). T4 concentrations exhibited a treatment effect, with a significant increase only at the mid dose. Observations at necropsy were minimal, and included alopecia in two animals in the low dose group, air present in the intestines in one animal each in the mid and high dose group, hydronephrosis in two, two, and six animals in the control, low, and mid dose groups, reduced LABC in two animals in the high dose group, reduced prostate in one and five animals in the mid and high dose groups, reduced seminal vesicles in one and four animals at the mid and high dose, and undescended testes in one animal each in the control and high dose groups (Table 43). Histopathological examination of the testes, epididymis, and thyroid was unremarkable.

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15.0 DISCUSSION AND CONCLUSIONS

RTI, as the lead laboratory for this assay for the EDSP, is suggesting that if this protocol is implemented, the study design may be too complex for Tier 1 but may be simplified or considered a Tier 2 test assay, preferably in place of the *in vitro* steroidogenesis and placental aromatase assays and the *in vivo* male Hershberger assay, the uterotrophic female assay, and either or both pubertal assays.

A summary of the results of this study, with respect to the F1 animals, is presented below:

F1 preweaning observations. Treatment with methoxychlor at doses up to 100 mg/kg/day during gestation and lactation did not produce significant dose-related effects on live litter size or AGD in male or female offspring. Minimal to no general toxicity was noted, as evidenced by the absence of a dose-related effect on pup body weight or the incidence of clinical signs. Neonatal morbidity/death was observed primarily at the mid and high dose groups, and was, to a large extent, secondary to the morbidity of two dams in the mid dose group, and one dam in the high dose group. At weaning, the F1 females and male (later assigned to the pubertal cohort) exhibited no effect of treatment on absolute or adjusted AGD.

F1 female uterotrophic cohort (n=35). Treatment with methoxychlor at doses up to 100 mg/kg/day during gestation, lactation, and after weaning on pnd 22-24 did not significantly affect F1 female body weight on pnd 21, 22, 23, or 24. No animals in this cohort achieved vaginal patency, although pinhole openings were observed in a few females at both the mid and high dose. At necropsy on pnd 24, both absolute and adjusted paired ovarian weight exhibited an effect (decrease) at both the mid and high dose. The uterus exhibited no treatment effect either in wet uterine weight (absolute or adjusted), or after histopathologic examination. Comparison of the absolute or adjusted wet uterine weight from the control animals in this study to historical control data in the authors' laboratory suggests that the uteri in the uterotrophic cohort of this study were heavier than routinely observed in F1 weanling rats (Tyl et al., 2004).[3]

F1 undosed female pubertal cohort (n=80). F1 females allowed to mature to pnd 42 without additional treatment after pnd 20, exhibited significantly accelerated vaginal opening (absolute and adjusted for body weight on pnd 28), and first estrus at both the mid and high dose levels. There were significant effects on the number of days from vaginal opening to first estrus or the end of the first cycle, average day of the start of the first cycle, and prolonged estrous. At necropsy, UVD, paired ovary weight (absolute, or adjusted for necropsy or pnd 21 weight) was decreased, whereas uterine weight (absolute or adjusted; with or without fluid) was increased by treatment with methoxychlor. Circulating T4, T3, and TSH levels all exhibited increases due to *in utero*/lactational exposure to methoxychlor. No treatment-related histopathology was

[3] In control 21 day-old CD® (SD) rats in the authors' laboratory (n=30), the mean absolute uterine weight is 0.080 ± 0.004 g; the mean adjusted uterine weight is 0.164 ± 0.007g.

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observed in the thyroid. Administration of methoxychlor was associated with the presence of ovarian hypoplasia and cystic follicles at the mid and high dose. The results suggest that some inhibition or delay of follicle development and/or ovulation had occurred. In addition, the uteri of animals in these dose groups exhibited slight hyperplasia and metaplasia of the epithelium. In most cases, changes in the uterine epithelium were present in animals with ovarian hypoplasia, suggesting a hormonal imbalance. However, not all changes in the ovaries were accompanied by changes in the uterus.

F1 dosed female pubertal cohort (n=79). F1 females allowed to mature to pnd 42 with additional treatment from pnd 22 to 42, exhibited significantly accelerated vaginal opening (absolute and adjusted for body weight on pnd 28), decreased age at first estrus, start, or end of the first cycle at all three doses of methoxychlor. A significantly prolonged period for the number of days from vaginal opening to the start or end of the first cycle was observable at the high dose, whereas an increase in the percent females with prolonged estrus was evident at the mid and high dose. At necropsy, UVD was decreased at both the mid and the high dose. Paired ovary weight (absolute, or adjusted for necropsy or pnd 21 weight) was decreased at both the mid and the high dose, whereas uterine weight (absolute or adjusted; with or without fluid) was not affected by treatment with methoxychlor. Circulating T4, T3, and TSH levels showed no effect of treatment. No treatment-related histopathological changes were noted in the thyroid. The mid and high dose animals exhibited histopathological changes in both the ovaries and uterus that mirrored that observed in the undosed F1 females.

F1 undosed male pubertal cohort (n=82). F1 males allowed to mature to pnd 70+ without additional exposure to methoxychlor exhibited slightly delayed preputial separation (absolute or adjusted for body weight on pnd 40) at the mid dose. Absolute and adjusted (pnd 21 body weight) paired testis weight was decreased at the high dose; paired adjusted (necropsy weight) testis weight exhibited a decreasing trend. The effects on other male reproductive organ weights (epididymis, prostate, LABC, Cowper's glands, seminal vesicles with coagulating glands, glans penis), were either unaffected or did not show a consistent treatment effect. The high dose animals exhibited increased spermatid head concentration and efficiency of daily sperm production. Thyroid hormones were not affected. No treatment-related histopathology was noted.

F1 dosed male pubertal cohort (n=80). F1 males allowed to mature to pnd 70+ with additional exposure to methoxychlor from pnd 22 to pnd 70+ exhibited delayed preputial separation (absolute or adjusted for body weight on pnd 40) at the mid and high dose. Absolute and adjusted (pnd 21 body weight) weights for the male reproductive organs exhibited effects at either the mid and high dose, or all three doses. The high dose animals exhibited decreased epididymal sperm concentration and daily sperm production. Circulating T4 levels were increased at the mid dose, but no effect was observed for T3 and TSH. No treatment-related histopathology was noted.

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There is no evidence from the data that a dosing mix-up between mid and high doses occurred during F0 gestation, F0 lactation, or during administration to the F1 postwean dosed cohorts. The vast majority of parameters assessed exhibited appropriate dose-response patterns. The presence of significant effects only at, or greatest at 50 mg/kg/day for only very specific endpoints, e.g., ovarian weights (females), circulating thyroid-related hormones for both sexes, estrous cyclicity effects (females), and effects on PPS (males), also occurred in the F1 female and male undosed cohorts.

Those cases where there were effects at both 50 and 100 mg/kg/day, but a greater effect at 50 mg/kg/day, may be due to saturation of absorption and/or metabolic capability at 50 mg/kg/day, i.e., no greater effects would occur at 100 mg/kg/day. Other than biological variability (which is unlikely), there is no explanation for the effects on a few, very specific, and consistent endpoints only at (or greater at) 50 mg/kg/day. These effects are observed in both dosed and undosed cohorts. In the females, altered ovarian weights may be responsible for hormone-mediated estrous cyclicity effects. In the F1 males, testes weights were reduced at all doses and this could be responsible for the delay in hormone-mediated PPS. The effects on circulating thyroid-related hormones, especially elevated TSH, may indicate that there were reductions in T4 and T3 (not detected analytically but detected by the organism) and may also impact (delay) pubertal (PPS) and post pubertal (estrous cyclicity) endpoints.

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16.0 REFERENCES

Agresti, A. (1990). Categorical Data Analysis. John Wiley and Sons, NY.

Anderson, S.A., P.A. Fail, B.J. McTaggart, R.W. Tyl, and L.E. Gray, Jr. (1994). Reproductive toxicity of methoxychlor (M) in corn oil to male and female Long-Evans hooded rats using the alternative reproduction test protocol (ART). *Biol. Reprod.* **50 (Suppl. 1),** 101.

Anderson, S.A., S.W. Pearce, P.A. Fail, B.J. McTaggart, R.W. Tyl, and L.E. Gray, Jr. (1995). Validation of the alternative reproductive test protocol (ART) to assess toxicity of methoxychlor in rats. *The Toxicologist* **15(1),** 164.

Aoyama, H., R.E. Chapin, K. Ebino, and S. Teramoto (2000). Endocrine disrupting effects of organochlorine pesticides and their reproductive and developmental toxicity. *Teratology* **62(3),** 7A-8A (Abstract No. SIII-3).

Armitage, P. (1955). Test for linear trends in proportions and frequencies. *Biometrics* **11,** 375-386.

Ashby, J., H. Tinwell, P.A. Lefevre, J. Odum, D. Paton, S.W. Millward, S. Tittensor, and A.N. Brooks (1997). Normal sexual development of rats exposed to butyl benzyl phthalate from conception to weaning. *Reg. Tox. Pharmacol.* **26,** 102-118.

Bal, H.S. (1984). Effect of methoxychlor on reproductive systems of the rat. *Proc. Soc. Exp. Biol. Med.* **176(2),** 187-196.

Biegel, L.B., J.C. Cook, M.E. Hurtt, and J.C. O'Connor (1998a). Effects of 17 beta-estradiol on serum hormone concentrations and estrous cycle in female Crl:CD BR rats: effects on parental and first generation rats. *Toxicol. Sci.* **44,** 143-154.

Chapin, R.E., M.W. Harris, M.D. Shelby, R.J. Smialowicz, V.C. Moser, S. Padilla, R.C. MacPhail, S. Berone, A.C. Lockhart, and M.A. Mauney (1996). The effects of perinatal/juvenile pesticide exposure on adult CNS, immune, and reproductive function in rats. *The Toxicologist* **30(Part 2),** 52.

Chapin, R.E., M.W. Harris, B.J. Davis, S.M. Ward, R.E. Wilson, M.A. Mauney, A.C. Lockhart, R.J. Smialowicz, V.C. Moser, L.T. Burka, and B.J. Collins (1997). The effects of perinatal/juvenile methoxychlor exposure on adult rat nervous, immune and reproductive system function. *Fundam. Appl. Toxicol.* **40(1),** 138-157.

Chapin, R.E., Delaney, J., Wang, Y., Lanning, L., Davis, B., Collins, B., Mintz, N., AND Wolfe, G. (1999). The effects of 4-nonylphenol in rats: a multigeneration reproduction study. *Toxicol. Sci.* **52(1),** 80-91

Charles River (1988). Embryo and Fetal Developmental Toxicity (Teratology) Control Data in the Charles River Crl:CD® BR Rat. Charles River Laboratories, Inc., Wilmington, MA.

US EPA ARCHIVE DOCUMENT

Cochran, W. (1954). Some methods for strengthening the common P2 tests. *Biometrics* **10,** 417-451.

Cummings, A.M., and Gray, L.E. Jr. (1987). Methoxychlor affects the decidual cell response of the uterus but not other progestational parameters in female rats. *Toxicol. Appl. Pharmacol.* **90(2),** 330-336.

Cummings, A.M., and Gray, L.E. Jr. (1989). Antifertility effect of methoxychlor in female rats: dose- and time-dependent blockage of pregnancy. *Toxicol. Appl. Pharmacol.* **97,** 454-462.

Cummings, A.M., and S.D. Perreault (1990). Methoxychlor accelerates embryo transport through the rat reproductive tract. Toxicol. Appl. Pharmacol. **102(1),** 110-116.

Cummings, A.M., and J. Laskey (1992). Methoxychlor administration during early pregnancy alters ovarian steroidogenesis. *The Toxicologist* **12(1),** 432.

Cummings, A.M., and J. Laskey (1993). Effect of methoxychlor on ovarian steroidogenesis: role in early pregnancy loss. *Reprod. Toxicol.* **7(1),** 17-23.

Cummings, A.M. and Metcalf, J.L. (1994). Mechanisms of the stimulation of rat uterine peroxidase activity by methoxychlor. Reprod Toxicol. **8(6),** 477-86.

Cummings, A.M., and J.L. Metcalf (1995a). Methoxychlor regulates rat uterine estrogen-induced protein. *Toxicol. Appl. Pharmacol.* **130(1),** 154-160.

Cummings, A.M., and J.L. Metcalf (1995b). Effects of estrogen, progesterone, and methoxychlor on surgically induced endometriosis in rats. *Fundam. Appl. Toxicol.* **27(2),** 287-290.

Cummings, A.M. (1997). Methoxychlor as a model for environmental estrogens. *Crit. Rev. Toxicol.* **27(4),** 367-379.

Cupp, A.S., and M.K. Skinner (2000). Effect of the endocrine disruptor methoxychlor and its metabolite HPTE on morphology and growth of the developing testis. *Biol. Reprod.* **62(Suppl. 1),** 286.

Cupp, A.S., and M.K. Skinner (2001). Actions of the endocrine disruptor methoxychlor and its estrogenic metabolite on *in vitro* embryonic rat seminiferous cord formation and perinatal testis growth. *Reprod. Toxicol.* **15(3),** 317-326.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50,** 1096-1121.

US EPA ARCHIVE DOCUMENT

Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics* **20,** 482-491.

Dussault, J.H., and Ruel, J. (1987). Thyroid hormones and brain development. *Annual Rev. Physiol.* **49,** 321-334.

Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) (1998). Final Report, Volume I.

Eroschenko, V.P. (1991). Ultrastructure of vagina and uterus in young mice after methoxychlor exposure. *Reprod. Toxicol.* **5(5),** 427-435.

Eroschenko, V.P., A.A. Abuel-Atta, and M.S. Grober (1995). Neonatal exposures to technical methoxychlor alters ovaries in adult mice. *Reprod. Toxicol.* **9(4),** 379-387.

Eroschenko, V.P., A.W. Rourke, and W.F. Sims (1996). Estradiol or methoxychlor stimulates estrogen receptor (ER) expression in uteri. *Reprod. Toxicol.* **10(4),** 265-271.

Eroschenko, V.P., W.J. Swartz, and L.C. Ford (1997). Decreased superovulation in adult mice following neonatal exposures to technical methoxychlor. *Reprod. Toxicol.* **11(6),** 807-814.

Eroschenko, V.P., T.J. Johnson, and A.W. Rourke (2000). Estradiol and pesticide methoxychlor do not exhibit additivity or synergism in the reproductive tract of adult ovariectomized mice. *J. Toxicol. Environ. Health* **60(6),** 407-421.

J.D. George and R. W. Tyl (2001). Detailed Review Paper on *In Utero*/Lactational Protocol. Endocrine Disruptor Screening Program, U. S. Enviromental Protection Agency. http://www.epa.gov/scipoly/oscpendo/docs/edmvs/in_utero_lactation_drp_nov_19_2001.pdf

Gilbert, S.F. (1997). Chapter 20. Sex determination. In: Developmental Biology, Fifth Edition. Sinauer Associates, Inc., Publishers, Sunderland, MA, pp. 773-804.

Goldman, J.M., R.L. Cooper, G.L. Rehnberg, J.F. Hein, W.K. McElroy, and L.E. Gray, Jr. (1986). Effects of low subchronic doses of methoxychlor on the rat hypothalamic-pituitary reproductive axis. *Toxicol. Appl. Pharmacol.* **86(3),** 474-483.

Goldman, J.M., S.C. Laws, S.K. Balchak, R.L. Cooper, and R.J. Kavlock (2000). Endocrine-disrupting chemicals: prepubertal exposures and effects on sexual maturation and thyroid activity in the female rat. A focus on the EDSTAC recommendations. *Crit. Rev. Toxicol.* **30(2),** 135-196.

Gray, L.E. Jr., J. Ostby, J. Ferrell, G. Rehnberg, R. Linder, R. Cooper, J. Goldman, V. Slott, and J. Laskey (1989). A dose-response analysis of methoxychlor-induced alterations of reproductive development and function in the rat. *Fundam. Appl. Toxicol.* **12,** 92-108.

US EPA ARCHIVE DOCUMENT

Gray, L.E. Jr., and Ostby J. (1998). Effects of pesticides and toxic substances on behavioral and morphological reproductive development: endocrine versus nonendocrine mechanisms. *Toxicol. and Indust. Health* **14(1/2),** 159-184.

Gray, L.E. Jr., J. Ostby, C. Wolf, C. Lambright, and W. Kelce (1998). Annual Review. The value of mechanistic studies in laboratory animals for the production of reproductive effects in wildlife: endocrine effects on mammalian sexual differentiation. *Environm. Toxicol. Chem.* **17(1),** 109-118.

Gray, L.E. Jr., J. Ostby, R.L. Cooper, and W.R. Kelce (1999). The estrogenic and antiandrogenic pesticide methoxychlor alters the reproductive tract and behavior without affecting pituitary size or LH and prolactin secretion in male rats. *Toxicol. Ind. Health* **15(1-2),** 37-47.

Hafez, E.S.E. (ed.) (1970). Reproduction and Breeding Techniques for Laboratory Animals. Lea and Febiger, Philadelphia, PA.

Hall, D.L., L.A. Payne, J.M. Putnam, and Y.M. Huet-Hudson (1997). Effect of methoxychlor on implantation and embryo development in the mouse. *Reprod. Toxicol.* **11(5),** 703-708.

Hanley, T.R. Jr., and P.G. Watanabe (1985). Measurement of solid feed consumption patterns in neonatal rats by 141 Ce-radiolabeled microspheres. *Toxicol Appl Pharmacol.* **77(3)**, 496-500.

Harris, M.W., R.E. Chapin, E.A. Haskins, J.D. Allen, B.J. Collins, B.J. Davis, A.C. Lockhart, and M. Mauney (1996). The effects of perinatal/juvenile pesticide exposure on adult reproductive function. I. Methoxychlor. *The Toxicologist* **30(1 Part 2),** 144.

Howdeshell, K.L., L.C. Alworth, R. Ruhlen, and F.S. vom Saal (1999). Prenatal exposure to diethylstilbestrol and methoxychlor alters uterine response to estrogen in adult mice. *Amer. Zool.* **39(5),** 25A.

Huber, P.J. (1967). The behavior of maximum likelihood estimates under nonstandard conditions. In: Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability 1, 221-233.

Hunt, P.A., K.E. Koechler, J. Susiarjo, C.A. Hodges, A. Llagan, R.C. Voight, S. Thomas, B.F. Thomas, and T.J. Hassold (2003). Bisphenol A exposure causes meiotic aneuploidy in female mouse. *Current Biology* **13,** 546-553.

Johnson, L., R.E. Chapin, M.W. Harris, R.L. Silge, A.C. Guidry, and W.R. Lee (2000). Perinatal/juvenile exposure to methoxychlor reduces Sertoli cell numbers in adult rats. *The Toxicologist* **54(1),** 364.

US EPA ARCHIVE DOCUMENT

Levene, H. (1960). Robust tests for the equality of variance. In: Contributions to Probability and Statistics (I. Olkin, S.G. Ghurye, W. Hoeffding, W.G. Madow, and H.B. Mann, Eds.), Palo Alto, CA, Liang, K., and S. Zeger (1986). Longitudinal data analysis using generalized linear models. *Biometrika* **73,** 13-22.

Mahendroo, M.S., K.M. Cala, D.L. Hess, and D.W. Russell (2001). Unexpected virilization in male mice lacking steroid 5 alpha-reductase enzymes. *Endocrinol.* **142(11),** 4652-4562.

Maness, S.C., D.P. McDonnell, and K.W. Gaido (1998). Inhibition of androgen receptor-dependent transcriptional activity by DDT isomers and methoxychlor in HepG2 human hepatoma cells. *Toxicol. Appl. Pharmacol.* **151(1),** 135-142.

Martinez, E.M., and W.J. Swartz (1991). Effects of methoxychlor on the reproductive system of the adult female mouse. 1. Gross and histologic observations. *Reprod. Toxicol.* **5(2),** 139-147.

Martinez, E.M., and W. J. Swartz (1992). Effects of methoxychlor on the reproductive system of the adult female mouse. 2. Ultrastructural observations. *Reprod. Toxicol.* **6(1),** 93-98.

McIntyre, B.S., Barlow, N.J., Wallace, D.G., Maness, S.C., Gaido, K.W., and Foster, P.M. (2000). Effects of *in utero* exposure to linuron on androgen-dependent reproductive development in the male Crl:CD(SD)BR rat. *Toxicol. Appl. Pharmacol.* **167(2),** 87-99.

McIntyre, B.S., N.J. Barlow, and P.M. Foster (2001). Androgen-mediated development in male rat offspring exposed to flutamide *in utero*: permanence and correlation of early postnatal changes in anogenital distance and nipple retention with malformations in androgen-dependent tissues. *Toxicol. Sci.* **62(2),** 236-249.

McIntyre, B.S., N.J. Barlow, and P.M. Foster (2002). Male rats exposed to linuron *in utero* exhibit permanent changes in anogenital distance, nipple retention, and epididymal malformations that result in subsequent testicular atrophy. *Toxicol. Sci.* **65(1),** 62-70

NRC (1996). Guide for the Care and Use of Laboratory Animals. Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. Revised 1996.

Oppenheimer, J.H., H.L. Schwartz, and K.A. Strait (1994). Thyroid hormone action 1994: the plot thickens. *Eur. J. Endocrinol.* **130(1),** 15-24.

Parker, K.L., and B.P. Schimmer (1997). Steroidogenic factor 1: a key determinant of endocrine development and function. *Endocrine Rev.* **18(3),** 361-377.

Perez-Castillo, A., J. Bernal, B. Ferreiro, and T. Pans (1985). The early ontogenesis of thyroid hormone receptor in the rat fetus. *Endocinology* **(117)**, 2457-2461.

US EPA ARCHIVE DOCUMENT

Porterfield, S.P., and C.E. Hendrich (1993). The role of thyroid hormones in prenatal neonatal neurological development – current perspectives. *Endocrine Rev.* **(14),** 94-106.

Porterfield, S.P., and S.A. Stein (1994). Thyroid hormones and neurological development: Update 1994. *Endocrine Rev.* **(3),** 357-363.

Quigley, C.A., A. DeBellis, K.B. Marschke, M.K. El-Awady, E.A. Wilson, and F.S. French (1995). Androgen receptor defects: historical, clinical and molecular perspectives. *Endocrine Rev.* **16(3),** 271-321.

Respess, D.S. Jr., R.L. Carr, N.M. Cox, C.P. McCoy, A.B. Moore, and J.E. Chambers (1999). Evaluation of the reproductive parameters in rats affected by the interactions of polychlorinated biphenyls and methoxychlor resulting from exposure during development. *The Toxicologist* **48(1),** 374-375.

Robb, G.W., R.P. Amann, and G.H. Killian (1978). Daily sperm production and epididymal sperm reserves of pubertal and adult rats. *J. Reprod. Fertil.* **54,** 103-107.

RTI (2001). SUDAAN User's Manual, Release 8.0. Research Triangle Park, NC: Research Triangle Institute.

Royall, R.M. (1986). Model robust confidence intervals using maximum likelihood estimators. *International Statistical Review* **54,** 221-226.

Sadovsky, Y., and C. Dorn (2000). Function of steroidogenic factor 1 during development and differentiation of the reproductive system. *Rev. of Reprod.* **5,** 136-142.

Salewski, E. (1964). Farbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.* **247,** 367.

Sar, M., R. Sriperumbudlar, B. McIntyre, E. Bartolucci, and L. You (2001). Effects of dietary exposure to genistein and methoxychlor on mammary gland development in juvenile rats. *The Toxicologist* **60(1),** 295.

SAS Institute Inc. (1999a). SAS® Language Reference: Concepts, Version 8, Cary, NC: SAS Institute Inc. 554 pp.

SAS Institute Inc. (1999b). SAS/STAT® Users' Guide, Version 8, Cary, NC: SAS Institute Inc. 3884 pp.

SAS Institute Inc. (1999c). SAS® Language Reference: Dictionary, Version 8, Cary, NC: SAS Institute Inc. 1244 pp.

SAS Institute Inc. (1999d). SAS® Procedures Guide, Version 8, Cary, NC: SAS Institute Inc. 1643 pp.

US EPA ARCHIVE DOCUMENT

SAS Institute Inc. (1999e). SAS® Companion for the Microsoft Windows Environment, Version 8, Cary, NC: SAS Institute Inc. 562 pp.

SAS Institute Inc. (2000). SAS/STAT® Software: Changes and Enhancements, Release 8.1, Cary, NC: SAS Institute Inc. 554 pp.

Schardein, J.L. (1999). Reproductive Hazards. In: Product Safety Evaluation Handbook (S. Gad, Ed.), Marcel Dekker, NY, pp. 299-380.

Sharpe, R.M., J.S. Fisher, M.M. Millar, S. Jobling, and J.P. Sumpter (1995). Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. *Env. Health Perspect.* **103,** 1136-1143.

Shimizu, N., K. Hayashi, H. Kawa-Katsu, K. Mezawa, T. Iida, Y. Kubo, H. Kushida, M. Kikuta, K. Takahashi, H. Hojo, H. Aoyama, and S. Teramato (2000). Teratogenicity studies in rats and rabbits with methoxychlor (Methoxychlor). *Teratology* **62(3),** 45A (Abstract No. P-116).

Snedecor , G.W., and W.G. Cochran (1967). Statistical Methods. Sixth Edition, Iowa State University Press, Ames, IA.

Stoker, T.E., C.L. Robinette, and R.L. Cooper (1999). Perinatal exposure to estrogenic compounds and the subsequent effects on the prostate of the adult rat: evaluation of inflammation in the ventral and lateral lobes. *Reprod. Toxicol.* **13(6),** 463-472.

Stoker, T.E., L.G. Parks, L.E. Gray, and R.L. Cooper (2000). Endocrine-disrupting chemicals: prepubertal exposures and effects on sexual maturation and thyroid function in the male rat. A focus on the EDSTAC recommendations. *Criti. Rev. Toxicol.* **30(2),** 197-252.

Swain, A., and R. Lovell-Badge (1999). Mammalian sex determination: a molecular drama. *Genes & Develop.* **13,** 755-767.

Swartz, W.J., and L.J. Vial, Jr. (1996). Exposure to methoxychlor early in pregnancy disrupts implantation. *FASEB J.* **10(3),** A260.

Swartz, W.J., and V.P. Eroschenko (1998). Neonatal exposure to technical methoxychlor alters pregnancy outcome in female mice. *Reprod. Toxicol.* **12(6),** 565-573.

Timiras, P.S., and E.U. Nzekwe (1989). Thyroid hormones and nervous system development. *Biol. Neonate* **55(6),** 376-85.

Tyl, R.W., C.B. Myers, M.C. Marr, D.R. Brine, P.A. Fail, J.C. Seely, and J.P. Van Miller (1999). Two-generation study with para-tert-octylphenol in rats. *Regul. Toxicol. Pharmacol.* **30,** 81-95.

US EPA ARCHIVE DOCUMENT

Tyl, R.W., C.B. Myers, M.C. Marr, T.Y. Chang, J.C. Seely, D.R. Brine, M.M. Veselica, P.A. Fail, R.L. Joiner, J.H. Butala, S.S. Dimond, R.N. Shiotsuka, G. Stropp, G.E. Veenstra, J.M. Waechter, and L.R. Harris (2001). Three-generation Reproductive Toxicity Study of Bisphenol A (BPA) Administered in the Diet to CD® (Sprague-Dawley) Rats. *The Toxicologist* **60(1),** 297 (Abstract No. 1410A).

Tyl, R.W., C.B. Myers, M.C. Marr, B.F. Thomas, A.R. Keimowitz, D.R. Brine, M.M. Veselica, P.A. Fail, T.Y. Chang, J.C. Seely, R.L. Joiner, J.H. Butala, S.S. Dimond, S.Z. Cagen, R.N. Shiotsuka, G.D. Stropp, and J.M. Waechter (2002). Three-generation reproductive toxicity study of dietary bisphenol A (BPA) in CD® (Sprague-Dawley) rats. *Toxicol. Sci.* (in press).

Tyl, R.W., C.B. Myers, M.C. Marr, P.A. Fail, J.C. Seely, D.R. Brine, R.A. Barter, and J.H. Butala (2004). Reproductive toxicity evaluation of dietary butyl benzl phthalate (BBP) in rats. *Reproductive Toxicology* **18,** 241-264.

U.S. Environmental Protection Agency (EPA) (1996). Part II, Environmental Protection Agency: Reproductive Toxicity Risk Assessment Guidelines; Notice. *Federal Register* **61 (212)**, 56274-56322 (October 31, 1996).

Waters, K.M., S. Safe, K.S. Korach, and K.W. Gaido (2000). Investigating the mechanism of methoxychlor toxicity through estrogen receptors alpha and beta using cDNA array technology. *The Toxicologist* **54(1),** 239.

Welshons, W.V., S.C. Nagel, K.A. Thayer, B.M. Judy, and F.S. vom Saal (1999). Low-dose bioactivity of xenoestrogens in animals: fetal exposure to low doses of methoxychlor and other xenoestrogens increases adult prostate size in mice. *Toxicol. Ind. Health* **15(1-2),** 12-25.

White, K.L. Jr., J.A. McCay, D.L. Musgrove, D.R. Germolec, R.R. Newbold, K.B. Delclos, and T.L. Guo (2001). Enhanced CD3-mediated splenocyte proliferation in F0 and F1 generations of SD rats following exposure to endocrine disruptors: ethinyl estradiol, nonylphenol, genistein, vinclozolin, and methoxychlor. *The Toxicologist* **60(1),** 29.

Wolf, C.J., A. Hotchkiss, J.S. Ostby, G.A. LeBlanc, and L.E. Gray, Jr. (2002). Effects of prenatal testosterone propionate on the sexual development of male and female rats: a dose-response study. *Toxicol. Sci.* **65,** 71-86.

Zeger, S. and K. Liang (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* **42,** 121-130.

Zeger, S., K.Y. Liang, and P.S. Albert (1988). Models for longitudinal data: a generalized estimating equation approach. *Biometrics* **44,** 1049-1060.

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Table 1. Analyses of Dose Formulations of Methoxychlor in Corn Oil[a]

RTI Rx Code	RTI Color Code	Battelle Sample Code	Sample Type[b]	Nominal Concentration (mg/ml)	Analytical Concentration (mg/ml)[c]	Mean % of Nominal ± RSD[d]
NA	NA	2-23-A Rep 1	predosing	0	0	ND[e]
NA	NA	2-23-B Rep 1 R-1 to R-3	predosing	5	5.23	105 ± 7
NA	NA	2-23-C Rep 1 R-1 to R-3	predosing	10	9.95	99 ± 5
NA	NA	2-23-D Rep 1 R-1 to R-3	predosing	20	19.7	99 ± 2
NA	NA	2-23-A Rep 3	predosing	0	0	ND
NA	NA	2-23-B Rep 3 R-1 to R-3	predosing	5	5.30	106 ± 5
NA	NA	2-23-C Rep 3 R-1 to R-3	predosing	10	10.7	107 ± 8
NA	NA	2-23-D Rep 3 R-1 to R-3	predosing	20	20.8	104 ± 3
NA	NA	2-23-A Rep 4	predosing	0	0	ND
NA	NA	2-23-B Rep 4 R-1 to R-3	predosing	5	4.62	92 ± 2
NA	NA	2-23-C Rep 4 R-1 to R-3	predosing	10	9.54	95 ± 2
NA	NA	2-23-D Rep 4 R-1 to R-3	predosing	20	18.2	91 ± 2
NA	NA	2-23-A Rep 5	predosing	0	0	ND
NA	NA	2-23-B Rep 5 R-1 to R-3	predosing	5	4.34	87 ± 1
NA	NA	2-23-C Rep 5 R-1 to R-3	predosing	10	9.82	98 ± 5
NA	NA	2-23-D Rep 5 R-1 to R-3	predosing	20	19.3	97 ± 2
NA	NA	2-23-A Rep 6	predosing	0	0	ND
NA	NA	2-23-B Rep 6 R-1 to R-3	predosing	5	5.40	108 ± 4
NA	NA	2-23-C Rep 6 R-1 to R-3	predosing	10	10.2	102 ± 1
NA	NA	2-23-D Rep 6 R-1 to R-3	predosing	20	19.4	97 ± 4
66560	Yellow	2-23-B Rep 1	in-life gd 6	5	4.45	89
66560	Yellow	2-23-B Rep 1	in-life pnd 0	5	4.57	91
66560	Yellow	2-23-B Rep 3	in-life pnd 7	5	5.04	101
66560	Yellow	2-23-B Rep 3	in-life pnd 14	5	4.92	98
66560	Yellow	2-23-B Rep 3	in-life pnd 21	5	4.91	98
79638	Blue	2-23-C Rep 1	In-life gd 6	10	9.29	93
79638	Blue	2-23-C Rep 1	in-life pnd 0	10	9.10	91

(continued)

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Table 1. Analyses of Dose Formulations of Methoxychlor in Corn Oil[a] (continued)

RTI Rx Code	RTI Color Code	Battelle Sample Code	Sample Type[b]	Nominal Concentration (mg/ml)	Analytical Concentration (mg/ml)[c]	Mean % of Nominal ± RSD[d]
79638	Blue	2-23-C Rep 3	in-life pnd 7	10	9.39	94
79638	Blue	2-23-C Rep 3	in-life pnd 14	10	8.53	85
79638	Blue	2-23-C Rep 3	in-life pnd 21	10	9.95	99
18661	Red	2-23-D Rep 1	In-life gd 6	20	17.4	87
18661	Red	2-23-D Rep 1	in-life pnd 0	20	18.0	90
18661	Red	2-23-D Rep 3	in-life pnd 7	20	18.2	91
18661	Red	2-23-D Rep 3	in-life pnd 14	20	16.7	83
18661	Red	2-23-D Rep 3	in-life pnd 21	20	16.9	85
93766	Green	2-23-A Rep 2	postdosing	0	0	--
66560	Yellow	2-23-B Rep 2	postdosing	5	4.27	85
79638	Blue	2-23-C Rep 2	postdosing	10	8.93	89
18661	Red	2-23-D Rep 2	postdosing	20	17.5	88
93766	Green	2-23-A Rep 3	postdosing	0	0.19	--
66560	Yellow	2-23-B Rep 3	postdosing	5	4.96	99
79638	Blue	2-23-C Rep 3	postdosing	10	9.13	91
18661	Red	2-23-D Rep 3	postdosing	20	16.4	82

[a] Dosing solutions were formulated in corn oil vehicle for administration at 5 ml/kg. The doses were therefore 0, 25, 50, and 100 mg/kg/day methoxychlor.

[b] Samples were taken prior to shipping from Battelle to RTI (preship), on the first day dosing (in-life) for gd 6 and pnd 0, 7, 14, and, and after dosing was completed (postdosing).

[c] n=3 for individual determinations.

[d] Data are presented as mean % (% relative standard deviation).

[e] ND = not detected; estimated limit of detection is 115 microg/ml.

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Table 2. Summary of the Fate of the F_0 Females (page 1 of 1)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females on Study	15	15	15	15
Fate of Females:				
Removed from Study	2[a]	4[b]		1[c]
Removed from Study after Gestation		1[d]		1[e]
Found Dead on Gestational Day 23				1[f]
Scheduled Sacrifice on Gestational 26[g]	1	1		2
Euthanized Moribund on Postnatal Day 1				1
Euthanized Moribund on Postnatal Day 2			1	
Euthanized Moribund on Postnatal Day 3			1	
Scheduled Sacrifice on Postnatal Day 21	12	9	13	9

[a]Female 24 was found dead on gestational day 19 (misdirected dose) and female 39 was removed from the study due to a misdirected dose confirmed at necropsy.
[b]Females 15 and 22 were removed from the study due to misdirected doses confirmed at necropsy. Female 41 was euthanized moribund on gestational day 17 (misdirected dose) and female 56 was euthanized moribund on gestational day 18 (misdirected dose).
[c]Female 52 was removed from the study due to a misdirected dose confirmed at necropsy.
[d]Female 43 was removed from the study after gestation because the correct postnatal day 0 could not be confirmed.
[e]Female 34 was removed from the study after gestation because the correct postnatal day 0 could not be confirmed.
[f]Female was found dead on gestational day 23 while in the process of delivering.
[g]These females were not pregnant.

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Table 3. Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Change During Gestation (page 1 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Pregnant Females	12	10	15	12
Body Weight (gd 0) (g)[a]				
	241.2 ± 3.2 N=12	240.2 ± 2.5 N=10	241.7 ± 2.8 N=15	241.9 ± 3.2 N=12
Body Weight (gd 6) (g)[a]				
	280.2 ± 3.6 N=12	276.3 ± 3.8 N=10	280.5 ± 2.8 N=15	272.1 ± 3.3 N=12
Body Weight (gd 9) (g)[a]				
	285.5 ‡‡ ± 4.6 §§ N=12	271.9 ± 4.4 N=10	274.9 ± 3.5 N=15	264.5 ** ± 3.6 N=12
Body Weight (gd 12) (g)[a]				
	307.5 ‡‡‡ ± 4.9 §§§ N=12	282.9 ** ± 3.9 N=10	285.8 ** ± 4.2 N=15	271.7 *** ± 4.2 N=12
Body Weight (gd 15) (g)[a]				
	322.5 ‡‡‡ ± 5.7 §§§ N=12	297.7 ** ± 4.7 N=10	295.1 ** ± 5.6 N=15	276.2 *** ± 4.5 N=12
Body Weight (gd 18) (g)[a]				
	361.7 ‡‡‡ ± 6.8 §§§ N=12	336.5 * ± 4.4 N=10	331.0 *** ± 5.7 N=15	309.7 *** ± 4.2 N=12
Body Weight (gd 20) (g)[a]				
	387.5 ‡‡‡ ± 10.8 §§§ N=12	362.5 ± 4.1 N=10	355.2 * ± 7.7 N=15	330.7 *** ± 6.1 N=12
Body Weight Change (gd 0 to 6) (g)[a]				
	39.0 ‡ ± 1.9 § N=12	36.1 ± 2.5 N=10	38.8 ± 2.4 N=15	30.1 * ± 1.7 N=12

(continued)

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Table 3. Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Change During Gestation (page 2 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (gd 6 to 9) (g)[a]				
	5.3 ‡‡ ± 3.3 §§ N=12	-4.5 * ± 2.2 N=10	-5.6 ** ± 2.6 N=15	-7.5 ** ± 1.8 N=12
Body Weight Change (gd 9 to 12) (g)[a]				
#	22.0 ††† ± 1.6 ŸŸŸ N=12	11.1 ÞÞÞ ± 1.5 N=10	10.9 ÞÞÞ ± 2.2 N=15	7.1 ÞÞÞ ± 2.0 N=12
Body Weight Change (gd 12 to 15) (g)[a]				
	15.0 ‡ ± 1.6 §§ N=12	14.8 ± 2.8 N=10	9.3 ± 3.0 N=15	4.5 * ± 2.0 N=12
Body Weight Change (gd 15 to 18) (g)[a]				
#	39.2 ± 1.9 Ÿ N=12	38.9 ± 1.7 N=10	35.9 ± 3.3 N=15	33.5 ± 2.1 N=12
Body Weight Change (gd 18 to 20) (g)[a]				
	25.9 ± 5.3 N=12	26.0 ± 1.6 N=10	24.2 ± 2.4 N=15	21.0 ± 2.5 N=12
Body Weight Change (gd 6 to 20, treatment period) (g)[a]				
	107.3 ‡‡‡ ± 8.0 §§§ N=12	86.2 ± 4.5 N=10	74.8 ** ± 7.0 N=15	58.6 *** ± 4.7 N=12
Body Weight Change (gd 0 to 20) (g)[a]				
	146.3 ‡‡‡ ± 8.9 §§§ N=12	122.3 ± 4.3 N=10	113.6 ** ± 7.9 N=15	88.8 *** ± 4.9 N=12

(continued)

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Table 3. Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Change During Gestation (page 3 of 3)

[a]Reported as the mean ± S.E.M.; gd = gestational day.
[#]Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.
[‡]$p<0.05$; ANOVA Test.
[‡‡]$p<0.01$; ANOVA Test.
[‡‡‡]$p<0.001$; ANOVA Test.
[§]$p<0.05$; Test for Linear Trend.
[§§]$p<0.01$; Test for Linear Trend.
[§§§]$p<0.001$; Test for Linear Trend.
[*]$p<0.05$; Dunnett's Test.
[**]$p<0.01$; Dunnett's Test.
[***]$p<0.001$; Dunnett's Test.
[†††]$p<0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.
[Ÿ]$p<0.05$; Linear trend test in robust regression model.
[ŸŸŸ]$p<0.001$; Linear trend test in robust regression model.
[ÞÞÞ]$p<0.001$; Individual t-test for pairwise comparisons to control in robust regression model.

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Table 4. Summary and Statistical Analysis of the F_0 Female Feed Consumption During Gestation
(page 1 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Pregnant Females	12	10	15	12
Feed Consumption (gd 0 to 6) (g/day)[a]				
	22.5 ± 0.7 N=12	21.6 ± 1.0 N=10	22.8 ± 0.4 N=15	21.6 ± 0.5 N=11[b]
Feed Consumption (gd 6 to 9) (g/day)[a]				
	19.1 ‡‡‡ ± 1.2 §§§ N=10[c]	15.3 * ± 0.9 N=10	15.1 * ± 1.0 N=15	12.3 *** ± 0.8 N=11[d]
Feed Consumption (gd 9 to 12) (g/day)[a]				
	19.0 ‡‡ ± 2.1 §§ N=11[c]	15.0 ± 1.0 N=10	15.6 ± 0.8 N=15	12.7 ** ± 0.5 N=12
Feed Consumption (gd 12 to 15) (g/day)[a]				
	22.2 ‡‡‡ ± 0.8 §§§ N=12	20.2 ± 1.0 N=10	15.8 *** ± 1.6 N=15	13.0 *** ± 0.8 N=12
Feed Consumption (gd 15 to 18) (g/day)[a]				
	24.0 ‡‡‡ ± 0.9 §§§ N=12	20.5 ± 1.1 N=10	19.5 ** ± 1.1 N=15	15.2 *** ± 0.6 N=12
Feed Consumption (gd 18 to 20) (g/day)[a]				
	21.0 ± 2.0 § N=12	19.6 ± 1.1 N=9[d]	19.9 ± 1.1 N=15	16.0 ± 0.9 N=12
Feed Consumption (gd 6 to 20, treatment period) (g/day)[a]				
	21.0 ‡‡‡ ± 0.9 §§§ N=10[e]	18.4 ± 0.6 N=9[e]	17.0 *** ± 0.7 N=15	13.7 *** ± 0.4 N=11[e]
Feed Consumption (gd 0 to 20) (g/day)[a]				
	21.4 ‡‡‡ ± 0.8 §§§ N=10[e]	19.2 ± 0.5 N=9[e]	18.7 ** ± 0.6 N=15	16.1 *** ± 0.4 N=11[e]

(continued)

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Table 4. Summary and Statistical Analysis of the F_0 Female Feed Consumption During Gestation
(page 2 of 2)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Feed Consumption (gd 0 to 6) (g/kg/day)[a]				
	86.3 ± 1.9 N=12	83.4 ± 3.4 N=10	87.3 ± 1.5 N=15	83.5 ± 1.5 N=11[b]
Feed Consumption (gd 6 to 9) (g/kg/day)[a]				
	67.7 ‡‡‡ ± 3.6 §§§ N=10[c]	55.5 ± 3.0 N=10	54.1 * ± 3.5 N=15	45.7 *** ± 2.9 N=11[d]
Feed Consumption (gd 9 to 12) (g/kg/day)[a]				
	63.9 ‡ ± 6.7 §§ N=11[c]	54.0 ± 3.4 N=10	55.5 ± 2.2 N=15	47.3 * ± 1.8 N=12
Feed Consumption (gd 12 to 15) (g/kg/day)[a]				
#	70.3 ††† ± 1.7 ŸŸŸ N=12	69.3 ± 3.1 N=10	53.8 ÞÞ ± 5.2 N=15	47.4 ÞÞÞ ± 2.7 N=12
Feed Consumption (gd 15 to 18) (g/kg/day)[a]				
	70.1 ‡‡‡ ± 2.3 §§§ N=12	64.7 ± 3.4 N=10	62.2 ± 3.0 N=15	52.0 *** ± 2.1 N=12
Feed Consumption (gd 18 to 20) (g/kg/day)[a]				
	55.1 ± 5.0 N=12	55.7 ± 3.2 N=9[d]	58.0 ± 3.1 N=15	49.8 ± 2.1 N=12
Feed Consumption (gd 6 to 20, treatment period) (g/kg/day)[a]				
	64.9 ‡‡‡ ± 1.6 §§§ N=10[e]	60.1 ± 1.8 N=9[e]	55.7 *** ± 1.8 N=15	47.3 *** ± 1.2 N=11[e]
Feed Consumption (gd 0 to 20) (g/kg/day)[a]				
	68.6 ‡‡‡ ± 1.5 §§§ N=10[e]	64.9 ± 1.4 N=9[e]	63.4 * ± 1.2 N=15	56.8 *** ± 0.9 N=11[e]

(continued)

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Table 4. Summary and Statistical Analysis of the F_0 Female Feed Consumption During Gestation (page 3 of 3)

[a]Reported as the mean ± S.E.M.; gd = gestational day.
[b]Decrease in N is due to the female pulling feed into the cage and therefore an accurate feed weight could not be obtained.
[c]Decrease in N is due to one or more feed consumption values being unrealistic (i.e. negative) and therefore they were excluded.
[d]Decrease in N is due to one feed consumption value being a statistical outlier and therefore it was excluded.
[e]Decrease in N is due to interim feed consumption value(s) for one or more females being missing and therefore the overall feed consumption value could not be calculated.
[#]Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.
[‡]$p<0.05$; ANOVA Test.
[‡‡]$p<0.01$; ANOVA Test.
[‡‡‡]$p<0.001$; ANOVA Test.
[§]$p<0.05$; Test for Linear Trend.
[§§]$p<0.01$; Test for Linear Trend.
[§§§]$p<0.001$; Test for Linear Trend.
[*]$p<0.05$; Dunnett's Test.
[**]$p<0.01$; Dunnett's Test.
[***]$p<0.001$; Dunnett's Test.
[†††]$p<0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.
[ŸŸŸ]$p<0.001$; Linear trend test in robust regression model.
[ÞÞ]$p<0.01$; Individual t-test for pairwise comparisons to control in robust regression model.
[ÞÞÞ]$p<0.001$; Individual t-test for pairwise comparisons to control in robust regression model.

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Table 5. Summary of the F_0 Female Clinical Observations During Gestation (page 1 of 3)

A. Clinical Observations Summarized by Group

Observation	Methoxychlor (mg/kg/day, po) 0	25	50	100
Alopecia	1	1	1	1
Animal received less than the required dose volume	3	1	1	1
Animal received more than the required dose volume			1	
Efflux of the dosing solution	2	6	1	
Found dead				1
Piloerection	1		7	1
Respiration: audible	1			
Rooting			1	3
Weight loss[a]	5	6	13	10

B. Clinical Observations Summarized by Group and Day

Day[b]	Observation[c]	Methoxychlor (mg/kg/day, po) 0	25	50	100
6	Animal received 96.6% of the required dose volume	1			
7	Animal received 103.7% of the required dose volume			1	
	Animal received 96.6% of the required dose volume	1			
	Weight loss: 8.69 g.	1			
	7.92 g. – 13.89 g.		6		
	5.74 g. – 19.38 g.			10	
	5.37 g. – 21.03 g.				7
8	Efflux of the dosing solution		1		
	Weight loss: 15.11 g. and 22.13 g.	2			
	8.94 g.			1	
9	Weight loss: 7.56 g.	1			
	6.05 g. – 8.63 g.			3	
10	Weight loss: 16.38 g. and 23.23 g.	2			
	6.19 g.		1		
	5.87 g. and 6.31 g.			2	
11	Efflux of the dosing solution				1
12	Animal received 96.7% of the required dose volume			1	
	Efflux of the dosing solution				1
	Respiration: audible	1			
	Rooting: post dosing			1	2
	Weight loss: 6.92 g.			1	
	7.56 g. and 9.57 g.				2

(continued)

US EPA ARCHIVE DOCUMENT

Table 5. Summary of the F_0 Female Clinical Observations During Gestation (page 2 of 3)

B. Clinical Observations Summarized by Group and Day

Day[b]	Observation[c]	Methoxychlor (mg/kg/day, po) 0	25	50	100
13	Efflux of the dosing solution	1	1	1	1
	Piloerection			1	
	Respiration: audible	1			
	Weight loss: 11.25 g.	1			
	7.94 g. – 12.68 g.			3	
	6.43 g. and 6.84 g.				2
14	Animal received 97.1% of the required dose volume	1			
	Piloerection			2	
	Respiration: audible	1			
	Weight loss: 6.17 g.		1		
	5.06 g. – 11.97 g.			3	
	5.37 g.				1
15	Efflux of the dosing solution		1		
	Piloerection			2	
	Respiration: audible	1			
	Rooting: post dosing				2
	Weight loss: 5.37 g.				1
16	Alopecia: limb(s)	1			
	Efflux of the dosing solution		1		
	Piloerection			2	
	Respiration: audible	1			
	Weight loss: 5.24 g.		1		
	5.36 g.			1	
17	Alopecia: limb(s)	1			1
	Efflux of the dosing solution		2		
	Piloerection			1	
	Respiration: audible	1			
	Rooting: post dosing				1
18	Alopecia: abdomen			1	
	limb(s)	1	1		1
	Efflux of the dosing solution		1		
	Piloerection			1	
	Respiration: audible	1			
19	Alopecia: abdomen			1	
	limb(s)	1	1		
	Animal received 97.0% of the required dose volume				1
	Efflux of the dosing solution				1
	Piloerection			4	
	Respiration: audible	1			
	Weight loss: 29.70 g.	1			
	6.75 g.			1	

(continued)

US EPA ARCHIVE DOCUMENT

Table 5. Summary of the F_0 Female Clinical Observations During Gestation (page 3 of 3)

B. Clinical Observations Summarized by Group and Day

Day[b]	Observation[c]	Methoxychlor (mg/kg/day, po) 0	25	50	100
20	Alopecia: abdomen			1	
	limb(s)	1	1		
	Animal received 97.3% of the required dose volume		1		
	Efflux of the dosing solution	1	1		
	Piloerection	1			
	Respiration: audible	1			
21	Alopecia: abdomen			1	
	limb(s)	1	1		
	Animal received 97.6% of the required dose volume	1			
	Efflux of the dosing solution				1
	Piloerection			2	
	Respiration: audible	1			
	Weight loss: 7.56 g.			1	
22	Alopecia: abdomen			1	
	Piloerection			2	1
	Weight loss: 7.66 g.			1	
	7.22 g.				1
23	Found dead				1

[a]Clinical weight loss is weight loss $\geq$ 5 gram in any one weigh period.
[b]Gestational day.
[c]Clinical observations are tabulated once per day per animal.

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Table 6. Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Change During Lactation (page 1 of 2)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females with Litters on Postnatal Day 0	12	9	15	10
Body Weight (pnd 0) (g)[a]				
	300.2 ‡‡‡ ± 7.6 §§§ N=12	264.8 ** ± 4.2 N=9	268.6 ** ± 8.2 N=14[b]	241.6 *** ± 6.8 N=10
Body Weight (pnd 4) (g)[a]				
	322.0 ‡‡‡ ± 7.2 §§§ N=12	291.6 ** ± 2.9 N=9	288.3 *** ± 5.8 N=13[c]	270.1 *** ± 4.8 N=9[d]
Body Weight (pnd 7) (g)[a]				
	327.3 ‡‡‡ ± 6.8 §§§ N=12	299.5 ** ± 3.8 N=9	299.1 ** ± 6.6 N=13	281.5 *** ± 5.5 N=9
Body Weight (pnd 14) (g)[a]				
	342.0 ‡ ± 7.7 §§ N=12	320.4 ± 2.9 N=9	325.5 ± 7.0 N=13	310.5 ** ± 5.3 N=9
Body Weight (pnd 21) (g)[a]				
	325.4 ‡ ± 7.0 § N=12	310.6 ± 6.0 N=9	316.4 ± 4.8 N=13	300.5 * ± 4.7 N=8[e]
Body Weight Change (pnd 0 to 4) (g)[a]				
	21.8 ± 2.7 N=12	26.8 ± 3.4 N=9	14.0 ± 3.7 N=12[b,c]	28.2 ± 6.7 N=9[d]
Body Weight Change (pnd 4 to 7) (g)[a]				
	5.3 ± 1.7 N=12	7.9 ± 3.3 N=9	10.8 ± 2.8 N=13	11.4 ± 3.4 N=9
Body Weight Change (pnd 7 to 14) (g)[a]				
	14.7 ‡ ± 3.1 §§ N=12	20.9 ± 3.0 N=9	26.5 * ± 3.4 N=13	29.0 ** ± 2.4 N=9

(continued)

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Table 6. Summary and Statistical Analysis of the F_0 Female Body Weights and Weight Change During Lactation (page 2 of 2)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (pnd 14 to 21) (g)[a]				
	-16.6 ± 3.2 N=12	-9.8 ± 3.3 N=9	-9.1 ± 4.2 N=13	-8.6 ± 2.9 N=8[e]
Body Weight Change (pnd 0 to 21) (g)[a]				
	25.2 ‡‡‡ ± 2.9 §§§ N=12	45.8 ** ± 6.1 N=9	39.9 ± 4.5 N=12[b]	58.7 *** ± 5.2 N=8[e]

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Decrease in N is due to the postnatal day 0 body weight inadvertently not being recorded for one female.
[c]Decrease in N is due to female 53 being euthanized moribund on postnatal day 2 and female 45 being euthanized moribund on postnatal day 3.
[d]Decrease in N is due to female 29 being euthanized moribund on postnatal day 1.
[e]Decrease in N is due to the postnatal day 21 body weight inadvertently not being recorded for one female.
‡p<0.05; ANOVA Test.
‡‡‡p<0.001; ANOVA Test.
§p<0.05; Test for Linear Trend.
§§p<0.01; Test for Linear Trend.
§§§p<0.001; Test for Linear Trend.
*p<0.05; Dunnett's Test.
**p<0.01; Dunnett's Test.
***p<0.001; Dunnett's Test.

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Table 7. Summary and Statistical Analysis of the F_0 Female Feed Consumption During Lactation
(page 1 of 2)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females with Litters on Postnatal Day 0	12	9	15	10
Feed Consumption (pnd 0 to 4) (g/day)[a]				
	32.7 ± 1.7 N=11[b]	32.1 ± 2.2 N=9	30.0 ± 1.6 N=13[c]	29.7 ± 3.8 N=7[b,d]
Feed Consumption (pnd 4 to 7) (g/day)[a]				
	46.8 ± 1.8 N=12	43.3 ± 1.9 N=9	41.2 ± 2.6 N=13	45.2 ± 4.2 N=9
Feed Consumption (pnd 7 to 14) (g/day)[a]				
	60.0 ± 2.3 N=12	55.7 ± 2.2 N=9	53.7 ± 2.7 N=13	54.5 ± 1.8 N=9
Feed Consumption (pnd 14 to 21) (g/day)[a]				
	71.3 ± 2.6 N=12	71.1 ± 2.7 N=9	70.2 ± 3.6 N=13	68.3 ± 1.2 N=8[e]
Feed Consumption (pnd 0 to 21) (g/day)[a]				
	56.6 ± 2.3 N=11[f]	54.6 ± 2.2 N=9	52.9 ± 2.1 N=13	51.8 ± 2.2 N=6[f]
Feed Consumption (pnd 0 to 4) (g/kg/day)[a]				
#	105.0 ± 4.6 N=11[b]	115.4 ± 7.7 N=9	108.6 ± 7.3 N=12[c,g]	117.1 ± 16.0 N=7[b]
Feed Consumption (pnd 4 to 7) (g/kg/day)[a]				
	143.8 ± 3.7 N=12	146.3 ± 5.6 N=9	139.6 ± 8.1 N=13	164.1 ± 15.9 N=9
Feed Consumption (pnd 7 to 14) (g/kg/day)[a]				
	178.9 ± 4.3 N=12	179.7 ± 6.5 N=9	171.0 ± 7.3 N=13	184.1 ± 4.6 N=9

(continued)

US EPA ARCHIVE DOCUMENT

Table 7. Summary and Statistical Analysis of the F_0 Female Feed Consumption During Lactation (page 2 of 2)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Feed Consumption (pnd 14 to 21) (g/kg/day)[a]				
	213.2 ± 5.3 N=12	225.2 ± 7.1 N=9	218.2 ± 10.7 N=13	224.4 ± 4.2 N=8[e]
Feed Consumption (pnd 0 to 21) (g/kg/day)[a]				
	174.5 ± 4.9 N=11[f]	183.5 ± 6.7 N=9	175.3 ± 7.0 N=12[f]	185.4 ± 7.8 N=6[f]

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Decrease in N is due to one or more females pulling feed into the cage and therefore an accurate feed weight could not be obtained.
[c]Decrease in N is due to female 53 being euthanized moribund on postnatal day 2 and female 45 being euthanized moribund on postnatal day 3.
[d]Decrease in N is due to female 29 being euthanized moribund on postnatal day 1.
[e]Decrease in N is due to the postnatal day 21 feed weight inadvertently not being recorded for one female.
[f]Decrease in N is due to interim feed consumption value(s) for one or more females being missing and therefore the overall feed consumption value could not be calculated.
[g]Decrease in N is due to the postnatal day 0 body weight inadvertently not being recorded for one female.
[#]Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.

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Table 8. Summary of the F_0 Female Clinical Observations During Lactation (page 1 of 6)

A. Clinical Observations Summarized by Group

Observation	Methoxychlor (mg/kg/day, po) 0	25	50	100
Alopecia	2	4	6	3
Chromodacryorrhea		1		
Efflux of the dosing solution	2	1	2	2
Euthanized moribund			2	1
Feces: soft	2		1	1
Hunched			1	
Mass: under right front leg	1			
Not nursing pups			1	
Piloerection	1		5	3
Respiration: audible	1			
Rooting	1	1	2	
Rough coat			2	
Salivation			3	
Sore(s)		1		
Struggled during dosing				1
Vaginal bleeding				1
Vaginal discharge, clear				1

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
0	Alopecia: limb(s)		1		
	Piloerection			2	3
	Respiration: audible	1			
	Vaginal discharge, clear				1
1	Alopecia: abdomen			2	
	limb(s)		1		
	Euthanized moribund				1
	Piloerection				1
	Rough coat			1	
	Vaginal bleeding				1
2	Alopecia: abdomen			1	
	anogenital area			1	
	limb(s)		1		
	multiple areas			1	
	Euthanized moribund			1	
	Hunched			1	
	Rough coat			2	

(continued)

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Table 8. Summary of the F_0 Female Clinical Observations During Lactation (page 2 of 6)

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
3	Alopecia: abdomen			1	
	anogenital area			1	
	limb(s)	1	2		
	multiple areas			1	
	Euthanized moribund			1	
	Not nursing pups			1	
	Piloerection			1	
	Respiration: audible	1			
	Rough coat			1	
4	Alopecia: abdomen			1	
	anogenital area			1	
	limb(s)	1	2		
	multiple areas			1	
	Efflux of the dosing solution	1	1		
	Piloerection	1		1	
	Respiration: audible	1			
	Rooting: post dosing	1	1		
5	Alopecia: abdomen			1	
	anogenital area			1	
	limb(s)	1	2		
	multiple areas			1	
	Efflux of the dosing solution			1	
	Mass: under right front leg, ~2 x 2 cm	1			
	Piloerection			1	
	Respiration: audible	1			
	Salivation: prior to dosing			1	
6	Alopecia: abdomen			1	
	anogenital area			1	
	chest			1	
	limb(s)	1	2	1	1
	multiple areas			1	
	Efflux of the dosing solution	1			
	Mass: under right front leg	1			
	Piloerection			1	
	Respiration: audible	1			
	Rooting: post dosing			1	
	Salivation: prior to dosing			1	

(continued)

US EPA ARCHIVE DOCUMENT

Table 8. Summary of the F_0 Female Clinical Observations During Lactation (page 3 of 6)

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
7	Alopecia: abdomen			1	
	anogenital area			1	
	chest			2	
	limb(s)	2	2	1	1
	multiple areas			1	
	Mass: under right front leg	1			
	Piloerection			1	
	Respiration: audible	1			
	Salivation: prior to dosing			1	
8	Alopecia: abdomen			1	
	anogenital area			1	
	chest			2	
	limb(s)	2	3	1	1
	multiple areas			1	
	Mass: under right front leg	1			
	Piloerection			1	
	Respiration: audible	1			
9	Alopecia: abdomen			1	
	anogenital area			1	
	chest			2	
	limb(s)	2	3	1	1
	multiple areas			1	
	Mass: under right front leg	1			
	Piloerection			1	
	Respiration: audible	1			
10	Alopecia: abdomen		1	1	
	anogenital area			1	
	chest			2	
	limb(s)	2	3	1	1
	multiple areas			1	
	Mass: under right front leg	1			
	Piloerection			2	
	Respiration: audible	1			
11	Alopecia: abdomen		1	1	
	anogenital area			1	
	chest			2	
	limb(s)	2	3	1	2
	multiple areas			1	
	Chromodacryorrhea: eye, left		1		
	Mass: under right front leg	1			
	Respiration: audible	1			
	Sore(s): head		1		

(continued)

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Table 8. Summary of the F_0 Female Clinical Observations During Lactation (page 4 of 6)

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
12	Alopecia: abdomen		1	1	
	anogenital area			1	
	chest			2	
	limb(s)	1	3	1	2
	multiple areas	1		1	
	Chromodacryorrhea: eye, left		1		
	Mass: under right front leg	1			
	Respiration: audible	1			
	Sore(s): head		1		
13	Alopecia: abdomen		1	1	
	anogenital area			1	
	chest			2	
	limb(s)	1	3	1	2
	multiple areas	1		1	
	Chromodacryorrhea: eye, left		1		
	Mass: under right front leg	1			
	Respiration: audible	1			
	Rooting: post dosing			1	
	Sore(s): head, healed		1		
14	Alopecia: abdomen		1	1	
	anogenital area			1	
	chest			1	
	limb(s)	1	3	1	2
	multiple areas	1		2	
	Chromodacryorrhea: eye, left		1		
	Efflux of the dosing solution				1
	Feces: soft				1
	Mass: under right front leg	1			
	Respiration: audible	1			
	Rooting: post dosing			1	
	Salivation: prior to dosing			1	
	Struggled during dosing				1
15	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	2
	multiple areas	1		3	
	Chromodacryorrhea: eye, left		1		
	Efflux of the dosing solution				1
	Feces: soft	1		1	
	Mass: under right front leg	1			
	Respiration: audible	1			
	Salivation: prior to dosing			1	

(continued)

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Table 8. Summary of the F_0 Female Clinical Observations During Lactation (page 5 of 6)

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
16	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	3
	multiple areas	1		3	
	Chromodacryorrhea: eye, left		1		
	Efflux of the dosing solution			1	
	Mass: under right front leg	1			
	Respiration: audible	1			
	Salivation: prior to dosing			1	
17	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	3
	multiple areas	1		3	
	Chromodacryorrhea: eye, left		1		
	Mass: under right front leg	1			
	Respiration: audible	1			
18	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	3
	multiple areas	1		3	
	Chromodacryorrhea: eye, left		1		
	Mass: under right front leg	1			
	Respiration: audible	1			
19	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	3
	multiple areas	1		3	
	Chromodacryorrhea: eye, left		1		
	Efflux of the dosing solution			1	
	Mass: under right front leg	1			
	Respiration: audible	1			
	Salivation: prior to dosing			1	
20	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	3
	multiple areas	1		3	
	Chromodacryorrhea: eye, left		1		
	Mass: under right front leg	1			
	Respiration: audible	1			
	Salivation: prior to dosing			1	

(continued)

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Table 8. Summary of the F_0 Female Clinical Observations During Lactation (page 6 of 6)

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
21	Alopecia: abdomen		1	1	
	anogenital area			1	
	limb(s)	1	3	1	2
	multiple areas	1		2	
	Chromodacryorrhea: eye, left		1		
	Feces: soft	1			
	Mass: under right front leg	1			
	Respiration: audible	1			

[a]Postnatal day.
[b]Clinical observations are tabulated once per day per animal.

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Table 9. Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 1 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. Females on Study				
	13	11	15	14
No. of Pregnant Females				
	12	10	15	12
Fertility Index (no. pregnant females/no. females that mated)				
	92.3	90.9	100.0	85.7
No. of Females with Live Litters (pnd 0)				
	12	10	15	11[a]
Gestational Index (no. females with live litters/no. females pregnant)				
	100.0	100.0	100.0	100.0
Gestational Length (days)[b]				
	22.1 ± 0.1 § N=12	22.2 ± 0.1 N=9[c]	22.1 ± 0.1 N=15	22.5 ± 0.2 N=10[d]
No. of Live Litters:				
Postnatal Day 0	12	9	15	10
Postnatal Day 4	12	9	13[e]	9[f]
Postnatal Day 7	12	9	13	9
Postnatal Day 14	12	9	13	9
Postnatal Day 21	12	9	13	9
Number of Live Pups on Postnatal Day 0[b]				
	14.3 ± 0.9 N=12	13.6 ± 1.1 N=8[g]	13.1 ± 0.9 N=15	12.0 ± 0.8 N=10
Number of Dead Pups on Postnatal Day 0[b]				
	0.3 ± 0.1 N=12	0.3 ± 0.2 N=8[g]	0.5 ± 0.2 N=15	0.5 ± 0.4 N=10
Total Number of Pups on Postnatal Day 0[b]				
	14.6 ± 0.9 N=12	13.9 ± 1.1 N=8[g]	13.5 ± 1.0 N=15	12.5 ± 0.7 N=10

(continued)

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Table 9. Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 2 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Stillbirth Index (no. dead on pnd 0/total no. on pnd 0)[b]				
	2.9 ± 1.5 N=12	1.5 ± 1.0 N=8[g]	3.1 ± 1.5 N=15	4.1 ± 3.3 N=10
Live Birth Index (no. live on pnd 0/total no. on pnd 0)[b]				
	97.1 ± 1.5 N=12	98.5 ± 1.0 N=8[g]	96.9 ± 1.5 N=15	95.9 ± 3.3 N=10
4 Day Survival Index (no. surviving 4 days/no. live on pnd 0)[b]				
	99.0 ± 0.7 N=12	99.2 ± 0.8 N=8[g]	86.2 ± 9.0 N=15	89.4 ± 9.9 N=10
7 Day Survival Index (no. surviving 7 days/no. live on pnd 4)[b]				
	100.0 ± 0.0 N=12	100.0 ± 0.0 N=9	100.0 ± 0.0 N=13	98.6 ± 1.4 N=9
14 Day Survival Index (no. surviving 14 days/no. live on pnd 7)[b]				
	100.0 ± 0.0 N=12	98.6 ± 1.4 N=9	99.1 ± 0.9 N=13	100.0 ± 0.0 N=9
21 Day Survival Index (no. surviving 21 days/no. live on pnd 14)[b]				
	100.0 ± 0.0 N=12	100.0 ± 0.0 N=9	99.1 ± 0.9 N=13	100.0 ± 0.0 N=9
Lactational Index (no. surviving 21 days/no. live on pnd 4)[b]				
	100.0 ± 0.0 N=12	98.6 ± 1.4 N=9	98.3 ± 1.2 N=13	98.6 ± 1.4 N=9

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Table 9. Summary and Statistical Analysis of the F_0 Reproductive and Lactational Indexes for the F_1 Litters (page 3 of 3)

[a]Female 14 was found dead on gestational day 23 while in the process of delivering. She had one dead pup in the vagina and fifteen dead pups in the uterus.
[b]Reported as the mean ± S.E.M.; pnd=postnatal day.
[c]Female 43 was pregnant but the correct postnatal day 0 could not be determined therefore this female was removed from the study after gestation and was included here only for the reproductive indexes.
[d]Female 34 was pregnant but the correct postnatal day 0 could not be determined therefore this female was removed from the study after gestation and was included here only for the reproductive indexes.
[e]Female 45 was euthanized moribund on postnatal day 3 and all of her pups were dead or euthanized moribund by postnatal day 3. Female 53 was euthanized moribund on postnatal day 2 and all of her pups were dead or euthanized moribund by postnatal day 2.
[f]Female 29 was euthanized moribund on postnatal day 1 and all of her pups were dead or euthanized moribund by postnatal day 1.
[g]Decrease in N is due to the number of live and dead pups on postnatal day 0 inadvertently not being recorded for one female.
§$p<0.05$; Test for Linear Trend.

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Table 10. Summary and Statistical Analysis of the F_1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation (page 1 of 6)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Live Litters:				
Postnatal Day 0	12	9	15	10
Postnatal Day 4	12	9	13[a]	9[b]
Postnatal Day 7	12	9	13	9
Postnatal Day 14	12	9	13	9
Postnatal Day 21	12	9	13	9
Average Number of Live Pups per Litter (pnd 0)[c]				
	14.3 ± 0.9 N=12	13.6 ± 1.1 N=8[d]	13.1 ± 0.9 N=15	12.0 ± 0.8 N=10
Average Number of Live Pups per Litter (pnd 4)[c]				
	14.1 ± 0.9 N=12	13.6 ± 0.9 N=9	12.6 ± 1.1 N=13[a]	12.3 ± 0.7 N=9[b]
Average Number of Live Pups per Litter (pnd 7)[c]				
	8.7 ± 0.3 N=12	8.7 ± 0.2 N=9	8.2 ± 0.5 N=13	8.6 ± 0.3 N=9
Average Number of Live Pups per LItter (pnd 14)[c]				
	8.7 ± 0.3 N=12	8.6 ± 0.2 N=9	8.1 ± 0.5 N=13	8.6 ± 0.3 N=9
Average Number of Live Pups per Litter (pnd 21)[c]				
	8.7 ± 0.3 N=12	8.6 ± 0.2 N=9	8.0 ± 0.5 N=13	8.6 ± 0.3 N=9
Average Male Pup Anogenital Distance (mm) per Litter (pnd 0)[c]				
	2.07 ± 0.04 N=12	2.10 ± 0.06 N=8[d]	2.04 ± 0.06 N=15	2.02 ± 0.05 N=10
Average **Adjusted** Male Pup Anogenital Distance (mm) per Litter (pnd 0)[e]				
	2.06 ± 0.05 N=12	2.09 ± 0.06 N=8[d]	2.03 ± 0.05 N=15	2.04 ± 0.06 N=10

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Table 10. Summary and Statistical Analysis of the F_1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation (page 2 of 6)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Average Female Pup Anogenital Distance (mm) per Litter (pnd 0)[c]				
	1.03 ‡ ± 0.02 N=12	0.91 * ± 0.03 N=8[d]	0.94 ± 0.03 N=15	0.96 ± 0.04 N=10
Average **Adjusted** Female Pup Anogenital Distance (mm) per Litter (pnd 0)[e]				
	1.03 ± 0.03 N=12	0.91 ± 0.03 N=8[d]	0.94 ± 0.03 N=15	0.96 ± 0.03 N=10
Average Pup Body Weight (g) per Litter (pnd 0)[c]				
	6.34 ± 0.15 N=12	6.39 ± 0.34 N=8[d]	6.20 ± 0.30 N=15	5.78 ± 0.12 N=10
Average **Male** Body Weight (g) per Litter (pnd 0)[c]				
	6.52 ± 0.17 N=12	6.54 ± 0.38 N=8[d]	6.37 ± 0.30 N=15	5.89 ± 0.13 N=10
Average **Female** Body Weight (g) per Litter (pnd 0)[c]				
	6.20 ± 0.14 N=12	6.23 ± 0.33 N=8[d]	6.02 ± 0.29 N=15	5.64 ± 0.12 N=10
Average Pup Body Weight (g) per Litter (pnd 2)[c]				
	7.85 ± 0.17 N=12	7.81 ± 0.43 N=9	7.23 ± 0.43 N=15	7.17 ± 0.18 N=9[b]
Average **Male** Body Weight (g) per Litter (pnd 2)[c]				
	8.01 ± 0.19 N=12	7.94 ± 0.45 N=9	7.35 ± 0.43 N=15	7.33 ± 0.20 N=9[b]
Average **Female** Body Weight (g) per Litter (pnd 2)[c]				
#	7.72 † ± 0.17 ŸŸ N=12	7.66 ± 0.43 N=9	7.12 ± 0.42 N=15	7.02 ÞÞ ± 0.17 N=9[b]

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Table 10. Summary and Statistical Analysis of the F_1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation (page 3 of 6)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Average Pup Body Weight (g) per Litter (pnd 4)[c]				
	10.42 ± 0.29 N=12	10.34 ± 0.56 N=9	10.06 ± 0.39 N=13[a]	9.71 ± 0.28 N=9
Average **Male** Body Weight (g) per Litter (pnd 4)[c]				
	10.57 ± 0.30 N=12	10.50 ± 0.56 N=9	10.19 ± 0.38 N=13[a]	9.86 ± 0.30 N=9
Average **Female** Body Weight (g) per Litter (pnd 4)[c]				
	10.29 ± 0.28 N=12	10.12 ± 0.56 N=9	9.92 ± 0.39 N=13[a]	9.58 ± 0.27 N=9
Average Pup Body Weight (g) per Litter (pnd 7)[c]				
	17.10 ± 0.43 N=12	16.53 ± 0.67 N=9	16.08 ± 0.57 N=13	15.76 ± 0.51 N=9
Average **Male** Body Weight (g) per Litter (pnd 7)[c]				
	17.39 ± 0.44 N=12	16.74 ± 0.70 N=9	16.33 ± 0.58 N=13	15.96 ± 0.51 N=9
Average **Female** Body Weight (g) per Litter (pnd 7)[c]				
	16.85 ± 0.45 N=12	16.33 ± 0.68 N=9	15.86 ± 0.56 N=13	15.60 ± 0.51 N=9
Average Pup Body Weight (g) per Litter (pnd 10)[c]				
	24.73 ± 0.52 N=12	23.55 ± 0.88 N=9	22.77 ± 0.85 N=13	22.73 ± 0.79 N=9
Average **Male** Body Weight (g) per Litter (pnd 10)[c]				
	25.11 ± 0.50 N=12	23.85 ± 0.89 N=9	23.02 ± 0.86 N=13	23.05 ± 0.77 N=9
Average **Female** Body Weight (g) per Litter (pnd 10)[c]				
	24.43 ± 0.57 N=12	23.27 ± 0.92 N=9	22.54 ± 0.84 N=13	22.46 ± 0.82 N=9

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Table 10. Summary and Statistical Analysis of the F_1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation (page 4 of 6)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Average Pup Body Weight (g) per Litter (pnd 14)[c]				
	35.48 ± 0.66 N=12	33.62 ± 1.18 N=9	32.46 ± 1.12 N=13	32.99 ± 1.24 N=9
Average **Male** Body Weight (g) per Litter (pnd 14)[c]				
	36.11 ± 0.63 N=12	34.18 ± 1.18 N=9	32.74 ± 1.11 N=13	33.40 ± 1.24 N=9
Average **Female** Body Weight (g) per Litter (pnd 14)[c]				
	34.98 ± 0.71 N=12	33.17 ± 1.21 N=9	32.23 ± 1.14 N=13	32.60 ± 1.23 N=9
Average Pup Body Weight (g) per Litter (pnd 17)[c]				
	42.64 ± 0.75 N=12	41.31 ± 1.24 N=9	39.88 ± 1.36 N=13	40.40 ± 1.58 N=9
Average **Male** Body Weight (g) per Litter (pnd 17)[c]				
	43.63 ± 0.72 N=12	42.11 ± 1.22 N=9	40.33 ± 1.37 N=13	41.07 ± 1.58 N=9
Average **Female** Body Weight (g) per Litter (pnd 17)[c]				
	41.85 ± 0.81 N=12	40.65 ± 1.28 N=9	39.48 ± 1.37 N=13	39.80 ± 1.58 N=9
Average Pup Body Weight (g) per Litter (pnd 21)[c]				
	56.72 ± 0.98 N=12	56.03 ± 2.16 N=9	56.11 ± 1.44 N=13	55.64 ± 1.79 N=9
Average **Male** Body Weight (g) per Litter (pnd 21)[c]				
	57.96 ± 1.04 N=12	57.32 ± 2.18 N=9	56.98 ± 1.53 N=13	56.82 ± 1.95 N=9
Average **Female** Body Weight (g) per Litter (pnd 21)[c]				
	55.70 ± 1.01 N=12	54.95 ± 2.22 N=9	55.35 ± 1.38 N=13	54.49 ± 1.61 N=9

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Table 10. Summary and Statistical Analysis of the F_1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation (page 5 of 6)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Percent Male Pups per Litter (pnd 0)[c]				
	45.4 ± 2.3 § N=12	53.5 ± 4.1 N=8[d]	53.2 ± 2.8 N=15	55.4 ± 3.3 N=10
Percent Male Pups per Litter (pnd 4)[c]				
	44.8 ‡ ± 2.0 N=12	56.6 * ± 3.6 N=9	53.2 ± 3.3 N=13[a]	52.9 ± 2.7 N=9[b]
Average Number of Nipples per Male Pup[f]				
	0.00 ± 0.00 N=46	0.08 ± 0.06 N=36	0.00 ± 0.00 N=49	0.00 ± 0.00 N=36
Percent Male Pups with One or More Nipples[f]				
	0.00 ± 0.00 N=46	5.56 ± 3.51 N=36	0.00 ± 0.00 N=49	0.00 ± 0.00 N=36
Average Number of Areolae per Male Pup[f]				
	0.09 ± 0.06 N=46	0.17 ± 0.07 N=36	0.14 ± 0.07 N=49	0.17 ± 0.11 N=36
Percent Male Pups with One or More Areolae[f]				
	4.35 ± 0.82 N=46	11.11 ± 4.19 N=36	8.16 ± 3.38 N=49	8.33 ± 5.62 N=36

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Table 10. Summary and Statistical Analysis of the F_1 Litter Size, Pup Body Weights, Anogenital Distance and Nipples During Lactation (page 6 of 6)

[a]Female 45 was euthanized moribund on postnatal day 3 and all of her pups were dead or euthanized moribund by postnatal day 3. Female 53 was euthanized moribund on postnatal day 2 and all of her pups were dead or euthanized moribund by postnatal day 2.
[b]Female 29 was euthanized moribund on postnatal day 1 and all of her pups were dead or euthanized moribund by postnatal day 1.
[c]Reported as the mean ± S.E.M.; pnd=postnatal day.
[d]Decrease in N is due to the number of live pups, number of dead pups, live pup body weight and anogenital distance on postnatal day 0 inadvertently not being recorded for one female.
[e]Reported as the adjusted mean or percentage ± S.E.M. (adjusted for body weight as covariate).
[f]Reported as the adjusted mean ± S.E.M. (adjusted for intralitter correlations).
[#]Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.
[‡]$p<0.05$; ANOVA Test.
[§]$p<0.05$; Test for Linear Trend.
[*]$p<0.05$; Dunnett's Test.
[†]$p<0.05$; Wald Chi-square Test for overall treatment effect in robust regression model.
[ŸŸ]$p<0.01$; Linear trend test in robust regression model.
[ÞÞ]$p<0.01$; Individual t-test for pairwise comparisons to control in robust regression model.

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Table 11. Summary of the F_1 Pup Clinical Observations on Postnatal Days 0 Through 21 (page 1 of 2)

Day[a]	Sex[b]	Clinical Observation	Methoxychlor (mg/kg/day, po) 0	25	50	100
0	F	Anal atresia; String like tail; Euthanized moribund			1	
		Found dead	3	1	6	3
	M	Found dead	1	1	1	2
1	F	Found dead			4	1
		No milk band; Cold; Euthanized moribund				1
	M	Found dead			1	3
		No milk band; Cold; Euthanized moribund				4
2	F	Found dead			3	
		Missing and presumed dead	1		2	
		No milk band; Barely alive; Euthanized moribund			6	
	M	Found dead			4	
		Missing and presumed dead			4	
		No milk band; Barely alive; Euthanized moribund			3	
3	F	No milk band; Euthanized moribund			1	
	M	No milk band; Euthanized moribund			3	
4	F	Bite mark on left side	1			
		Found dead	1			
	M	Found dead		1		
7	F	Found dead				1
9	F	Found dead			1	
10	F	Bite mark on left side is scabbed over and healing	1			
11	F	Umbilical hernia; Bite mark on left side	1			
12	M	Found dead after tail tattooing		1		
14	F	Alopecia: rump		4		
		Back: sore and bump; Umbilical hernia	1			
	M	Alopecia: rump		4		

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Table 11. Summary of the F_1 Pup Clinical Observations on Postnatal Days 0 Through 21 (page 2 of 2)

			Methoxychlor (mg/kg/day, po)			
Day[a]	Sex[b]	Clinical Observation	0	25	50	100
17	F	Alopecia: rump		4		
		Found dead			1	
	M	Alopecia: rump		4		

[a]Postnatal day.
[b]F is female and M is male.

US EPA ARCHIVE DOCUMENT

Table 12. Summary of the F_1 Pup Gross Necropsy Findings on Postnatal Days 0 Through 21
(page 1 of 2)

Day[a]	Sex[b]	Gross Necropsy Findings	Methoxychlor (mg/kg/day, po) 0	25	50	100
0	F	Ductus closed; Abdominal organs too autolyzed to evaluate	1			
		Ductus closed; Air in lungs; No milk in stomach		1	1	
		Ductus open; No air in lungs	2		2	2
		Ductus open; No air in lungs; Abdominal organs too autolyzed to evaluate			1	
		Ductus open; No air in lungs; No milk in stomach				1
		Ductus open; No milk in stomach			2	
		Euthanized moribund; Anal atresia; String like tail; Ductus closed; Milk in stomach; Large intestines ended with no attachment to an external orifice			1	
	M	Ductus open; Air in lungs; No milk in stomach		1		
		Ductus open; No air in lungs	1		1	2
1	F	Abdominal organs too autolyzed to evaluate			1	
		Euthanized moribund; No milk in stomach				1
		No milk in stomach			3	1
	M	Abdominal organs too autolyzed to evaluate				1
		Ductus open; No milk in stomach				2
		Euthanized moribund; No milk in stomach				4
		No milk in stomach			1	
2	F	Euthanized moribund; Cannibalized, unable to evaluate			2	
		Euthanized moribund; No milk in stomach			4	
		No milk in stomach			3	
	M	Euthanized moribund; No milk in stomach			3	
		No milk in stomach			4	

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US EPA ARCHIVE DOCUMENT

Table 12. Summary of the F_1 Pup Gross Necropsy Findings on Postnatal Days 0 Through 21
(page 2 of 2)

			Methoxychlor (mg/kg/day, po)			
Day[a]	Sex[b]	Gross Necropsy Findings	0	25	50	100
3	F	Euthanized moribund; No milk in stomach			1	
	M	Euthanized moribund; No milk in stomach			3	
4	F	Abdominal organs too autolyzed to evaluate	1			
	M	Too autolyzed to evaluate		1		
7	F	Bedding in mouth; Abdominal organs too autolyzed to evaluate				1
9	F	Abdominal organs too autolyzed to evaluate			1	
12	M	Pup found dead after tail tattooing; No findings		1		
17	F	Bite mark on left side of neck and one on back of head			1	

[a]Postnatal day.
[b]F is female and M is male.

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Table 13. Summary and Statistical Analysis of the F_0 Female Hormone Data at Necropsy (page 1 of 1)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females at Scheduled Sacrifice	12	9	13	9
Thyroxine Hormone (T4) (ug/dL)[a]				
	3.98 ± 0.25 N=12	3.66 ± 0.37 N=9	3.82 ± 0.29 N=13	3.79 ± 0.30 N=9
Thyroid Stimulating Hormone (TSH) (ng/ml)[a]				
	13.96 ± 1.23 N=12	12.15 ± 0.90 N=9	11.06 ± 1.22 N=13	13.46 ± 1.38 N=9

[a]Reported as the mean ± S.E.M.

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Table 14. Summary of the F_0 Female Gross Necropsy Findings (page 1 of 1)

Scheduled Necropsy

Finding	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Alopecia: abdomen			1	
chest			1	
limb(s)		2		
multiple areas	1		1	

Unscheduled Necropsy - Gestation

Finding	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Chromodacryorrhea: front paws, mouth and nose				1
Uterus and Vagina: 7 pups in each horn and one in vagina				1

Unscheduled Necropsy - Lactation

Finding	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Fur in anogenital area stained with old and fresh blood				1
Rust colored fur: limb(s) and nose				1
Uterus: 3 retained middle resorptions in right horn and 2 retained middle resorptions in left horn				1

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Table 15. Summary of the Fate of the F_1 Uterotrophic Females (page 1 of 1)

	Methoxychlor (mg/kg/day, sc injection)			
	0	25	50	100
No. of Females on Study	13	8	8	10
Fate of Females:				
Removed from Study[a]	1	2	0	1
Post Wean Holding Period	0	0	0	0
Scheduled Sacrifice on Postnatal Day 24	12	6	8	9

[a]These animals were removed from the study because their dam was removed from the study.

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Table 16. Summary and Statistical Analysis of the F_1 Uterotrophic Female Body Weights and Weight Changes During the Post Wean Holding Period (page 1 of 1)

	Methoxychlor (mg/kg/day, sc injection)			
	0	25	50	100
No. of Females	12	6	8	9
Body Weight (pnd 21) (g)[a]				
	55.51 ± 1.34 N=12	53.51 ± 2.46 N=6	54.82 ± 2.10 N=8	55.13 ± 2.09 N=9
Body Weight (pnd 22) (g)[a]				
	59.95 ± 1.44 N=12	55.48 ± 2.63 N=6	57.15 ± 2.13 N=8	56.49 ± 2.25 N=9
Body Weight (pnd 23) (g)[a]				
	65.24 ± 1.74 N=12	61.25 ± 2.98 N=6	62.22 ± 2.16 N=8	60.51 ± 2.22 N=9
Body Weight (pnd 24) (g)[a]				
	70.92 ± 1.89 N=12	67.29 ± 2.76 N=6	68.31 ± 2.15 N=8	66.33 ± 2.24 N=9
Body Weight Change (pnd 21 to 22) (g)[a]				
	4.43 ‡ ± 0.93 §§ N=12	1.96 ± 0.49 N=6	2.33 ± 0.45 N=8	1.36 * ± 0.52 N=9
Body Weight Change (pnd 22 to 23) (g)[a]				
	5.29 ± 0.47 § N=12	5.78 ± 0.41 N=6	5.07 ± 0.17 N=8	4.02 ± 0.53 N=9
Body Weight Change (pnd 23 to 24) (g)[a]				
	5.68 ± 0.33 N=12	6.03 ± 0.37 N=6	6.09 ± 0.29 N=8	5.82 ± 0.49 N=9
Body Weight Change (pnd 21 to 24) (g)[a]				
	15.41 ± 1.25 §§ N=12	13.77 ± 0.76 N=6	13.49 ± 0.66 N=8	11.20 ± 1.14 N=9

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
‡p<0.05; ANOVA Test.
§p<0.05; Test for Linear Trend.
§§p<0.01; Test for Linear Trend.
*p<0.05; Dunnett's Test.

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Table 17. Summary of the F_1 Uterotrophic Female Clinical Observations During the Post Wean Holding Period (page 1 of 1)

A. Clinical Observations Summarized by Group

	Methoxychlor (mg/kg/day, sc injection)			
Observation	0	25	50	100
Vaginal Opening: pin hole only			6	2

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, sc injection)			
Day[a]	Observation[b]	0	25	50	100
21	Vaginal Opening: pin hole only			3	
22	Vaginal Opening: pin hole only			4	2
23	Vaginal Opening: pin hole only			6	2
24	Vaginal Opening: pin hole only			6	2

[a]Postnatal day.
[b]Clinical observations are tabulated once per day per animal.

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Table 18. Summary and Statistical Analysis of the F_1 Uterotrophic Female Necropsy Weights and Hormone Data (page 1 of 2)

	Methoxychlor (mg/kg/day, sc injection)			
	0	25	50	100
No. of Females	12	6	8	9
Sacrifice Body Weight (g)[a]				
	71.62 ± 1.89 N=11[b]	67.02 ± 2.59 N=6	68.42 ± 1.98 N=8	66.24 ± 2.27 N=9
Paired Ovary Weight (g)[a]				
	0.0416 ‡‡‡ ± 0.0013 §§§ N=11[c]	0.0375 ± 0.0016 N=6	0.0290 *** ± 0.0018 N=8	0.0326 ** ± 0.0021 N=9
Uterus Weight (with fluid) (g)[a]				
	0.1193 ± 0.0075 N=12	0.1070 ± 0.0079 N=6	0.1021 ± 0.0085 N=8	0.0999 ± 0.0066 N=9
Adjusted Paired Ovary Weight (g)[d]				
	0.0411 ΩΩΩ ± 0.0017 λλ N=10[b,c]	0.0377 ± 0.0021 N=6	0.0290 φφφ ± 0.0018 N=8	0.0328 φφ ± 0.0018 N=9
Adjusted Uterus Weight (with fluid) (g)[d]				
	0.1199 ± 0.0073 N=11[b]	0.1077 ± 0.0096 N=6	0.1022 ± 0.0082 N=8	0.1010 ± 0.0079 N=9
Adjusted Paired Ovary Weight (g)[e]				
	0.0415 ΩΩΩ ± 0.0015 λλ N=11[c]	0.0377 ± 0.0021 N=6	0.0290 φφφ ± 0.0018 N=8	0.0325 φφ ± 0.0017 N=9
Adjusted Uterus Weight (with fluid) (g)[e]				
	0.1189 ± 0.0067 N=12	0.1080 ± 0.0095 N=6	0.1021 ± 0.0082 N=8	0.0998 ± 0.0077 N=9

(continued)

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Table 18. Summary and Statistical Analysis of the F_1 Uterotrophic Female Necropsy Weights and Hormone Data (page 2 of 2)

	Methoxychlor (mg/kg/day, sc injection)			
	0	25	50	100
Estradiol (pg/ml)[a]				
	29.82 ± 1.65 N=12	31.51 ± 2.12 N=6	30.64 ± 1.34 N=8	28.29 ± 1.96 N=9
Thyroxine Hormone (T4) (ug/dL)[a]				
	3.28 ± 0.16 N=12	3.42 ± 0.26 N=6	3.75 ± 0.15 N=8	3.00 ± 0.23 N=9
Thyroid Stimulating Hormone (TSH) (ng/ml)[a]				
#	5.28 †† ± 0.17 N=12	7.46 Þ ± 0.88 N=6	5.94 ÞÞ ± 0.15 N=8	6.28 Þ ± 0.40 N=9

[a]Reported as the mean ± S.E.M.
[b]Decrease in N is due to the body weight for one animal inadvertently not being recorded prior to blood being taken.
[c]Decrease in N is due to one paired ovary weight being a statistical outlier and therefore it was excluded.
[d]Reported as the adjusted mean ± S.E.M. (sacrifice weight as covariate).
[e]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
#Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
‡‡‡p<0.001; ANOVA Test.
§§§p<0.001; Test for Linear Trend.
**p<0.01; Dunnett's Test.
***p<0.001; Dunnett's Test.
ΩΩΩp<0.001; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
λλp<0.01; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
λλλp<0.001; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
φφp<0.01; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
φφφp<0.001; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
††p<0.01; Wald Chi-square Test for overall treatment effect in robust regression model.
Þp<0.05; Individual t-test for pairwise comparisons to control in robust regression model.
ÞÞp<0.01; Individual t-test for pairwise comparisons to control in robust regression model.

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Table 19. Summary of the F_1 Uterotrophic Female Gross Necropsy Findings (page 1 of 1)

Scheduled Necropsy

	Methoxychlor (mg/kg/day, sc injection)			
Finding	0	25	50	100
No Findings				

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Table 20. Summary of the Fate of the F_1 Undosed Pubertal Females (page 1 of 1)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Females on Study	25	23	23	20
Fate of Females:				
Removed from Study[a]	2	5	0	4
Post Wean Holding Period	0	0	0	0
Scheduled Sacrifice on Postnatal Day 42	23	18	23	16

[a]These animals were removed from the study because their dam was removed from the study.

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Table 21. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 1 of 4)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Females	23	18	23	16
Anogenital Distance on Postnatal Day 21 (mm)[a]				
	10.04 ± 0.27 N=23	10.06 ± 0.34 N=18	10.13 ± 0.25 N=22[b]	9.71 ± 0.20 N=15[b]
Adjusted Anogenital Distance on Postnatal Day 21 (mm)[c]				
	10.02 ± 0.22 N=23	10.10 ± 0.25 N=18	9.95 ± 0.23 N=22[b]	9.96 ± 0.28 N=15[b]
Body Weight (pnd 21) (g)[a]				
#	55.36 ± 0.95 N=23	54.86 ± 1.51 N=18	56.40 ± 0.75 N=23	53.59 ± 1.12 N=16
Body Weight (pnd 22) (g)[a]				
	60.20 ± 1.04 N=23	59.12 ± 1.54 N=18	60.13 ± 0.82 N=23	56.90 ± 1.58 N=16
Body Weight (pnd 24) (g)[a]				
#	71.17 ± 1.09 N=23	70.34 ± 1.77 N=18	71.72 ± 0.87 N=23	68.34 ± 1.55 N=16
Body Weight (pnd 26) (g)[a]				
	82.34 ± 1.30 N=23	81.85 ± 1.87 N=18	83.49 ± 1.08 N=23	79.57 ± 1.72 N=16
Body Weight (pnd 28) (g)[a]				
	94.44 ± 1.46 N=23	93.74 ± 2.17 N=18	96.20 ± 1.30 N=23	91.69 ± 2.06 N=16
Body Weight (pnd 30) (g)[a]				
	107.59 ± 1.78 N=23	107.69 ± 2.30 N=18	110.94 ± 1.51 N=23	105.93 ± 2.17 N=16

(continued)

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Table 21. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 2 of 4)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight (pnd 32) (g)[a]				
	121.10 ± 1.92 N=23	121.95 ± 2.49 N=18	125.57 ± 1.66 N=23	119.12 ± 2.40 N=16
Body Weight (pnd 34) (g)[a]				
	134.47 ± 2.17 N=23	135.95 ± 2.71 N=18	139.90 ± 1.78 N=23	133.35 ± 2.76 N=16
Body Weight (pnd 36) (g)[a]				
	147.72 ± 2.37 N=23	146.92 ± 3.00 N=18	153.41 ± 1.98 N=23	145.89 ± 2.79 N=16
Body Weight (pnd 38) (g)[a]				
	160.42 ± 2.63 N=23	160.40 ± 3.13 N=18	166.14 ± 2.08 N=23	157.86 ± 2.74 N=16
Body Weight (pnd 40) (g)[a]				
	171.07 ± 2.60 N=23	168.75 ± 2.99 N=18	177.13 ± 2.41 N=23	169.15 ± 2.93 N=16
Body Weight (pnd 42) (g)[a]				
	185.53 ± 3.03 N=23	180.68 ± 3.53 N=18	190.91 ± 2.67 N=23	181.68 ± 3.32 N=16
Body Weight Change (pnd 21 to 22) (g)[a]				
	4.84 ± 0.25 §§ N=23	4.26 ± 0.27 N=18	3.72 ± 0.24 N=23	3.31 ± 0.82 N=16
Body Weight Change (pnd 22 to 24) (g)[a]				
	10.96 ± 0.25 N=23	11.22 ± 0.39 N=18	11.59 ± 0.32 N=23	11.44 ± 0.68 N=16

(continued)

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Table 21. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 3 of 4)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight Change (pnd 24 to 26) (g)[a]				
	11.17 ± 0.39 N=23	11.50 ± 0.32 N=18	11.76 ± 0.33 N=23	11.23 ± 0.37 N=16
Body Weight Change (pnd 26 to 28) (g)[a]				
	12.11 ± 0.35 N=23	11.89 ± 0.40 N=18	12.72 ± 0.38 N=23	12.12 ± 0.49 N=16
Body Weight Change (pnd 28 to 30) (g)[a]				
	13.15 ± 0.52 N=23	13.95 ± 0.39 N=18	14.74 ± 0.46 N=23	14.24 ± 0.46 N=16
Body Weight Change (pnd 30 to 32) (g)[a]				
	13.51 ± 0.45 N=23	14.26 ± 0.34 N=18	14.63 ± 0.51 N=23	13.19 ± 0.45 N=16
Body Weight Change (pnd 32 to 34) (g)[a]				
	13.37 ± 0.42 N=23	14.00 ± 0.47 N=18	14.34 ± 0.45 N=23	14.23 ± 0.58 N=16
Body Weight Change (pnd 34 to 36) (g)[a]				
	13.25 ‡‡ ± 0.47 N=23	10.97 ** ± 0.49 N=18	13.50 ± 0.50 N=23	12.54 ± 0.61 N=16
Body Weight Change (pnd 36 to 38) (g)[a]				
	12.70 ± 0.64 N=23	13.48 ± 0.50 N=18	12.74 ± 0.47 N=23	11.97 ± 0.47 N=16
Body Weight Change (pnd 38 to 40) (g)[a]				
	10.65 ‡‡ ± 0.51 N=23	8.35 * ± 0.72 N=18	10.98 ± 0.57 N=23	11.29 ± 0.68 N=16
Body Weight Change (pnd 40 to 42) (g)[a]				
	14.46 ± 0.76 N=23	11.92 ± 1.08 N=18	13.78 ± 0.96 N=23	12.53 ± 0.88 N=16

(continued)

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Table 21. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 4 of 4)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight Change (pnd 21 to 42) (g)[a]				
	130.17 ± 2.58 N=23	125.82 ± 2.56 N=18	134.51 ± 2.38 N=23	128.09 ± 3.02 N=16

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Decrease in N is due to one anogenital distance measurement inadvertently not being recorded.
[c]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
#Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.
‡‡$p<0.01$; ANOVA Test.
§§$p<0.01$; Test for Linear Trend.
*$p<0.05$; Dunnett's Test.
**$p<0.01$; Dunnett's Test.

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Table 22. Summary of the F_1 Undosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 1 of 1)

A. Clinical Observations Summarized by Group

Observation	Methoxychlor (mg/kg/day) 0	25	50	100
Chromodacryorrhea		1		
Umbilical hernia	1			
Vaginal Opening: pin hole only	4	3	8	6
Vaginal Opening: vaginal thread		1		

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day) 0	25	50	100
22	Vaginal Opening: pin hole only			8	1
23	Vaginal Opening: pin hole only			6	2
24	Vaginal Opening: pin hole only				1
25	Vaginal Opening: pin hole only				1
26	Vaginal Opening: pin hole only				2
27	Vaginal Opening: pin hole only				2
28	Vaginal Opening: pin hole only				1
30	Vaginal Opening: pin hole only		1		
31	Vaginal Opening: pin hole only	3	2		2
32	Chromodacryorrhea: eye, left		1		
	Vaginal Opening: pin hole only	1			2
	vaginal thread		1		
33	Chromodacryorrhea: eye, left		1		
	Vaginal Opening: pin hole only	1			1
34	Chromodacryorrhea: eye, left, gone		1		
	Vaginal Opening: pin hole only	2			1
38	Umbilical hernia	1			
39	Umbilical hernia	1			
40	Umbilical hernia	1			
41	Umbilical hernia	1			
42	Umbilical hernia	1			

[a]Postnatal day.
[b]Clinical observations are tabulated once per day per animal.

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Table 23. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Vaginal Opening and Vaginal Cytology Data (page 1 of 3)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Females	23	18	23	16
Average Postnatal Day of Vaginal Opening[a]				
	32.6 ‡‡‡ ± 0.4 §§§ N=23	31.3 ± 0.4 N=18	23.5 *** ± 0.4 N=23	29.5 *** ± 0.8 N=16
Average Body Weight (g) on Day of Acquisition[a]				
	124.43 ‡‡‡ ± 2.78 §§§ N=23	117.43 ± 2.60 N=18	69.29 *** ± 2.80 N=23	102.94 *** ± 5.75 N=16
Adjusted Average Postnatal Day of Vaginal Opening[b]				
	32.6 ΩΩΩ ± 0.4 λλλ N=23	31.3 ± 0.5 N=18	23.6 φφφ ± 0.5 N=23	29.4 φφφ ± 0.6 N=16
Average Number of Days Since Vaginal Opening till First Estrus[a]				
	1.0 ‡‡‡ ± 0.3 § N=23	1.3 ± 0.5 N=18	7.3 *** ± 0.5 N=23	1.8 ± 0.7 N=15[c]
Average Postnatal Day of First Estrus[a]				
	33.5 ‡‡ ± 0.5 §§ N=23	32.7 ± 0.6 N=18	30.8 ** ± 0.5 N=23	31.1 * ± 0.7 N=15[c]
Number of Females Cycling				
	20	18	21	13
Percent of Females Cycling				
	86.96	100.00	91.30	81.25

(continued)

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Table 23. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Vaginal Opening and Vaginal Cytology Data (page 2 of 3)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Average Number of Days Since Vaginal Opening till Start of First Cycle[a,d]				
	0.9 ‡‡‡ ± 0.3 N=20	1.1 ± 0.4 N=18	5.0 *** ± 0.7 N=21	1.8 ± 1.0 N=13
Average Postnatal Day of Start of First Cycle[a,d]				
	33.3 ‡‡‡ ± 0.5 §§ N=20	32.4 ± 0.6 N=18	28.6 *** ± 0.6 N=21	30.8 ± 1.1 N=13
Average Number of Days Since Vaginal Opening till End of First Cycle[b,d]				
#	4.8 ††† ± 0.4 ŸŸ N=20	4.8 ± 0.5 N=18	11.0 ÞÞÞ ± 0.7 N=21	6.7 ± 1.1 N=13
Average Postnatal Day of End of First Cycle[a,d]				
	37.2 ± 0.5 N=20	36.2 ± 0.6 N=18	34.6 ± 0.6 N=21	35.8 ± 1.0 N=13
Number of Females with Prolonged Estrus				
	0	2	17	3
Percent of Females with Prolonged Estrus				
	0.00 £££ ΨΨ	11.11	73.91 ΦΦΦ	18.75
Number of Females with Prolonged Diestrus				
	0	1	3	4
Percent of Females with Prolonged Diestrus				
	0.00 ΨΨ	5.56	13.04	25.00

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Table 23. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Vaginal Opening and Vaginal Cytology Data (page 3 of 3)

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Reported as the adjusted mean ± S.E.M. (body weight on postnatal day 28 as covariate).
[c]Decrease in N is due to one female never being in estrus.
[d]Includes only those females that were cycling.
[#]Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
‡p<0.05; ANOVA Test.
‡‡p<0.01; ANOVA Test.
‡‡‡p<0.001; ANOVA Test.
§§p<0.01; Test for Linear Trend.
§§§p<0.001; Test for Linear Trend.
*p<0.05; Dunnett's Test.
**p<0.01; Dunnett's Test.
***p<0.001; Dunnett's Test.
ΩΩΩp<0.001; Analysis of Covariance with body weight at acquisition or body weight on postnatal day 28 as the covariate.
λλλp<0.001; Linear Trend Analysis of Covariance with body weight at acquisition or body weight on postnatal day 28 as the covariate.
φφφp<0.001; Dunnett's Test with body weight at acquisition or body weight on postnatal day 28 as the covariate.
†††p<0.001; Wald Chi-square Test for overall treatment effect in robust regression model.
ŸŸp<0.01; Linear trend test in robust regression model.
ÞÞÞp<0.001; Individual t-test for pairwise comparisons to control in robust regression model.
£££p<0.001; Chi-Square Test.
ψψp<0.01; Cochran-Armitage Test.
ΦΦΦp<0.001; Fishers' Exact Test.

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Table 24. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 1 of 5)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Females	23	18	23	16
Sacrifice Body Weight (g)[a]				
	181.42 ± 2.88 N=23	178.50 ± 3.40 N=18	188.20 ± 2.63 N=23	178.47 ± 3.13 N=16
Anogenital Distance (mm)[a]				
	11.94 ± 0.27 N=23	11.56 ± 0.20 N=18	11.93 ± 0.22 N=23	11.85 ± 0.21 N=16
Adjusted Anogenital Distance (mm)[b]				
	11.96 ± 0.20 N=23	11.69 ± 0.23 N=18	11.72 ± 0.20 N=23	11.98 ± 0.24 N=16
Number of Areolae per Female[a]				
	12.0 ± 0.0 N=23	12.0 ± 0.0 N=18	12.0 ± 0.0 N=23	12.0 ± 0.0 N=16
Number of Nipples per Female[a]				
	12.0 ± 0.0 N=23	12.0 ± 0.0 N=18	12.0 ± 0.0 N=23	12.0 ± 0.0 N=16
Urethral-Vaginal Distance (mm)[a]				
#	2.68 **†** ± 0.14 **Ÿ** N=23	2.38 ± 0.08 N=18	2.17 **ÞÞ** ± 0.08 N=23	2.30 **Þ** ± 0.11 N=16
Pituitary Weight (g)[a]				
	0.0117 ± 0.0006 N=22[c]	0.0120 ± 0.0006 N=17[c]	0.0124 ± 0.0004 N=23	0.0124 ± 0.0007 N=15[c]
Thyroid Weight (g)[a]				
	0.0211 ± 0.0007 N=23	0.0218 ± 0.0010 N=18	0.0241 ± 0.0010 N=23	0.0212 ± 0.0008 N=16

(continued)

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Table 24. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 2 of 5)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Liver Weight (g)[a]				
	9.5648 ± 0.2451 N=23	9.6344 ± 0.3010 N=18	10.0847 ± 0.1829 N=23	9.6773 ± 0.2425 N=16
Paired Adrenal Gland Weight (g)[a]				
	0.0497 ± 0.0016 N=22[d]	0.0467 ± 0.0018 N=18	0.0490 ± 0.0012 N=23	0.0476 ± 0.0024 N=15[d]
Paired Kidney Weight (g)[a]				
	1.8706 ± 0.0350 N=23	1.8076 ± 0.0351 N=18	1.9581 ± 0.0451 N=23	1.8775 ± 0.0424 N=16
Paired Ovary Weight (g)[a]				
	0.1012 ‡‡‡ ± 0.0038 N=23	0.1014 ± 0.0031 N=18	0.0762 *** ± 0.0035 N=23	0.0973 ± 0.0062 N=16
Uterus with Fluid Weight (g)[a]				
	0.3129 ‡‡ ± 0.0161 § N=23	0.3058 ± 0.0109 N=18	0.4220 ** ± 0.0304 N=23	0.3790 ± 0.0356 N=16
Uterus without Fluid Weight (g)[a]				
	0.2963 ‡‡ ± 0.0160 § N=23	0.2935 ± 0.0110 N=18	0.3647 ** ± 0.0173 N=23	0.3372 ± 0.0235 N=16
Adjusted Pituitary Weight (g)[b]				
	0.0117 ± 0.0005 N=22[c]	0.0122 ± 0.0006 N=17[c]	0.0121 ± 0.0005 N=23	0.0126 ± 0.0006 N=15[c]
Adjusted Thyroid Weight (g)[b]				
	0.0211 ± 0.0008 N=23	0.0220 ± 0.0009 N=18	0.0238 ± 0.0009 N=23	0.0214 ± 0.0010 N=16

(continued)

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Table 24. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 3 of 5)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Adjusted Liver Weight (g)[b]				
	9.6126 ± 0.1239 N=23	9.8804 ± 0.1412 N=18	9.6719 ± 0.1276 N=23	9.9252 ± 0.1496 N=16
Adjusted Paired Adrenal Gland Weight (g)[b]				
	0.0498 ± 0.0014 N=22[d]	0.0477 ± 0.0016 N=18	0.0477 ± 0.0015 N=23	0.0483 ± 0.0018 N=15[d]
Adjusted Paired Kidney Weight (g)[b]				
	1.8777 ± 0.0251 N=23	1.8441 ± 0.0286 N=18	1.8969 ± 0.0258 N=23	1.9142 ± 0.0303 N=16
Adjusted Paired Ovary Weight (g)[b]				
	0.1016 **ΩΩΩ** ± 0.0036 N=23	0.1033 ± 0.0041 N=18	0.0729 **φφφ** ± 0.0037 N=23	0.0993 ± 0.0043 N=16
Adjusted Uterus with Fluid Weight (g)[b]				
	0.3151 **ΩΩ** ± 0.0216 **λλ** N=23	0.3173 ± 0.0246 N=18	0.4027 **φ** ± 0.0222 N=23	0.3906 ± 0.0260 N=16
Adjusted Uterus without Fluid Weight (g)[b]				
	0.2977 **Ω** ± 0.0152 **λ** N=23	0.3005 ± 0.0173 N=18	0.3529 **φ** ± 0.0157 N=23	0.3443 ± 0.0184 N=16
Adjusted Pituitary Weight (g)[e]				
	0.0117 ± 0.0005 N=22[b]	0.0121 ± 0.0006 N=17[b]	0.0123 ± 0.0005 N=23	0.0126 ± 0.0006 N=15[b]
Adjusted Thyroid Weight (g)[e]				
	0.0211 ± 0.0008 N=23	0.0219 ± 0.0009 N=18	0.0240 ± 0.0008 N=23	0.0214 ± 0.0010 N=16

(continued)

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Table 24. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 4 of 5)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Adjusted Liver Weight (g)[e]				
	9.5484 ± 0.2050 N=23	9.6670 ± 0.2318 N=18	9.9658 ± 0.2069 N=23	9.8350 ± 0.2486 N=16
Adjusted Paired Adrenal Gland Weight (g)[e]				
	0.0495 ± 0.0015 N=22[d]	0.0470 ± 0.0017 N=18	0.0485 ± 0.0015 N=23	0.0483 ± 0.0019 N=15[d]
Adjusted Paired Kidney Weight (g)[e]				
	1.8683 ± 0.0351 N=23	1.8123 ± 0.0397 N=18	1.9412 ± 0.0354 N=23	1.8998 ± 0.0426 N=16
Adjusted Paired Ovary Weight (g)[e]				
	0.1011 **ΩΩΩ** ± 0.0038 N=23	0.1017 ± 0.0042 N=18	0.0751 **φφφ** ± 0.0038 N=23	0.0988 ± 0.0046 N=16
Adjusted Uterus with Fluid Weight (g)[e]				
	0.3125 **ΩΩ** ± 0.0232 **λ** N=23	0.3066 ± 0.0263 N=18	0.4193 **φφ** ± 0.0234 N=23	0.3825 ± 0.0282 N=16
Adjusted Uterus without Fluid Weight (g)[e]				
	0.2962 **ΩΩ** ± 0.0161 **λ** N=23	0.2937 ± 0.0182 N=18	0.3638 **φ** ± 0.0163 N=23	0.3385 ± 0.0196 N=16
Thyroxine Hormone (T4) (ug/dL)[a]				
	3.93 **‡‡‡** ± 0.20 N=23	3.41 ± 0.14 N=18	4.82 ****** ± 0.21 N=23	4.00 ± 0.20 N=16
Triiodothyronine Hormone (T3) (ng/dL)[a]				
	76.14 ± 2.68 **§** N=23	74.97 ± 3.19 N=18	84.62 ± 3.18 N=23	84.44 ± 3.59 N=16

(continued)

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Table 24. Summary and Statistical Analysis of the F_1 Undosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 5 of 5)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Thyroid Stimulating Hormone (TSH) (ng/ml)[a]				
	7.39 ‡‡‡ ± 0.35 §§ N=23	8.14 ± 0.48 N=18	10.50 *** ± 0.57 N=23	9.19 ± 0.81 N=16

[a]Reported as the mean ± S.E.M.
[b]Reported as the adjusted mean ± S.E.M. (sacrifice weight as covariate).
[c]Decrease in N is due to one pituitary weight being a statistical outlier and therefore it was excluded.
[d]Decrease in N is due to one paired adrenal gland weight being a statistical outlier and therefore it was excluded.
[e]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
#Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
†p<0.05; Wald Chi-square Test for overall treatment effect in robust regression model.
Ÿp<0.05; Linear trend test in robust regression model.
Þp<0.05; Individual t-test for pairwise comparisons to control in robust regression model.
ÞÞp<0.01; Individual t-test for pairwise comparisons to control in robust regression model.
‡‡p<0.01; ANOVA Test.
‡‡‡p<0.001; ANOVA Test.
§p<0.05; Test for Linear Trend.
§§p<0.01; Test for Linear Trend.
**p<0.01; Dunnett's Test.
***p<0.001; Dunnett's Test.
Ωp<0.05; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
ΩΩp<0.01; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
ΩΩΩp<0.001; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
λp<0.05; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
λλp<0.01; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
φp<0.05; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
φφp<0.01; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
φφφp<0.001; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.

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Table 25. Summary of the F_1 Undosed Pubertal Female Gross Necropsy Findings (page 1 of 1)

Scheduled Necropsy

Finding	Methoxychlor (mg/kg/day)			
	0	25	50	100
3 x 3 mm hole in abdominal muscle at umbilicus, no protrusion of viscera	1			
Kidney: hydronephrosis, bilateral			1	
hydronephrosis, right		2		1
Thymus: enlarged	1			
Uterus: fluid filled			1	1
fluid filled, bilateral			4	1
fluid present			1	
fluid present, bilateral				1

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Table 26. Summary of the Fate of the F_1 Dosed Pubertal Females (page 1 of 1)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females on Study	25	23	23	20
Fate of Females:				
Removed from Study[a]	2	5	0	4
Post Wean Holding Period	0	0	1[b]	0
Scheduled Sacrifice on Postnatal Day 42	23	18	22	16

[a]These animals were removed from the study because their dam was removed from the study.
[b]Female 329 was found dead on postnatal day 34 after dosing (misdirected dose).

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Table 27. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 1 of 4)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females	23	18	23	16
Anogenital Distance on Postnatal Day 21 (mm)[a]				
	10.12 ± 0.25 N=22[b]	10.27 ± 0.22 N=18	10.34 ± 0.22 N=23	10.05 ± 0.26 N=15[b]
Adjusted Anogenital Distance on Postnatal Day 21 (mm)[c]				
	10.08 ± 0.24 N=22[b]	10.26 ± 0.16 N=18	10.31 ± 0.23 N=23	10.16 ± 0.25 N=15[b]
Body Weight (pnd 21) (g)[a]				
#	55.83 ± 0.73 N=23	55.05 ± 1.90 N=18	55.50 ± 0.93 N=23	53.25 ± 1.15 N=16
Body Weight (pnd 22) (g)[a]				
#	59.74 ± 0.75 **Ÿ** N=23	59.07 ± 1.99 N=18	58.57 ± 1.04 N=23	56.76 ± 1.24 N=16
Body Weight (pnd 24) (g)[a]				
#	70.73 **††** ± 0.96 **ŸŸ** N=23	70.52 ± 2.17 N=18	69.78 ± 1.19 N=23	65.58 **ÞÞÞ** ± 1.18 N=16
Body Weight (pnd 26) (g)[a]				
#	80.84 **†††** ± 1.02 **ŸŸŸ** N=23	81.48 ± 2.39 N=18	80.28 ± 1.33 N=23	75.26 **ÞÞÞ** ± 1.14 N=16
Body Weight (pnd 28) (g)[a]				
#	92.77 **†††** ± 1.29 **ŸŸŸ** N=23	93.54 ± 2.70 N=18	92.52 ± 1.56 N=23	84.03 **ÞÞÞ** ± 1.36 N=16
Body Weight (pnd 30) (g)[a]				
#	104.75 **†††** ± 1.46 **ŸŸŸ** N=23	106.20 ± 3.04 N=18	105.85 ± 1.71 N=23	95.66 **ÞÞÞ** ± 1.53 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 27. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 2 of 4)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight (pnd 32) (g)[a]				
#	117.88 ††† ± 1.76 ŸŸŸ N=23	119.96 ± 3.32 N=18	119.17 ± 1.87 N=23	107.84 ÞÞÞ ± 1.68 N=16
Body Weight (pnd 34) (g)[a]				
#	131.32 ††† ± 2.04 ŸŸŸ N=23	133.57 ± 3.57 N=18	133.05 ± 2.01 N=23	120.33 ÞÞÞ ± 1.90 N=16
Body Weight (pnd 36) (g)[a]				
	144.21 ‡‡ ± 2.24 §§ N=23	145.38 ± 3.73 N=18	146.57 ± 2.30 N=22[d]	131.65 ** ± 2.10 N=16
Body Weight (pnd 38) (g)[a]				
	157.54 ‡‡ ± 2.69 §§ N=23	157.48 ± 3.96 N=18	156.93 ± 2.46 N=22	142.88 ** ± 2.44 N=16
Body Weight (pnd 40) (g)[a]				
#	168.42 ††† ± 2.88 ŸŸŸ N=23	167.06 ± 4.48 N=18	167.96 ± 2.46 N=22	150.85 ÞÞÞ ± 2.27 N=16
Body Weight (pnd 42) (g)[a]				
	177.56 ‡‡‡ ± 2.81 §§§ N=23	174.20 ± 4.17 N=18	176.22 ± 2.40 N=22	159.77 *** ± 2.33 N=16
Body Weight Change (pnd 21 to 22) (g)[a]				
	3.91 ± 0.26 N=23	4.02 ± 0.28 N=18	3.07 ± 0.31 N=23	3.50 ± 0.36 N=16
Body Weight Change (pnd 22 to 24) (g)[a]				
	11.00 ‡‡ ± 0.35 §§ N=23	11.45 ± 0.37 N=18	11.21 ± 0.38 N=23	8.83 ** ± 0.78 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 27. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 3 of 4)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (pnd 24 to 26) (g)[a]				
#	10.11 ± 0.29 N=23	10.96 ± 0.35 N=18	10.50 ± 0.27 N=23	9.67 ± 0.88 N=16
Body Weight Change (pnd 26 to 28) (g)[a]				
	11.93 ‡‡‡ ± 0.34 §§§ N=23	12.06 ± 0.49 N=18	12.24 ± 0.34 N=23	8.77 *** ± 0.43 N=16
Body Weight Change (pnd 28 to 30) (g)[a]				
	11.97 ‡ ± 0.37 N=23	12.66 ± 0.52 N=18	13.33 * ± 0.34 N=23	11.63 ± 0.37 N=16
Body Weight Change (pnd 30 to 32) (g)[a]				
	13.13 ± 0.49 N=23	13.77 ± 0.51 N=18	13.32 ± 0.37 N=23	12.18 ± 0.36 N=16
Body Weight Change (pnd 32 to 34) (g)[a]				
	13.44 ± 0.67 N=23	13.61 ± 0.63 N=18	13.88 ± 0.36 N=23	12.50 ± 0.50 N=16
Body Weight Change (pnd 34 to 36) (g)[a]				
	12.88 ‡ ± 0.45 N=23	11.81 ± 0.57 N=18	13.52 ± 0.45 N=22	11.32 ± 0.54 N=16
Body Weight Change (pnd 36 to 38) (g)[a]				
#	13.33 † ± 0.69 N=23	12.10 ± 2.68 N=18	10.36 ÞÞ ± 0.75 N=22	11.23 Þ ± 0.75 N=16
Body Weight Change (pnd 38 to 40) (g)[a]				
#	10.88 †† ± 0.81 N=23	9.58 ± 2.91 N=18	11.03 ± 0.85 N=22	7.97 ÞÞ ± 0.63 N=16
Body Weight Change (pnd 40 to 42) (g)[a]				
	9.14 ± 0.96 N=23	7.14 ± 1.09 N=18	8.26 ± 0.79 N=22	8.92 ± 0.75 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 27. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 4 of 4)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (pnd 21 to 42) (g)[a]				
	121.73 ‡‡‡ §§§ ± 2.52 N=23	119.15 ± 3.11 N=18	120.80 ± 1.85 N=22	106.51 *** ± 2.20 N=16

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Decrease in N is due to one anogenital distance measurement inadvertently not being recorded.
[c]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
[d]Decrease in N is due to female 329 being found dead on postnatal day 34 after dosing (misdirected dose).
#Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
†p<0.05; Wald Chi-square Test for overall treatment effect in robust regression model.
††p<0.01; Wald Chi-square Test for overall treatment effect in robust regression model.
†††p<0.001; Wald Chi-square Test for overall treatment effect in robust regression model.
Ÿp<0.05; Linear trend test in robust regression model.
ŸŸp<0.01; Linear trend test in robust regression model.
ŸŸŸp<0.001; Linear trend test in robust regression model.
Þp<0.05; Individual t-test for pairwise comparisons to control in robust regression model.
ÞÞp<0.01; Individual t-test for pairwise comparisons to control in robust regression model.
ÞÞÞp<0.001; Individual t-test for pairwise comparisons to control in robust regression model.
‡p<0.05; ANOVA Test.
‡‡p<0.01; ANOVA Test.
‡‡‡p<0.001; ANOVA Test.
§§p<0.01; Test for Linear Trend.
§§§p<0.001; Test for Linear Trend.
*p<0.05; Dunnett's Test.
**p<0.01; Dunnett's Test.
***p<0.001; Dunnett's Test.

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Table 28. Summary of the F_1 Dosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 1 of 2)

A. Clinical Observations Summarized by Group

Observation	Methoxychlor (mg/kg/day, po) 0	25	50	100
Efflux of the dosing solution	3	2	8	4
Found dead after dosing			1	
Lethargic, post dosing			1	
Rooting: post dosing		1	3	7
Salivation: prior to dosing		1	1	6
Vaginal Opening: pin hole only	10	9	18	4

B. Clinical Observations Summarized by Group and Day

Day[a]	Observation[b]	Methoxychlor (mg/kg/day, po) 0	25	50	100
22	Vaginal Opening: pin hole only			3	
23	Vaginal Opening: pin hole only			8	
24	Vaginal Opening: pin hole only			13	
25	Efflux of the dosing solution			1	
	Vaginal Opening: pin hole only			14	1
26	Efflux of the dosing solution		1		
	Vaginal Opening: pin hole only			10	3
27	Vaginal Opening: pin hole only		1	10	1
28	Vaginal Opening: pin hole only		2	5	
29	Efflux of the dosing solution				3
	Rooting: post dosing				1
	Vaginal Opening: pin hole only		8	5	
30	Efflux of the dosing solution	1		2	
	Vaginal Opening: pin hole only	2	5	4	
31	Efflux of the dosing solution	1		4	
	Rooting: post dosing			1	
	Vaginal Opening: pin hole only	2	2	2	
32	Efflux of the dosing solution			1	
	Vaginal Opening: pin hole only	3	1		
33	Efflux of the dosing solution				1
	Rooting: post dosing				1
	Salivation: prior to dosing				1
	Vaginal Opening: pin hole only	3	1		

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US EPA ARCHIVE DOCUMENT

Table 28. Summary of the F_1 Dosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 2 of 2)

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, po)			
Day[a]	Observation[b]	0	25	50	100
34	Found dead after dosing			1	
	Lethargic, post dosing			1	
	Rooting: post dosing				2
	Salivation: prior to dosing				3
	Vaginal Opening: pin hole only	4	1		
35	Salivation: prior to dosing				2
36	Rooting: post dosing				2
	Salivation: prior to dosing				1
37	Rooting: post dosing			1	
	Salivation: prior to dosing				1
38	Efflux of the dosing solution	1			
	Rooting: post dosing				3
	Salivation: prior to dosing				4
39	Efflux of the dosing solution		1		
	Rooting: post dosing		1		1
	Salivation: prior to dosing		1		2
40	Rooting: post dosing			1	
	Salivation: prior to dosing			1	4
41	Efflux of the dosing solution			1	
	Rooting: post dosing			2	1
	Salivation: prior to dosing				4

[a]Postnatal day.
[b]Clinical observations are tabulated once per day per animal.

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Table 29. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Vaginal Opening and Vaginal Cytology Data (page 1 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females	23	18	23	16
Average Postnatal Day of Vaginal Opening[a]				
#	33.0 **†††** ± 0.3 **ŸŸŸ** N=23	30.1 **ÞÞÞ** ± 0.5 N=18	27.9 **ÞÞÞ** ± 0.5 N=23	25.9 **ÞÞÞ** ± 0.4 N=16
Average Body Weight (g) on Day of Acquisition[a]				
#	125.37 **†††** ± 2.25 **ŸŸŸ** N=23	106.02 **ÞÞÞ** ± 4.51 N=16[b]	92.46 **ÞÞÞ** ± 3.22 N=22[b]	74.29 **ÞÞÞ** ± 1.80 N=16
Adjusted Average Postnatal Day of Vaginal Opening[c]				
	33.1 **ЖЖЖ** ± 0.3 **ШШШ** N=23	30.2 **ααα** ± 0.5 N=18	28.0 **ααα** ± 0.5 N=23	25.6 **ααα** ± 0.4 N=16
Average Number of Days Since Vaginal Opening till First Estrus[a]				
	1.3 ± 0.4 N=23	1.4 ± 0.6 N=18	1.8 ± 0.4 N=22[d]	2.1 ± 0.6 N=16
Average Postnatal Day of First Estrus[a]				
	34.3 **‡‡‡** ± 0.5 **§§§** N=23	31.5 ** ± 0.5 N=18	29.8 *** ± 0.6 N=22[d]	28.0 *** ± 0.6 N=16
Number of Females Cycling				
	21	15	14	15
Percent of Females Cycling				
	91.30 **£**	83.33	63.64	93.75

(continued)

US EPA ARCHIVE DOCUMENT

Table 29. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Vaginal Opening and Vaginal Cytology Data (page 2 of 3)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Average Number of Days Since Vaginal Opening till Start of First Cycle[a,e]				
#	1.0 †† ± 0.3 ŸŸ N=21	0.7 ± 0.4 N=15	0.7 ± 0.3 N=14	4.2 ÞÞ ± 1.0 N=15
Average Postnatal Day of Start of First Cycle[a,e]				
#	34.0 ††† ± 0.5 ŸŸ N=21	30.9 ÞÞÞ ± 0.6 N=15	28.0 ÞÞÞ ± 0.5 N=14	30.3 ÞÞ ± 1.0 N=15
Average Number of Days Since Vaginal Opening till End of First Cycle[a,e]				
#	4.6 ††† ± 0.4 ŸŸŸ N=21	4.6 ± 0.5 N=15	6.1 ± 0.7 N=14	8.7 ÞÞÞ ± 1.0 N=15
Average Postnatal Day of End of First Cycle[a,e]				
#	37.5 ††† ± 0.5 Ÿ N=21	34.8 ÞÞ ± 0.7 N=15	33.4 ÞÞÞ ± 0.7 N=14	34.7 Þ ± 1.1 N=15
Number of Females with Prolonged Estrus				
	0	0	17	7
Percent of Females with Prolonged Estrus				
	0.00 £££ ΨΨΨ	0.00	77.27 ΦΦΦ	43.75 ΦΦΦ
Number of Females with Prolonged Diestrus				
	1	2	5	2
Percent of Females with Prolonged Diestrus				
	4.35	11.11	22.73	12.50

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US EPA ARCHIVE DOCUMENT

Table 29. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Vaginal Opening and Vaginal Cytology Data (page 3 of 3)

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Decrease in N is due to one or more body weights inadvertently not being recorded.
[c]Reported as the adjusted mean ± S.E.M. (body weight on postnatal day 28 as covariate).
[d]Decrease in N is due to female 329 being found dead on postnatal day 34 after dosing (misdirected dose) and therefore her data was excluded.
[e]Includes only those females that were cycling.
[#]Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
[††]p<0.01; Wald Chi-square Test for overall treatment effect in robust regression model.
[†††]p<0.001; Wald Chi-square Test for overall treatment effect in robust regression model.
[Ÿ]p<0.05; Linear trend test in robust regression model.
[ŸŸ]p<0.01; Linear trend test in robust regression model.
[ŸŸŸ]p<0.001; Linear trend test in robust regression model.
[Þ]p<0.05; Individual t-test for pairwise comparisons to control in robust regression model.
[ÞÞ]p<0.01; Individual t-test for pairwise comparisons to control in robust regression model.
[ÞÞÞ]p<0.001; Individual t-test for pairwise comparisons to control in robust regression model.
[ЖЖЖ]p<0.001; Wald Chi-square Test for overall treatment effect in robust regression model with body at acquisition or postnatal day 28 weight as covariate.
[ШШШ]p<0.001; Linear trend test in robust regression model with body weight at acquisition or postnatal day 28 as covariate.
[ααα]p<0.001; Individual t-test for pairwise comparisons to control in robust regression model with body weight at acquisition or postnatal day 28 as covariate.
[‡‡‡]p<0.001; ANOVA Test.
[§§§]p<0.001; Test for Linear Trend.
[**]p<0.01; Dunnett's Test.
[***]p<0.001; Dunnett's Test.
[£]p<0.05; Chi-Square Test.
[£££]p<0.001; Chi-Square Test.
[ψψψ]p<0.001; Cochran-Armitage Test.
[ΦΦΦ]p<0.001; Fishers' Exact Test.

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Table 30. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 1 of 5)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Females	23	18	22[a]	16
Sacrifice Body Weight (g)[b]				
#	177.39 ††† ¨¨¨ ŸŸŸ ± 2.97 N=23	173.30 ± 4.26 N=18	175.25 ± 2.48 N=22	158.15 ÞÞÞ ± 2.34 N=16
Anogenital Distance (mm)[b]				
	11.76 ± 0.23 N=23	11.09 ± 0.27 N=18	11.67 ± 0.22 N=22	11.93 ± 0.22 N=16
Adjusted Anogenital Distance (mm)[c]				
	11.56 ЖЖЖ ± 0.17 ШШ N=23	11.05 ± 0.25 N=18	11.55 ± 0.22 N=22	12.42 αα ± 0.21 N=16
Number of Areolae per Female[b]				
	12.0 ± 0.0 N=23	12.0 ± 0.0 N=18	12.0 ± 0.0 N=22	12.0 ± 0.0 N=16
Number of Nipples per Female[b]				
	12.0 ± 0.0 N=23	12.0 ± 0.0 N=18	12.0 ± 0.0 N=22	12.0 ± 0.0 N=16
Urethral-Vaginal Distance (mm)[b]				
	2.68 ‡‡‡ ± 0.10 §§§ N=23	2.51 ± 0.09 N=18	2.17 *** ± 0.08 N=22	2.21 ** ± 0.11 N=16
Pituitary Weight (g)[b]				
	0.0114 ‡ ± 0.0007 § N=22[d]	0.0123 ± 0.0008 N=16[d]	0.0102 ± 0.0005 N=21[d]	0.0097 ± 0.0005 N=16
Thyroid Weight (g)[b]				
	0.0204 ‡‡‡ ± 0.0006 N=23	0.0216 ± 0.0005 N=18	0.0233 ** ± 0.0007 N=22	0.0185 ± 0.0008 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 30. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 2 of 5)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Liver Weight (g)[b]				
#	9.4109 †† ± 0.2811 ŸŸ N=23	9.1774 ± 0.3236 N=18	9.2076 ± 0.1724 N=22	8.3066 ÞÞ ± 0.2117 N=16
Paired Adrenal Gland Weight (g)[b]				
	0.0461 ± 0.0018 N=23	0.0463 ± 0.0021 N=18	0.0437 ± 0.0017 N=22	0.0457 ± 0.0017 N=15[e]
Paired Kidney Weight (g)[b]				
	1.7968 ‡‡ ± 0.0415 §§§ N=23	1.7117 ± 0.0440 N=18	1.7258 ± 0.0353 N=22	1.5716 *** ± 0.0361 N=16
Paired Ovary Weight (g)[b]				
	0.0962 ‡‡‡ ± 0.0039 §§§ N=23	0.0920 ± 0.0042 N=18	0.0642 *** ± 0.0034 N=22	0.0695 *** ± 0.0038 N=16
Uterus with Fluid Weight (g)[b]				
	0.3361 ± 0.0234 N=23	0.3208 ± 0.0182 N=18	0.3114 ± 0.0194 N=22	0.2815 ± 0.0190 N=16
Uterus without Fluid Weight (g)[b]				
	0.3078 ± 0.0154 N=23	0.3092 ± 0.0180 N=18	0.2921 ± 0.0147 N=22	0.2689 ± 0.0168 N=16
Adjusted Pituitary Weight (g)[c]				
	0.0109 Ж ± 0.0005 N=22[d]	0.0123 ± 0.0007 N=16[d]	0.0097 ± 0.0005 N=21[d]	0.0110 ± 0.0006 N=16
Adjusted Thyroid Weight (g)[c]				
	0.0202 ЖЖЖ ± 0.0006 N=23	0.0216 ± 0.0005 N=18	0.0232 αα ± 0.0007 N=22	0.0189 ± 0.0009 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 30. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 3 of 5)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Adjusted Liver Weight (g)[c]				
	9.0171 ± 0.1246 N=23	9.0805 ± 0.1296 N=18	8.9690 ± 0.1013 N=22	9.3098 ± 0.1257 N=16
Adjusted Paired Adrenal Gland Weight (g)[c]				
	0.0453 ± 0.0017 N=23	0.0461 ± 0.0019 N=18	0.0432 ± 0.0016 N=22	0.0479 ± 0.0017 N=15[e]
Adjusted Paired Kidney Weight (g)[c]				
	1.7443 ± 0.0277 N=23	1.6988 ± 0.0231 N=18	1.6940 ± 0.0255 N=22	1.7053 ± 0.0265 N=16
Adjusted Paired Ovary Weight (g)[c]				
	0.0948 **ЖЖЖ** ± 0.0037 **ШШШ** N=23	0.0916 ± 0.0040 N=18	0.0633 **ααα** ± 0.0031 N=22	0.0733 **ααα** ± 0.0042 N=16
Adjusted Uterus with Fluid Weight (g)[c]				
	0.3325 ± 0.0232 N=23	0.3199 ± 0.0168 N=18	0.3092 ± 0.0194 N=22	0.2907 ± 0.0205 N=16
Adjusted Uterus without Fluid Weight (g)[c]				
	0.3044 ± 0.0155 N=23	0.3084 ± 0.0167 N=18	0.2900 ± 0.0148 N=22	0.2776 ± 0.0180 N=16
Adjusted Pituitary Weight (g)[f]				
	0.0112 **ЖЖ** ± 0.0007 **Ш** N=22[d]	0.0124 ± 0.0006 N=16[d]	0.0100 ± 0.0005 N=21[d]	0.0100 ± 0.0006 N=16
Adjusted Thyroid Weight (g)[f]				
	0.0203 **ЖЖЖ** ± 0.0006 N=23	0.0216 ± 0.0005 N=18	0.0233 **αα** ± 0.0007 N=22	0.0186 ± 0.0008 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 30. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 4 of 5)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Adjusted Liver Weight (g)[f]				
	9.3322 **Ж** ± 0.2534 **Ш** N=23	9.1738 ± 0.2699 N=18	9.1687 ± 0.1434 N=22	8.4773 **α** ± 0.2025 N=16
Adjusted Paired Adrenal Gland Weight (g)[f]				
	0.0457 ± 0.0016 N=23	0.0463 ± 0.0020 N=18	0.0435 ± 0.0016 N=22	0.0466 ± 0.0015 N=15[e]
Adjusted Paired Kidney Weight (g)[f]				
	1.7844 **ЖЖ** ± 0.0365 **ШШШ** N=23	1.7111 ± 0.0318 N=18	1.7196 ± 0.0336 N=22	1.5985 **ααα** ± 0.0361 N=16
Adjusted Paired Ovary Weight (g)[f]				
	0.0956 **ЖЖЖ** ± 0.0037 **ШШШ** N=23	0.0919 ± 0.0039 N=18	0.0639 **ααα** ± 0.0031 N=22	0.0710 **ααα** ± 0.0042 N=16
Adjusted Uterus with Fluid Weight (g)[f]				
	0.3349 ± 0.0230 N=23	0.3207 ± 0.0173 N=18	0.3109 ± 0.0191 N=22	0.2840 ± 0.0190 N=16
Adjusted Uterus without Fluid Weight (g)[f]				
	0.3067 ± 0.0150 N=23	0.3092 ± 0.0171 N=18	0.2915 ± 0.0145 N=22	0.2714 ± 0.0169 N=16
Thyroxine Hormone (T4) (ug/dL)[b]				
	4.37 **‡‡** ± 0.22 N=23	4.13 ± 0.15 N=18	4.77 ± 0.19 N=22	3.71 ± 0.21 N=16
Triiodothyronine Hormone (T3) (ng/dL)[b]				
	85.01 ± 3.74 N=23	78.57 ± 3.20 N=18	82.65 ± 4.19 N=22	76.38 ± 4.53 N=16

(continued)

US EPA ARCHIVE DOCUMENT

Table 30. Summary and Statistical Analysis of the F_1 Dosed Pubertal Female Necropsy Measurements, Organ Weights and Hormone Data (page 5 of 5)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Thyroid Stimulating Hormone (TSH) (ng/ml)[b]				
	8.26 ± 0.52 N=23	8.80 ± 0.86 N=18	9.96 ± 0.76 N=22	9.06 ± 0.64 N=16

[a]Female 329 was found dead on postnatal day 34 after dosing (misdirected dose).
[b]Reported as the mean ± S.E.M.
[c]Reported as the adjusted mean ± S.E.M. (sacrifice weight as covariate).
[d]Decrease in N is due to one pituitary weight being a statistical outlier and therefore it was excluded.
[e]Decrease in N is due to one paired adrenal gland weight being a statistical outlier and therefore it was excluded.
[f]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
#Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
††p<0.01; Wald Chi-square Test for overall treatment effect in robust regression model.
†††p<0.001; Wald Chi-square Test for overall treatment effect in robust regression model.
ŸŸp<0.01; Linear trend test in robust regression model.
ŸŸŸp<0.001; Linear trend test in robust regression model.
ÞÞp<0.01; Individual t-test for pairwise comparisons to control in robust regression model.
ÞÞÞp<0.001; Individual t-test for pairwise comparisons to control in robust regression model.
‡p<0.05; ANOVA Test.
‡‡p<0.01; ANOVA Test.
‡‡‡p<0.001; ANOVA Test.
§p<0.05; Test for Linear Trend.
§§§p<0.001; Test for Linear Trend.
**p<0.01; Dunnett's Test.
***p<0.001; Dunnett's Test.
Жp<0.05; Wald Chi-square Test for overall treatment effect in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
ЖЖp<0.01; Wald Chi-square Test for overall treatment effect in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
ЖЖЖp<0.001; Wald Chi-square Test for overall treatment effect in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
Шp<0.05; Linear trend test in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
ШШp<0.01; Linear trend test in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
ШШШp<0.001; Linear trend test in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
αp<0.05; Individual t-test for pairwise comparisons to control in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
ααp<0.01; Individual t-test for pairwise comparisons to control in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.
αααp<0.001; Individual t-test for pairwise comparisons to control in robust regression model with body weight at sacrifice or on postnatal day 21 as the covariate.

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Table 31. Summary of the F_1 Dosed Pubertal Female Gross Necropsy Findings (page 1 of 1)

Scheduled Necropsy

	Methoxychlor (mg/kg/day, po)			
Finding	0	25	50	100
Kidney: hydronephrosis, bilateral			1	
hydronephrosis, right		1	2	
Uterus: fluid filled, bilateral	1		1	

Unscheduled Necropsy

	Methoxychlor (mg/kg/day, po)			
Finding	0	25	50	100
Thoracic cavity: oily solution present, dosing error			1	

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Table 32. Summary of the Fate of the F_1 Undosed Pubertal Males (page 1 of 1)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Males on Study	25	22	24	19
Fate of Males:				
Removed from Study[a]	2	5	0	1
Post Wean Holding Period	0	0	0	0
Scheduled Sacrifice on Postnatal Day 75, 76 or 77	23	17	24	18

[a]These animals were removed from the study because their dam was removed from the study.

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Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 1 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Males	23	17	24	18
Anogenital Distance on Postnatal Day 21 (mm)[a]				
	15.62 ± 0.36 N=23	15.44 ± 0.35 N=17	15.00 ± 0.28 N=24	15.80 ± 0.32 N=18
Adjusted Anogenital Distance on Postnatal Day 21 (mm)[b]				
	15.61 ± 0.27 N=23	15.43 ± 0.32 N=17	15.00 ± 0.27 N=24	15.82 ± 0.31 N=18
Body Weight (pnd 21) (g)[a]				
	57.74 ± 1.13 N=23	57.78 ± 1.81 N=17	57.68 ± 0.95 N=24	57.53 ± 1.42 N=18
Body Weight (pnd 22) (g)[a]				
	62.94 ± 1.29 N=23	63.44 ± 1.96 N=17	62.09 ± 1.11 N=24	63.59 ± 1.57 N=18
Body Weight (pnd 24) (g)[a]				
	75.60 ± 1.41 N=23	76.62 ± 2.16 N=17	75.29 ± 1.33 N=24	74.60 ± 1.61 N=18
Body Weight (pnd 26) (g)[a]				
	88.81 ± 1.72 N=23	89.50 ± 2.37 N=17	88.54 ± 1.60 N=24	87.06 ± 1.89 N=18
Body Weight (pnd 28) (g)[a]				
	103.06 ± 2.07 N=23	104.58 ± 2.77 N=17	103.42 ± 1.86 N=24	100.48 ± 2.21 N=18
Body Weight (pnd 30) (g)[a]				
	119.88 ± 2.52 N=23	121.48 ± 2.92 N=17	119.50 ± 2.19 N=24	116.65 ± 2.40 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 2 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight (pnd 32) (g)[a]				
	137.46 ± 2.93 N=23	139.35 ± 3.47 N=17	137.24 ± 2.50 N=24	132.18 ± 2.64 N=18
Body Weight (pnd 34) (g)[a]				
	155.70 ± 3.20 N=23	158.22 ± 3.94 N=17	155.26 ± 2.96 N=24	150.13 ± 2.93 N=18
Body Weight (pnd 36) (g)[a]				
	174.68 ± 3.77 N=23	175.80 ± 4.19 N=17	173.58 ± 3.27 N=24	166.57 ± 3.15 N=18
Body Weight (pnd 38) (g)[a]				
	194.44 ± 4.00 § N=23	194.67 ± 4.32 N=17	191.32 ± 3.39 N=24	184.37 ± 3.45 N=18
Body Weight (pnd 40) (g)[a]				
	212.29 ± 4.21 § N=23	212.47 ± 4.66 N=17	208.46 ± 3.62 N=24	201.20 ± 3.72 N=18
Body Weight (pnd 42) (g)[a]				
	231.89 ± 4.61 § N=23	230.27 ± 5.04 N=17	225.95 ± 3.89 N=24	217.70 ± 4.11 N=18
Body Weight (pnd 44) (g)[a]				
	250.48 ± 4.85 § N=23	247.85 ± 5.04 N=17	244.43 ± 4.00 N=24	235.67 ± 4.26 N=18
Body Weight (pnd 46) (g)[a]				
	273.40 ± 5.51 § N=23	268.91 ± 5.38 N=17	268.83 ± 5.96 N=24	256.20 ± 4.59 N=18
Body Weight (pnd 48) (g)[a]				
	292.72 ± 5.76 § N=23	290.07 ± 6.15 N=17	284.82 ± 4.54 N=24	275.41 ± 4.73 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 3 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight (pnd 50) (g)[a]				
	311.76 ± 5.96 § N=23	307.68 ± 6.66 N=17	303.27 ± 4.90 N=24	292.16 ± 5.34 N=18
Body Weight (pnd 52) (g)[a]				
	330.63 ± 6.48 § N=23	325.83 ± 6.73 N=17	320.37 ± 5.37 N=24	310.38 ± 5.30 N=18
Body Weight (pnd 54) (g)[a]				
	351.87 ± 6.42 § N=23	346.41 ± 7.83 N=17	341.85 ± 5.53 N=24	332.05 ± 5.99 N=18
Body Weight (pnd 56) (g)[a]				
	369.38 ± 6.91 § N=23	363.24 ± 7.83 N=17	359.05 ± 6.28 N=24	345.83 ± 5.88 N=18
Body Weight (pnd 58) (g)[a]				
	383.11 ± 7.13 §§ N=23	376.78 ± 8.35 N=17	370.90 ± 6.33 N=24	357.78 ± 6.06 N=18
Body Weight (pnd 60) (g)[a]				
	400.04 ± 7.63 § N=23	393.88 ± 8.71 N=17	385.53 ± 6.42 N=24	375.42 ± 6.43 N=18
Body Weight (pnd 62) (g)[a]				
	416.00 ± 7.52 § N=23	408.79 ± 9.22 N=17	401.64 ± 7.07 N=24	389.03 ± 6.75 N=18
Body Weight (pnd 64) (g)[a]				
	427.56 ± 7.46 §§ N=23	417.55 ± 9.63 N=17	414.39 ± 7.17 N=24	398.24 ± 6.67 N=18
Body Weight (pnd 66) (g)[a]				
	438.07 ± 8.35 § N=23	428.29 ± 9.53 N=17	424.53 ± 7.80 N=24	410.16 ± 6.91 N=18

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US EPA ARCHIVE DOCUMENT

Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 4 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight (pnd 68) (g)[a]				
	454.34 ± 8.30 § N=23	441.61 ± 10.09 N=17	440.34 ± 8.14 N=24	424.09 ± 7.29 N=18
Body Weight (pnd 70) (g)[a]				
	466.49 ± 8.53 § N=23	456.32 ± 10.44 N=17	452.23 ± 8.50 N=24	437.12 ± 7.37 N=18
Body Weight (pnd 72) (g)[a]				
	477.19 ± 8.55 § N=23	466.33 ± 11.40 N=17	462.60 ± 8.61 N=24	446.08 ± 7.56 N=18
Body Weight (pnd 74) (g)[a]				
	486.86 ± 8.55 § N=23	475.51 ± 11.36 N=17	470.89 ± 8.86 N=24	456.58 ± 7.77 N=18
Body Weight (pnd 76) (g)[a,c]				
	509.62 ± 11.66 N=13	460.58 ± 8.96 N=10	476.66 ± 11.06 N=13[d]	462.45 ± 7.54 N=12
Body Weight Change (pnd 21 to 22) (g)[a]				
	5.20 ± 0.25 N=23	5.66 ± 0.25 N=17	4.41 ± 0.28 N=24	6.06 ± 0.84 N=18
Body Weight Change (pnd 22 to 24) (g)[a]				
	12.66 ‡ ± 0.28 § N=23	13.18 ± 0.42 N=17	13.20 ± 0.48 N=24	11.00 ± 0.94 N=18
Body Weight Change (pnd 24 to 26) (g)[a]				
	13.21 ± 0.38 N=23	12.88 ± 0.31 N=17	13.25 ± 0.44 N=24	12.47 ± 0.47 N=18

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US EPA ARCHIVE DOCUMENT

Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 5 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight Change (pnd 26 to 28) (g)[a]				
	14.25 ± 0.50 N=23	15.08 ± 0.54 N=17	14.87 ± 0.39 N=24	13.41 ± 0.47 N=18
Body Weight Change (pnd 28 to 30) (g)[a]				
	16.82 ± 0.52 N=23	16.90 ± 0.40 N=17	16.08 ± 0.57 N=24	16.18 ± 0.45 N=18
Body Weight Change (pnd 30 to 32) (g)[a]				
	17.58 ± 0.59 N=23	17.86 ± 0.74 N=17	17.74 ± 0.66 N=24	15.53 ± 1.11 N=18
Body Weight Change (pnd 32 to 34) (g)[a]				
	18.24 ± 0.43 N=23	18.88 ± 0.71 N=17	18.01 ± 0.71 N=24	17.95 ± 1.30 N=18
Body Weight Change (pnd 34 to 36) (g)[a]				
	18.98 ± 0.73 § N=23	17.57 ± 0.36 N=17	18.33 ± 0.85 N=24	16.44 ± 0.72 N=18
Body Weight Change (pnd 36 to 38) (g)[a]				
	19.76 ‡ ± 0.53 §§ N=23	18.87 ± 0.50 N=17	17.74 * ± 0.47 N=24	17.80 * ± 0.61 N=18
Body Weight Change (pnd 38 to 40) (g)[a]				
	17.85 ± 0.64 N=23	17.80 ± 0.60 N=17	17.14 ± 0.67 N=24	16.83 ± 0.70 N=18
Body Weight Change (pnd 40 to 42) (g)[a]				
	19.61 ‡‡ ± 0.60 §§ N=23	17.80 ± 0.69 N=17	17.48 * ± 0.54 N=24	16.51 ** ± 0.77 N=18
Body Weight Change (pnd 42 to 44) (g)[a]				
	18.59 ± 0.65 N=23	17.58 ± 0.96 N=17	18.49 ± 0.48 N=24	17.97 ± 0.66 N=18

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US EPA ARCHIVE DOCUMENT

Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 6 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight Change (pnd 44 to 46) (g)[a]				
	22.92 ± 1.44 N=23	21.06 ± 0.86 N=17	24.39 ± 4.43 N=24	20.53 ± 0.94 N=18
Body Weight Change (pnd 46 to 48) (g)[a]				
	19.32 ± 1.45 N=23	21.17 ± 0.99 N=17	16.00 ± 4.30 N=24	19.21 ± 0.76 N=18
Body Weight Change (pnd 48 to 50) (g)[a]				
	19.04 ± 0.73 N=23	17.61 ± 0.91 N=17	18.45 ± 0.97 N=24	16.75 ± 1.08 N=18
Body Weight Change (pnd 50 to 52) (g)[a]				
	18.87 ± 1.41 N=23	18.15 ± 1.13 N=17	17.09 ± 1.40 N=24	18.23 ± 1.41 N=18
Body Weight Change (pnd 52 to 54) (g)[a]				
	21.25 ± 1.24 N=23	20.58 ± 1.74 N=17	21.48 ± 1.16 N=24	21.66 ± 1.72 N=18
Body Weight Change (pnd 54 to 56) (g)[a]				
	17.51 ± 0.79 § N=23	16.83 ± 1.09 N=17	17.20 ± 1.20 N=24	13.78 ± 1.52 N=18
Body Weight Change (pnd 56 to 58) (g)[a]				
	13.72 ± 1.00 N=23	13.54 ± 1.29 N=17	11.85 ± 0.79 N=24	11.95 ± 1.13 N=18
Body Weight Change (pnd 58 to 60) (g)[a]				
	16.93 ± 1.28 N=23	17.10 ± 1.35 N=17	14.64 ± 0.95 N=24	17.64 ± 1.26 N=18
Body Weight Change (pnd 60 to 62) (g)[a]				
	15.96 ± 0.80 N=23	14.91 ± 1.02 N=17	16.10 ± 1.15 N=24	13.61 ± 1.15 N=18

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US EPA ARCHIVE DOCUMENT

Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 7 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Body Weight Change (pnd 62 to 64) (g)[a]				
	11.56 ± 1.03 N=23	8.76 ± 1.14 N=17	12.75 ± 1.26 N=24	9.21 ± 1.31 N=18
Body Weight Change (pnd 64 to 66) (g)[a]				
	10.51 ± 1.91 N=23	10.74 ± 1.62 N=17	10.14 ± 1.40 N=24	11.91 ± 1.77 N=18
Body Weight Change (pnd 66 to 68) (g)[a]				
	16.26 ± 1.31 N=23	13.32 ± 1.51 N=17	15.81 ± 0.86 N=24	13.93 ± 1.16 N=18
Body Weight Change (pnd 68 to 70) (g)[a]				
	12.15 ± 1.34 N=23	14.71 ± 0.87 N=17	11.88 ± 1.13 N=24	13.03 ± 0.74 N=18
Body Weight Change (pnd 70 to 72) (g)[a]				
	10.70 ± 0.78 N=23	10.01 ± 1.24 N=17	10.37 ± 1.03 N=24	8.96 ± 1.07 N=18
Body Weight Change (pnd 72 to 74) (g)[a]				
#	9.67 ± 0.71 N=23	9.18 ± 0.95 N=17	8.29 ± 0.75 N=24	10.50 ± 1.24 N=18
Body Weight Change (pnd 74 to 76) (g)[a,c]				
	11.39 ± 1.94 N=13	8.61 ± 1.70 N=10	10.85 ± 1.52 N=13[d]	9.02 ± 1.08 N=12
Body Weight Change (pnd 21 to 74) (g)[a]				
	429.12 ± 7.58 § N=23	417.74 ± 10.17 N=17	413.21 ± 8.20 N=24	399.05 ± 7.20 N=18

(continued)

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Table 33. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 8 of 8)

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
[c]Includes only those males that had not yet been necropsied. Statistical analysis was not done on this endpoint since not all of the males were represented.
[d]Decrease in N is due to one body weight inadvertently not being recorded.
#Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
‡p<0.05; ANOVA Test.
‡‡p<0.01; ANOVA Test.
§p<0.05; Test for Linear Trend.
§§p<0.01; Test for Linear Trend.
*p<0.05; Dunnett's Test.
**p<0.01; Dunnett's Test.

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Table 34. Summary of the F_1 Undosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 1 of 1)

A. Clinical Observations Summarized by Group

	Methoxychlor (mg/kg/day)			
Observation	0	25	50	100
Alopecia	1	1		3

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day)			
Day[a]	Observation[b]	0	25	50	100
64	Alopecia: face				2
65	Alopecia: face				2
	limb(s)		1		
66	Alopecia: face				3
	limb(s)		1		
67	Alopecia: face				3
	limb(s)		1		
68	Alopecia: face				3
	limb(s)		1		
69	Alopecia: face				3
	limb(s)		1		
70	Alopecia: face	1			3
	limb(s)		1		
71	Alopecia: face	1			3
	limb(s)		1		
72	Alopecia: face	1			3
	limb(s)		1		
73	Alopecia: face	1			3
	limb(s)		1		
74	Alopecia: face	1			3
	limb(s)		1		
75	Alopecia: face	1			3
	limb(s)		1		

[a]Postnatal day.
[b]Clinical observations are tabulated once per day per animal.

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Table 35. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Preputial Separation Data (page 1 of 1)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Males	23	17	24	18
Average Postnatal Day of Preputial Separation[a]				
	39.9 ‡ ± 0.3 N=23	40.1 ± 0.4 N=17	41.1 * ± 0.3 N=24	39.9 ± 0.4 N=18
Average Body Weight (g) on Day of Acquisition[a]				
	213.03 ‡ ± 4.40 N=23	212.90 ± 5.53 N=17	219.27 ± 3.94 N=24	199.31 ± 4.42 N=18
Adjusted Average Postnatal Day of Preputial Separation[b]				
	40.0 Ω ± 0.3 N=23	40.1 ± 0.4 N=17	41.1 φ ± 0.3 N=24	39.7 ± 0.4 N=18

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Reported as the adjusted mean ± S.E.M. (body weight on postnatal day 40 as covariate).
‡p<0.05; ANOVA Test.
*p<0.05; Dunnett's Test.
Ωp<0.05; Analysis of Covariance with body weight at acquisition or body weight on postnatal day 40 as the covariate.
φp<0.05; Dunnett's Test with body weight at acquisition or body weight on postnatal day 40 as the covariate.

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Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 1 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
No. of Males	23	17	24	18
Number of Nipples per Male[a]				
	0.0 ± 0.0 N=23	0.0 ± 0.0 N=17	0.0 ± 0.0 N=24	0.0 ± 0.0 N=18
Sacrifice Body Weight (g)[a]				
	492.8 ± 9.3 § N=23	478.9 ± 10.9 N=17	476.7 ± 8.8 N=24	461.0 ± 7.9 N=18
Pituitary Weight (g)[a]				
	0.0129 ± 0.0005 N=23	0.0132 ± 0.0004 N=17	0.0135 ± 0.0004 N=23[b]	0.0133 ± 0.0005 N=18
Thyroid Weight (g)[a]				
	0.0335 ± 0.0011 N=22[c]	0.0364 ± 0.0012 N=17	0.0359 ± 0.0011 N=23[c]	0.0325 ± 0.0010 N=17[d]
Liver Weight (g)[a]				
	21.7048 ± 0.7175 N=23	21.4430 ± 0.8372 N=17	20.7540 ± 0.6518 N=24	20.2161 ± 0.5285 N=18
Paired Adrenal Gland Weight (g)[a]				
#	0.0662 ± 0.0023 N=22[e]	0.0662 ± 0.0041 N=17	0.0632 ± 0.0020 N=24	0.0624 ± 0.0016 N=18
Paired Kidney Weight (g)[a]				
	3.7511 ± 0.0789 N=23	3.7036 ± 0.0819 N=17	3.7616 ± 0.1027 N=24	3.5964 ± 0.0876 N=18
Glans Penis Weight (g)[a]				
	0.1614 ± 0.0102 N=23	0.1742 ± 0.0192 N=17	0.1739 ± 0.0145 N=24	0.1559 ± 0.0160 N=18

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US EPA ARCHIVE DOCUMENT

Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 2 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Paired Testis Weight (g)[a]				
	3.4421 ‡ §§ ± 0.0485 N=21[b]	3.3600 ± 0.0697 N=17	3.3215 ± 0.0574 N=24	3.1923 ** ± 0.0397 N=18
Right Epididymis Weight (g)[a]				
#	0.5134 ± 0.0171 N=23	0.5453 ± 0.0085 N=17	0.5310 ± 0.0099 N=23[f]	0.5218 ± 0.0085 N=18
Left Epididymis Weight (g)[a]				
	0.5106 ± 0.0136 N=23	0.5227 ± 0.0117 N=17	0.5174 ± 0.0094 N=24	0.5118 ± 0.0084 N=18
Seminal Vesicles with Coagulating Glands Weight (g)[a]				
	1.2313 ± 0.0486 N=23	1.2175 ± 0.0564 N=17	1.2193 ± 0.0392 N=24	1.2195 ± 0.0427 N=18
Ventral Prostate Weight (g)[a]				
	0.5332 ± 0.0293 N=23	0.5396 ± 0.0219 N=16[b]	0.4907 ± 0.0277 N=24	0.5283 ± 0.0269 N=18
Dorsolateral Prostate Weight (g)[a]				
	0.4164 ± 0.0255 N=23	0.4389 ± 0.0298 N=17	0.4169 ± 0.0173 N=23[b]	0.4519 ± 0.0259 N=18
Prostate Weight (g)[a]				
	0.9496 ± 0.0413 N=23	0.9834 ± 0.0447 N=16[g]	0.9142 ± 0.0362 N=23[g]	0.9802 ± 0.0415 N=18
Levator Ani plus Bulbcavernosus Muscle Complex Weight (g)[a]				
	1.0927 ± 0.0242 N=23	1.1774 ± 0.0365 N=17	1.1887 ± 0.0401 N=24	1.1726 ± 0.0348 N=18
Cowper's Gland Weight (g)[a]				
	0.1144 ± 0.0056 N=23	0.1240 ± 0.0062 N=16[h]	0.1113 ± 0.0071 N=23[h]	0.1103 ± 0.0062 N=18

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US EPA ARCHIVE DOCUMENT

Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 3 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Adjusted Pituitary Weight (g)[i]				
	0.0126 ± 0.0004 N=23	0.0132 ± 0.0004 N=17	0.0136 ± 0.0004 N=23[b]	0.0136 ± 0.0004 N=18
Adjusted Thyroid Weight (g)[i]				
	0.0325 **Ω** ± 0.0009 N=22[c]	0.0362 **φ** ± 0.0010 N=17	0.0361 **φ** ± 0.0009 N=23[c]	0.0336 ± 0.0011 N=17[d]
Adjusted Liver Weight (g)[i]				
	21.7369 ± 0.3101 N=23	21.3954 ± 0.3545 N=17	20.8569 ± 0.2984 N=24	21.3606 ± 0.3511 N=18
Adjusted Paired Adrenal Gland Weight (g)[i]				
	0.0650 ± 0.0021 N=22[e]	0.0662 ± 0.0039 N=17	0.0633 ± 0.0019 N=24	0.0637 ± 0.0017 N=18
Adjusted Paired Kidney Weight (g)[i]				
	3.6468 ± 0.0598 N=23	3.6985 ± 0.0683 N=17	3.7727 ± 0.0575 N=24	3.7197 ± 0.0677 N=18
Adjusted Glans Penis Weight (g)[i]				
	0.1627 ± 0.0142 N=23	0.1742 ± 0.0163 N=17	0.1738 ± 0.0137 N=24	0.1544 ± 0.0161 N=18
Adjusted Paired Testis Weight (g)[i]				
	3.3940 ± 0.0490 **λ** N=21[b]	3.3596 ± 0.0532 N=17	3.3273 ± 0.0448 N=24	3.2409 ± 0.0528 N=18
Adjusted Right Epididymis Weight (g)[i]				
	0.5075 ± 0.0156 N=23	0.5447 ± 0.0064 N=17	0.5324 ± 0.0096 N=23[f]	0.5282 ± 0.0087 N=18
Adjusted Left Epididymis Weight (g)[i]				
	0.5028 ± 0.0097 N=23	0.5223 ± 0.0111 N=17	0.5182 ± 0.0094 N=24	0.5210 ± 0.0110 N=18

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Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 4 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Adjusted Seminal Vesicles with Coagulating Glands Weight (g)[i]				
	1.2181 ± 0.0443 N=23	1.2168 ± 0.0506 N=17	1.2207 ± 0.0426 N=24	1.2351 ± 0.0501 N=18
Adjusted Ventral Prostate Weight (g)[i]				
	0.5256 ± 0.0262 N=23	0.5394 ± 0.0309 N=16[b]	0.4915 ± 0.0252 N=24	0.5372 ± 0.0297 N=18
Adjusted Dorsolateral Prostate Weight (g)[i]				
	0.4074 ± 0.0228 N=23	0.4383 ± 0.0260 N=17	0.4182 ± 0.0224 N=23[b]	0.4622 ± 0.0258 N=18
Adjusted Prostate Weight (g)[i]				
	0.9324 ± 0.0376 N=23	0.9827 ± 0.0442 N=16[g]	0.9167 ± 0.0369 N=23[g]	0.9997 ± 0.0425 N=18
Adjusted Levator Ani plus Bulbcavernosus Muscle Complex Weight (g)[i]				
	1.0753 **Ω** ± 0.0317 **λ** N=23	1.1765 ± 0.0363 N=17	1.1906 **φ** ± 0.0305 N=24	1.1932 **φ** ± 0.0359 N=18
Adjusted Cowper's Gland Weight (g)[i]				
	0.1143 ± 0.0061 N=23	0.1240 ± 0.0072 N=16[h]	0.1113 ± 0.0060 N=23[h]	0.1103 ± 0.0069 N=18
Adjusted Pituitary Weight (g)[j]				
	0.0129 ± 0.0004 N=23	0.0132 ± 0.0004 N=17	0.0136 ± 0.0004 N=23[b]	0.0133 ± 0.0004 N=18
Adjusted Thyroid Weight (g)[j]				
	0.0335 ± 0.0010 N=22[c]	0.0363 ± 0.0012 N=17	0.0360 ± 0.0010 N=23[c]	0.0325 ± 0.0012 N=17[d]

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US EPA ARCHIVE DOCUMENT

Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 5 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Adjusted Liver Weight (g)[j]				
	21.6896 ± 0.5622 N=23	21.4172 ± 0.6539 N=17	20.7550 ± 0.5503 N=24	20.2586 ± 0.6355 N=18
Adjusted Paired Adrenal Gland Weight (g)[j]				
	0.0661 ± 0.0021 N=22[e]	0.0662 ± 0.0039 N=17	0.0632 ± 0.0018 N=24	0.0625 ± 0.0017 N=18
Adjusted Paired Kidney Weight (g)[j]				
	3.7495 ± 0.0782 N=23	3.7009 ± 0.0909 N=17	3.7617 ± 0.0765 N=24	3.6009 ± 0.0884 N=18
Adjusted Glans Penis Weight (g)[j]				
	0.1614 ± 0.0139 N=23	0.1743 ± 0.0162 N=17	0.1739 ± 0.0136 N=24	0.1557 ± 0.0158 N=18
Adjusted Paired Testis Weight (g)[j]				
	3.4340 **Ω** ± 0.0491 **λλ** N=21[b]	3.3609 ± 0.0545 N=17	3.3240 ± 0.0459 N=24	3.1974 **φφ** ± 0.0530 N=18
Adjusted Right Epididymis Weight (g)[j]				
	0.5129 ± 0.0164 N=23	0.5447 ± 0.0076 N=17	0.5319 ± 0.0094 N=23[f]	0.5219 ± 0.0072 N=18
Adjusted Left Epididymis Weight (g)[j]				
	0.5105 ± 0.0100 N=23	0.5224 ± 0.0116 N=17	0.5174 ± 0.0098 N=24	0.5123 ± 0.0113 N=18
Adjusted Seminal Vesicles with Coagulating Glands Weight (g)[j]				
	1.2310 ± 0.0438 N=23	1.2170 ± 0.0509 N=17	1.2193 ± 0.0429 N=24	1.2202 ± 0.0495 N=18
Adjusted Ventral Prostate Weight (g)[j]				
	0.5332 ± 0.0259 N=23	0.5388 ± 0.0311 N=16[b]	0.4909 ± 0.0254 N=24	0.5289 ± 0.0293 N=18

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US EPA ARCHIVE DOCUMENT

Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 6 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Adjusted Dorsolateral Prostate Weight (g)[j]				
	0.4164 ± 0.0228 N=23	0.4388 ± 0.0265 N=17	0.4166 ± 0.0228 N=23[b]	0.4524 ± 0.0257 N=18
Adjusted Prostate Weight (g)[j]				
	0.9498 ± 0.0378 N=23	0.9820 ± 0.0453 N=16[g]	0.9140 ± 0.0378 N=23[g]	0.9815 ± 0.0427 N=18
Adjusted Levator Ani plus Bulbcavernosus Muscle Complex Weight (g)[j]				
	1.0922 ± 0.0306 N=23	1.1765 ± 0.0355 N=17	1.1887 ± 0.0299 N=24	1.1741 ± 0.0345 N=18
Adjusted Cowper's Gland Weight (g)[j]				
	0.1143 ± 0.0060 N=23	0.1240 ± 0.0072 N=16[h]	0.1113 ± 0.0060 N=23[h]	0.1103 ± 0.0068 N=18
Percent Motile Sperm[a,k]				
	59.9 ± 2.8 N=23			66.8 ± 2.5 N=18
Percent Progressively Motile Sperm[a,k]				
	50.4 ± 2.9 N=23			54.1 ± 2.8 N=18
Epididymal Sperm Concentration (10^6/g)[a,k]				
	411.92 ± 18.03 N=23			386.82 ± 11.73 N=18
Spermatid Head Concentration (10^6/g)[a,k]				
	77.91 **Δ** ± 3.53 N=23			93.48 ± 5.18 N=18

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Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 7 of 8)

	Methoxychlor (mg/kg/day)			
	0	25	50	100
Daily Sperm Production per Testis (10^6/testis/day)[a,k]				
	28.17 ± 1.51 N=23			32.36 ± 1.91 N=18
Efficiency of Daily Sperm Production (10^6/g. testis/day)[a,k]				
	16.90 **Δ** ± 0.77 N=23			20.28 ± 1.12 N=18
Thyroxine Hormone (T4) (ug/dL)[a]				
	5.90 ± 0.14 N=23	6.08 ± 0.20 N=17	6.12 ± 0.23 N=24	5.47 ± 0.19 N=18
Triiodothyronine Hormone (T3) (ng/ml)[a]				
	70.88 ± 2.80 N=23	70.97 ± 3.06 N=17	70.02 ± 4.02 N=24	69.30 ± 3.96 N=18
Thyroid Stimulating Hormone (TSH) (ng/ml)[a]				
	11.56 ± 0.75 N=23	12.91 ± 1.31 N=17	10.43 ± 0.66 N=24	11.70 ± 1.02 N=18

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Table 36. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 8 of 8)

[a]Reported as the mean ± S.E.M.
[b]Decrease in N is due to one weight being a statistical outlier and therefore it was excluded.
[c]Decrease in N is due to one thyroid being lost prior to weighing.
[d]Decrease in N is due to the tissue cassette containing one thyroid being mislabeled and therefore it was excluded.
[e]Decrease in N is due to one adrenal gland being lost prior to weighing.
[f]Decrease in N is due to one right epididymis weight inadvertently not being recorded.
[g]Decrease in N is due to one ventral prostate or dorsolateral prostate weight being a statistical outlier and therefore it was excluded and the total prostate weight could not be calculated.
[h]Decrease in N is due to the right cowper's gland being missing and therefore a paired cowper's gland weight could not be determined.
[i]Reported as the adjusted mean ± S.E.M. (sacrifice weight as covariate).
[j]Reported as the adjusted mean ± S.E.M. (postnatal day 21 as covariate).
[k]The control and high dose groups only were statistically analyzed for this endpoint.
[#]Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.
[‡]$p<0.05$; ANOVA Test.
[§]$p<0.05$; Test for Linear Trend.
[§§]$p<0.01$; Test for Linear Trend.
[**]$p<0.01$; Dunnett's Test.
[Ω]$p<0.05$; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[λ]$p<0.05$; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[λλ]$p<0.01$; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[φ]$p<0.05$; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
[φφ]$p<0.01$; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
[Δ]$p<0.05$; Student's T-test.

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Table 37. Summary of the F_1 Undosed Pubertal Male Gross Necropsy Findings (page 1 of 1)

Scheduled Necropsy

	Methoxychlor (mg/kg/day)			
Finding	0	25	50	100
Alopecia: face				1
Caecum: gas present			1	
Cowper's Gland: missing, right		1	1	
Kidney: hydronephrosis, bilateral	2			
hydronephrosis, right	5	2	4	4
two 2 mm clear cysts on surface, right				1
Large Intestines: air present		1		1

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Table 38. Summary of the Fate of the F_1 Dosed Pubertal Males (page 1 of 1)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Males on Study	25	22	24	19
Fate of Males:				
Removed from Study[a]	2	5	0	1
Post Wean Holding Period	1[b]	0	1[c]	0
Scheduled Sacrifice on Postnatal Day 75, 76 or 77	22	17	23	18

[a]These animals were removed from the study because their dam was removed from the study.
[b]Male 100 was found dead on postnatal day 24 prior to dosing.
[c]Male 472 was found dead on postnatal day 26 prior to dosing (misdirected dose).

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Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 1 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Males	23	17	24	18
Anogenital Distance on Postnatal Day 21 (mm)[a]				
	15.13 ± 0.33 N=23	14.99 ± 0.37 N=17	15.08 ± 0.29 N=24	15.77 ± 0.36 N=17[b]
Adjusted Anogenital Distance on Postnatal Day 21 (mm)[c]				
	15.09 ± 0.31 N=23	15.02 ± 0.37 N=17	15.05 ± 0.31 N=24	15.84 ± 0.37 N=17[b]
Body Weight (pnd 21) (g)[a]				
	58.33 ± 0.74 N=23	56.68 ± 1.59 N=17	58.05 ± 1.14 N=24	56.11 ± 1.57 N=18
Body Weight (pnd 22) (g)[a]				
	62.96 ± 0.89 N=23	61.41 ± 1.69 N=17	61.98 ± 1.26 N=24	60.98 ± 1.75 N=18
Body Weight (pnd 24) (g)[a]				
	75.67 ± 1.09 N=22[d]	73.20 ± 1.74 N=17	72.09 ± 1.92 N=24	72.02 ± 1.87 N=18
Body Weight (pnd 26) (g)[a]				
	88.73 ± 1.36 N=22	86.81 ± 2.06 N=17	87.90 ± 1.74 N=23[e]	83.81 ± 1.68 N=18
Body Weight (pnd 28) (g)[a]				
	103.39 ± 1.56 § N=22	101.78 ± 2.40 N=17	102.71 ± 1.79 N=23	96.52 ± 1.74 N=18
Body Weight (pnd 30) (g)[a]				
	119.11 ‡‡ ± 1.80 §§ N=22	116.04 ± 2.75 N=17	118.33 ± 2.16 N=23	108.78 ** ± 2.11 N=18

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Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 2 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight (pnd 32) (g)[a]				
	136.96 ‡‡ ± 2.19 §§§ N=22	134.23 ± 3.21 N=17	134.10 ± 2.49 N=23	124.18 ** ± 2.24 N=18
Body Weight (pnd 34) (g)[a]				
	157.16 ‡‡‡ ± 2.58 §§§ N=22	152.43 ± 3.50 N=17	151.17 ± 2.74 N=23	138.62 *** ± 3.15 N=18
Body Weight (pnd 36) (g)[a]				
	175.75 ‡‡‡ ± 2.87 §§§ N=22	168.84 ± 3.71 N=17	168.03 ± 3.17 N=23	153.42 *** ± 2.93 N=18
Body Weight (pnd 38) (g)[a]				
	195.36 ‡‡‡ ± 3.24 §§§ N=22	187.40 ± 4.10 N=17	184.68 ± 3.25 N=23	169.89 *** ± 3.20 N=18
Body Weight (pnd 40) (g)[a]				
	214.33 ‡‡‡ ± 3.72 §§§ N=22	204.13 ± 3.94 N=17	200.53 * ± 3.95 N=23	182.60 *** ± 3.09 N=18
Body Weight (pnd 42) (g)[a]				
	232.84 ‡‡‡ ± 4.24 §§§ N=22	219.09 ± 4.16 N=17	213.18 ** ± 4.07 N=23	196.63 *** ± 3.61 N=18
Body Weight (pnd 44) (g)[a]				
	250.98 ‡‡‡ ± 4.34 §§§ N=21[f]	239.52 ± 4.55 N=17	229.51 ** ± 4.41 N=23	212.67 *** ± 3.62 N=18
Body Weight (pnd 46) (g)[a]				
	272.25 ‡‡‡ ± 5.02 §§§ N=22	253.82 * ± 5.11 N=17	243.64 *** ± 4.52 N=23	222.72 *** ± 3.74 N=18
Body Weight (pnd 48) (g)[a]				
	290.78 ‡‡‡ ± 5.42 §§§ N=22	267.37 ** ± 5.17 N=17	256.26 *** ± 4.68 N=23	233.84 *** ± 4.26 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 3 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight (pnd 50) (g)[a]				
	310.78 ‡‡‡ ± 6.24 §§§ N=22	283.77 ** ± 5.89 N=17	271.96 *** ± 5.25 N=23	248.82 *** ± 4.31 N=18
Body Weight (pnd 52) (g)[a]				
	331.38 ‡‡‡ ± 6.63 §§§ N=22	302.12 ** ± 6.20 N=17	287.48 *** ± 5.46 N=23	262.37 *** ± 4.93 N=18
Body Weight (pnd 54) (g)[a]				
	351.14 ‡‡‡ ± 7.40 §§§ N=21[g]	311.36 *** ± 6.50 N=17	297.42 *** ± 5.66 N=23	271.31 *** ± 4.90 N=18
Body Weight (pnd 56) (g)[a]				
	366.52 ‡‡‡ ± 7.28 §§§ N=22	324.46 *** ± 6.98 N=17	306.57 *** ± 5.76 N=23	281.48 *** ± 4.89 N=18
Body Weight (pnd 58) (g)[a]				
	384.09 ‡‡‡ ± 7.61 §§§ N=22	335.41 *** ± 7.62 N=17	316.23 *** ± 5.90 N=23	287.89 *** ± 4.81 N=18
Body Weight (pnd 60) (g)[a]				
	400.58 ‡‡‡ ± 8.05 §§§ N=22	344.07 *** ± 7.82 N=17	325.04 *** ± 5.79 N=23	298.65 *** ± 5.46 N=18
Body Weight (pnd 62) (g)[a]				
	415.64 ‡‡‡ ± 8.48 §§§ N=22	354.76 *** ± 8.19 N=17	333.20 *** ± 6.14 N=23	306.32 *** ± 5.27 N=18
Body Weight (pnd 64) (g)[a]				
	430.76 ‡‡‡ ± 8.99 §§§ N=22	363.91 *** ± 8.76 N=17	341.37 *** ± 6.32 N=23	313.42 *** ± 5.61 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 4 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight (pnd 66) (g)[a]				
	445.22 ‡‡‡ ± 9.21 §§§ N=22	374.81 *** ± 9.20 N=17	354.29 *** ± 6.12 N=23	321.23 *** ± 5.65 N=18
Body Weight (pnd 68) (g)[a]				
	456.50 ‡‡‡ ± 9.70 §§§ N=22	379.94 *** ± 9.46 N=17	356.33 *** ± 6.55 N=23	324.06 *** ± 5.96 N=18
Body Weight (pnd 70) (g)[a]				
	468.12 ‡‡‡ ± 9.56 §§§ N=22	386.66 *** ± 9.50 N=17	362.74 *** ± 6.58 N=23	330.77 *** ± 5.92 N=18
Body Weight (pnd 72) (g)[a]				
	478.00 ‡‡‡ ± 9.80 §§§ N=22	395.77 *** ± 10.09 N=17	368.24 *** ± 7.01 N=23	337.16 *** ± 6.21 N=18
Body Weight (pnd 74) (g)[a]				
	486.30 ‡‡‡ ± 9.99 §§§ N=22	402.83 *** ± 9.89 N=17	373.48 *** ± 6.99 N=23	339.53 *** ± 5.94 N=18
Body Weight (pnd 76) (g)[a,h]				
	507.17 ± 13.41 N=13	397.98 ± 5.05 N=10	387.24 ± 8.29 N=13	353.96 ± 8.36 N=12
Body Weight Change (pnd 21 to 22) (g)[a]				
	4.63 ± 0.35 N=23	4.74 ± 0.28 N=17	3.94 ± 0.32 N=24	4.87 ± 0.44 N=18
Body Weight Change (pnd 22 to 24) (g)[a]				
	12.44 ± 0.37 N=22[d]	11.79 ± 0.45 N=17	10.10 ± 1.04 N=24	11.04 ± 0.35 N=18
Body Weight Change (pnd 24 to 26) (g)[a]				
#	13.06 †† ± 0.42 N=22	13.61 ± 0.56 N=17	14.86 ± 0.87 N=23[e]	11.79 Þ ± 0.39 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 5 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (pnd 26 to 28) (g)[a]				
	14.66 ‡‡ ± 0.43 §§ N=22	14.97 ± 0.41 N=17	14.81 ± 0.58 N=23	12.71 * ± 0.47 N=18
Body Weight Change (pnd 28 to 30) (g)[a]				
#	15.72 ††† ± 0.35 ŸŸŸ N=22	14.25 Þ ± 0.48 N=17	15.62 ± 0.79 N=23	12.26 ÞÞÞ ± 0.59 N=18
Body Weight Change (pnd 30 to 32) (g)[a]				
	17.85 ‡‡ ± 0.50 §§ N=22	18.20 ± 0.66 N=17	15.77 ± 0.88 N=23	15.40 * ± 0.47 N=18
Body Weight Change (pnd 32 to 34) (g)[a]				
	20.20 ‡‡ ± 0.54 §§§ N=22	18.20 ± 0.49 N=17	17.07 ± 1.02 N=23	14.43 *** ± 1.64 N=18
Body Weight Change (pnd 34 to 36) (g)[a]				
	18.59 ‡‡‡ ± 0.47 §§§ N=22	16.40 * ± 0.54 N=17	16.86 ± 0.64 N=23	14.80 *** ± 0.78 N=18
Body Weight Change (pnd 36 to 38) (g)[a]				
	19.61 ‡‡ ± 0.75 §§ N=22	18.56 ± 0.79 N=17	16.65 ** ± 0.56 N=23	16.47 ** ± 0.75 N=18
Body Weight Change (pnd 38 to 40) (g)[a]				
	18.97 ‡‡‡ ± 0.73 §§§ N=22	16.74 ± 0.85 N=17	15.85 * ± 0.92 N=23	12.72 *** ± 0.95 N=18
Body Weight Change (pnd 40 to 42) (g)[a]				
	18.51 ‡‡‡ ± 0.97 §§ N=22	14.96 * ± 0.70 N=17	12.65 *** ± 0.80 N=23	14.02 ** ± 1.03 N=18
Body Weight Change (pnd 42 to 44) (g)[a]				
	20.22 ‡‡ ± 1.34 §§ N=21[f]	20.43 ± 0.95 N=17	16.33 * ± 0.77 N=23	16.04 * ± 0.91 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 6 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (pnd 44 to 46) (g)[a]				
	19.18 ‡‡‡ ± 1.73 §§§ N=21[f]	14.30 * ± 1.09 N=17	14.14 * ± 1.21 N=23	10.05 *** ± 0.70 N=18
Body Weight Change (pnd 46 to 48) (g)[a]				
	18.53 ‡‡‡ ± 0.78 §§§ N=22	13.55 *** ± 1.01 N=17	12.62 *** ± 0.70 N=23	11.13 *** ± 1.10 N=18
Body Weight Change (pnd 48 to 50) (g)[a]				
	20.00 ‡ ± 1.63 §§ N=22	16.40 ± 1.13 N=17	15.70 * ± 1.03 N=23	14.97 * ± 0.77 N=18
Body Weight Change (pnd 50 to 52) (g)[a]				
	20.60 ‡‡‡ ± 1.00 §§§ N=22	18.36 ± 0.88 N=17	15.52 *** ± 0.88 N=23	13.55 *** ± 1.11 N=18
Body Weight Change (pnd 52 to 54) (g)[a]				
	18.46 ‡‡‡ ± 1.31 §§§ N=21[g]	9.24 *** ± 0.98 N=17	9.95 *** ± 1.21 N=23	8.94 *** ± 0.74 N=18
Body Weight Change (pnd 54 to 56) (g)[a]				
	16.81 ‡‡‡ ± 1.49 §§§ N=21[g]	13.10 ± 1.17 N=17	9.15 *** ± 1.23 N=23	10.16 ** ± 1.02 N=18
Body Weight Change (pnd 56 to 58) (g)[a]				
	17.57 ‡‡‡ ± 0.78 §§§ N=22	10.94 *** ± 1.01 N=17	9.66 *** ± 1.16 N=23	6.41 *** ± 0.73 N=18
Body Weight Change (pnd 58 to 60) (g)[a]				
	16.49 ‡‡‡ ± 1.05 §§ N=22	8.66 *** ± 1.11 N=17	8.80 *** ± 0.88 N=23	10.77 *** ± 1.08 N=18
Body Weight Change (pnd 60 to 62) (g)[a]				
	15.06 ‡‡‡ ± 0.78 §§§ N=22	10.69 ** ± 0.91 N=17	8.16 *** ± 1.14 N=23	7.67 *** ± 0.69 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 7 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight Change (pnd 62 to 64) (g)[a]				
	15.12 ‡‡‡ ± 0.92 §§§ N=22	9.15 *** ± 1.25 N=17	8.17 *** ± 0.78 N=23	7.09 *** ± 1.01 N=18
Body Weight Change (pnd 64 to 66) (g)[a]				
	14.46 ‡ ± 1.13 §§ N=22	10.90 ± 1.01 N=17	12.92 ± 2.28 N=23	7.82 * ± 0.81 N=18
Body Weight Change (pnd 66 to 68) (g)[a]				
	11.27 ‡‡‡ ± 0.98 §§§ N=22	5.13 * ± 0.86 N=17	2.04 *** ± 2.44 N=23	2.82 ** ± 0.66 N=18
Body Weight Change (pnd 68 to 70) (g)[a]				
	11.63 ‡‡‡ ± 0.91 §§ N=22	6.72 ** ± 1.05 N=17	6.41 *** ± 1.05 N=23	6.72 ** ± 0.93 N=18
Body Weight Change (pnd 70 to 72) (g)[a]				
	9.88 ‡ ± 1.39 § N=22	9.11 ± 1.43 N=17	5.49 * ± 1.12 N=23	6.39 ± 0.98 N=18
Body Weight Change (pnd 72 to 74) (g)[a]				
	8.29 ‡‡ ± 1.31 §§§ N=22	7.06 ± 1.16 N=17	5.24 ± 0.85 N=23	2.37 ** ± 1.16 N=18
Body Weight Change (pnd 74 to 76) (g)[a,h]				
	11.84 ± 5.64 N=13	4.92 ± 1.50 N=10	4.41 ± 1.23 N=13	9.24 ± 1.12 N=12
Body Weight Change (pnd 21 to 74) (g)[a]				
	427.73 ‡‡‡ ± 9.68 §§§ N=22	346.15 *** ± 9.33 N=17	315.21 *** ± 6.81 N=23	283.43 *** ± 6.30 N=18

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US EPA ARCHIVE DOCUMENT

Table 39. Summary and Statistical Analysis of the F_1 Undosed Pubertal Male Anogenital Distance, Body Weights and Weight Changes During the Post Wean Holding Period (page 8 of 8)

[a]Reported as the mean ± S.E.M.; pnd = postnatal day.
[b]Decrease in N is due to one anogenital distance measurement inadvertently not being recorded.
[c]Reported as the adjusted mean ± S.E.M. (postnatal day 21 body weight as covariate).
[d]Decrease in N is due to male 100 being found dead on postnatal day 24 prior to dosing.
[e]Decrease in N is due to male 472 being found dead on postnatal day 26 prior to dosing (misdirected dose).
[f]Decrease in N is due to one male not having a water bottle overnight and therefore the body weight for this postnatal day was excluded.
[g]Decrease in N is due to one body weight inadvertently not being recorded.
[h]Includes only those males that had not yet been necropsied. Statistical analysis was not done on this endpoint since not all of the males were represented.
[#]Levene's test for homogeneity of variances was significant ($p<0.05$), therefore robust regression methods were used to test all treatment effects.
[‡]$p<0.05$; ANOVA Test.
[‡‡]$p<0.01$; ANOVA Test.
[‡‡‡]$p<0.001$; ANOVA Test.
[§]$p<0.05$; Test for Linear Trend.
[§§]$p<0.01$; Test for Linear Trend.
[§§§]$p<0.001$; Test for Linear Trend.
[*]$p<0.05$; Dunnett's Test.
[**]$p<0.01$; Dunnett's Test.
[***]$p<0.001$; Dunnett's Test.
[††]$p<0.01$; Wald Chi-square Test for overall treatment effect in robust regression model.
[†††]$p<0.001$; Wald Chi-square Test for overall treatment effect in robust regression model.
[ŸŸŸ]$p<0.001$; Linear trend test in robust regression model.
[Þ]$p<0.05$; Individual t-test for pairwise comparisons to control in robust regression model.
[ÞÞÞ]$p<0.001$; Individual t-test for pairwise comparisons to control in robust regression model.

US EPA ARCHIVE DOCUMENT

Table 40. Summary of the F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 1 of 5)

A. Clinical Observations Summarized by Group

	Methoxychlor (mg/kg/day, po)			
Observation	0	25	50	100
Alopecia		1		
Ataxia	1			
Chromodacryorrhea	2	2	2	
Efflux of the dosing solution	3	1	8	8
Found dead	1		1	
Lethargic			1	
Mouth: bled after dosing	1			
No water bottle overnight	1			
Paw: right front 4th metatarsal swollen				1
Piloerection			3	1
Respiration: audible			1	
Rooting: post dosing	5	8	13	14
Salivation: prior to dosing	5	7	8	12
Scab(s)		1		
Teeth: upper incisors missing or lower incisors trimmed		1		
Urine: blood present	1			

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, po)			
Day[a]	Observation[b]	0	25	50	100
23	Piloerection			1	1
24	Ataxia	1			
	Chromodacryorrhea: nose	1			
	Efflux of the dosing solution				1
	Found dead	1			
	Lethargic			1	
	Piloerection			1	
	Urine: blood present	1			
25	Piloerection			1	
	Respiration: audible			1	
26	Found dead			1	
	Piloerection			2	
28	Efflux of the dosing solution				1
29	Efflux of the dosing solution				1
30	Chromodacryorrhea: eye, left, slight		1		
	Efflux of the dosing solution	1			1
	Salivation: prior to dosing	1			

(continued)

US EPA ARCHIVE DOCUMENT

Table 40. Summary of the F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 2 of 5)

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, po)			
Day[a]	Observation[b]	0	25	50	100
31	Rooting: post dosing				2
32	Efflux of the dosing solution			1	2
	Efflux of the dosing solution, with food	1			
	Rooting: post dosing	1		1	3
33	Rooting: post dosing	3			4
	Salivation: prior to dosing				4
34	Paw: right front 4th metatarsal swollen				1
	Rooting: post dosing			1	3
	Salivation: prior to dosing				3
35	Chromodacryorrhea: eye, left		1		
	Paw: right front 4th metatarsal swollen, healing				1
	Rooting: post dosing			1	1
36	Chromodacryorrhea: nose		1		
	Rooting: post dosing			2	6
37	Chromodacryorrhea: nose		1		
	Efflux of the dosing solution			1	
	Rooting: post dosing	2		5	1
	Salivation: prior to dosing		1	2	
38	Rooting: post dosing			2	3
	Salivation: prior to dosing	2	1		1
39	Efflux of the dosing solution			1	1
	Salivation: prior to dosing	1	1		3
40	Rooting: post dosing				1
	Salivation: prior to dosing		1	1	2
41	Rooting: post dosing		1		3
	Salivation: prior to dosing	1	1	2	4
42	Rooting: post dosing			2	1
	Salivation: prior to dosing		2	3	2
43	Chromodacryorrhea: nose	1			
	Rooting: post dosing			1	
	Salivation: prior to dosing		1		1
44	No water bottle overnight	1			
	Salivation: prior to dosing		2	1	3
45	Rooting: post dosing				1
	Salivation: prior to dosing		1		2

(continued)

US EPA ARCHIVE DOCUMENT

Table 40. Summary of the F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 3 of 5)

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, po)			
Day[a]	Observation[b]	0	25	50	100
46	Chromodacryorrhea: eye, left		1		
	Rooting: post dosing	1		1	
	Salivation: prior to dosing		2	1	3
47	Efflux of the dosing solution			1	
	Rooting: post dosing		1	1	2
	Salivation: prior to dosing		1	2	2
48	Rooting: post dosing			1	1
	Salivation: prior to dosing		2		
49	Chromodacryorrhea: eye, left		1		
	Rooting: post dosing				2
	Salivation: prior to dosing		2		3
50	Chromodacryorrhea: eye, left		1		
	Rooting: post dosing		1		4
	Salivation: prior to dosing		1	1	
51	Chromodacryorrhea: eye, left		1		
	Rooting: post dosing		1	1	1
	Salivation: prior to dosing		2	1	2
52	Chromodacryorrhea: eye, left		1		
	Rooting: post dosing			1	1
	Salivation: prior to dosing		1	2	2
53	Efflux of the dosing solution				1
	Rooting: post dosing		2	1	
	Salivation: prior to dosing	1	2	1	
	Teeth: upper incisors missing[c]		1		
54	Rooting: post dosing			1	3
	Salivation: prior to dosing		3	4	3
55	Chromodacryorrhea: nose			1	
	Efflux of the dosing solution				1
	Rooting: post dosing			1	
	Salivation: prior to dosing		3	2	1
56	Rooting: post dosing		1	4	2
	Salivation: prior to dosing		3	1	3
	Teeth: trimmed lower incisors		1		
57	Alopecia: limb(s)		1		
	Efflux of the dosing solution			2	
	Rooting: post dosing	1	1	4	
	Salivation: prior to dosing		2		2

(continued)

US EPA ARCHIVE DOCUMENT

Table 40. Summary of the F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 4 of 5)

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, po)			
Day[a]	Observation[b]	0	25	50	100
58	Alopecia: limb(s)		1		
	Rooting: post dosing		2	5	4
	Salivation: prior to dosing		3	3	2
59	Alopecia: limb(s)		1		
	Rooting: post dosing		2	3	3
	Salivation: prior to dosing		2		
60	Alopecia: limb(s)		1		
	Rooting: post dosing		1	3	2
	Salivation: prior to dosing	1	4	2	3
61	Alopecia: limb(s)		1		
	Efflux of the dosing solution			1	
	Efflux of the dosing solution, through nose and mouth	1			
	Rooting: post dosing			3	1
	Salivation: prior to dosing		3		1
	Teeth: trimmed lower incisors		1		
62	Alopecia: limb(s)		1		
	Rooting: post dosing				1
	Salivation: prior to dosing		3	3	2
63	Alopecia: limb(s)		1		
	Rooting: post dosing		1	4	2
	Salivation: prior to dosing		3	3	1
	Teeth: trimmed lower incisors		1		
64	Alopecia: limb(s)		1		
	Rooting: post dosing			4	2
	Salivation: prior to dosing	1	1	5	4
65	Alopecia: limb(s)		1		
	Salivation: prior to dosing		5	4	
66	Alopecia: limb(s)		1		
	Rooting: post dosing		1		
	Salivation: prior to dosing		3	3	1
67	Alopecia: limb(s)		1		
	Efflux of the dosing solution		1		
	Rooting: post dosing			1	1
	Salivation: prior to dosing		3	2	1
	Scab(s): face		1		

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US EPA ARCHIVE DOCUMENT

Table 40. Summary of the F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 5 of 5)

B. Clinical Observations Summarized by Group and Day

		Methoxychlor (mg/kg/day, po)			
Day[a]	Observation[b]	0	25	50	100
68	Alopecia: limb(s)		1		
	Mouth: bled after dosing	1			
	Rooting: post dosing		1	1	2
	Salivation: prior to dosing		4	4	3
	Scab(s): face		1		
	Teeth: trimmed lower incisors		1		
69	Alopecia: limb(s)		1		
	Salivation: prior to dosing		2	2	1
	Scab(s): face		1		
70	Alopecia: limb(s)		1		
	Efflux of the dosing solution			1	
	Rooting: post dosing				1
	Salivation: prior to dosing		2	3	4
	Scab(s): face		1		
71	Alopecia: limb(s)		1		
	Chromodacryorrhea: eye, right			1	
	Rooting: post dosing			2	1
	Salivation: prior to dosing		2	3	
	Scab(s): face		1		
72	Rooting: post dosing			1	
	Salivation: prior to dosing		3	1	
	Scab(s): face		1		
73	Rooting: post dosing		2		
	Salivation: prior to dosing		3	1	
	Scab(s): face		1		
74	Efflux of the dosing solution			1	
	Salivation: prior to dosing		2	2	
	Scab(s): face		1		
75	Alopecia: limb(s)		1		
	Salivation: prior to dosing		2	1	
	Scab(s): face		1		

[a]Postnatal day.
[b]Clinical observations are tabulated once per day per animal.
[c]No further notation was made unless a change occurred.

US EPA ARCHIVE DOCUMENT

Table 41. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Preputial Separation Data (page 1 of 1)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Males	22[a]	17	23[b]	18
Average Postnatal Day of Preputial Separation[c]				
	40.4 **‡‡‡** ± 0.3 **§§§** N=22	40.6 ± 0.4 N=17	44.0 *** ± 0.7 N=23	44.6 *** ± 0.6 N=18
Average Body Weight (g) on Day of Acquisition[c]				
	217.04 **‡** ± 3.25 N=21[d]	209.07 ± 3.24 N=17	226.61 ± 4.01 N=23	214.25 ± 5.25 N=18
Adjusted Average Postnatal Day of Preputial Separation[e]				
	41.0 **ΩΩΩ** ± 0.5 **λλλ** N=22	40.8 ± 0.5 N=17	44.0 **φφφ** ± 0.5 N=23	43.7 **φφ** ± 0.6 N=18

[a]Decrease in N is due to male 100 being found dead on postnatal day 24 prior to dosing.
[b]Decrease in N is due to male 472 being found dead on postnatal day 26 prior to dosing (misdirected dose).
[c]Reported as the mean ± S.E.M.; pnd = postnatal day.
[d]Decrease in N is due to one body weight at acquisition inadvertently not being recorded.
[e]Reported as the adjusted mean ± S.E.M. (body weight on postnatal day 40 as covariate).
‡p<0.05; ANOVA Test.
‡‡‡p<0.001; ANOVA Test.
§§§p<0.001; Test for Linear Trend.
***p<0.001; Dunnett's Test.
ΩΩΩp<0.001; Analysis of Covariance with body weight at acquisition or body weight on postnatal day 40 as the covariate.
λλλp<0.001; Linear Trend Analysis of Covariance with body weight at acquisition or body weight on postnatal day 40 as the covariate.
φφp<0.01; Dunnett's Test with body weight at acquisition or body weight on postnatal day 40 as the covariate.
φφφp<0.001; Dunnett's Test with body weight at acquisition or body weight on postnatal day 40 as the covariate.

US EPA ARCHIVE DOCUMENT

Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 1 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. of Males	22[a]	17	23[b]	18
Number of Nipples per Male[c]				
	0.0 ± 0.0 N=22	0.0 ± 0.0 N=17	0.0 ± 0.0 N=23	0.0 ± 0.0 N=17[d]
Sacrifice Body Weight (g)[c]				
	494.4 ‡‡‡ ± 10.5 §§§ N=22	404.4 *** ± 9.3 N=17	377.9 *** ± 7.0 N=23	346.0 *** ± 6.4 N=18
Pituitary Weight (g)[c]				
	0.0131 ‡‡ ± 0.0005 §§§ N=22	0.0126 ± 0.0004 N=17	0.0121 ± 0.0004 N=23	0.0107 ** ± 0.0005 N=17[e]
Thyroid Weight (g)[c]				
	0.0332 ± 0.0011 N=22	0.0322 ± 0.0015 N=17	0.0336 ± 0.0010 N=23	0.0321 ± 0.0010 N=18
Liver Weight (g)[c]				
	22.8236 ‡‡‡ ± 0.7242 §§§ N=22	17.9381 *** ± 0.7021 N=17	17.1118 *** ± 0.4388 N=23	15.7331 *** ± 0.4325 N=18
Paired Adrenal Gland Weight (g)[c]				
	0.0640 ± 0.0023 § N=22	0.0638 ± 0.0028 N=17	0.0660 ± 0.0027 N=23	0.0732 ± 0.0030 N=18
Paired Kidney Weight (g)[c]				
	3.7339 ‡‡‡ ± 0.1150 §§§ N=22	3.2204 ** ± 0.0818 N=17	3.0099 *** ± 0.0967 N=23	2.6152 *** ± 0.0978 N=18
Glans Penis Weight (g)[c]				
	0.1552 ± 0.0144 N=22	0.1403 ± 0.0107 N=17	0.1583 ± 0.0119 N=23	0.1300 ± 0.0112 N=18

(continued)

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Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 2 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Paired Testis Weight (g)[c]				
	3.4152 ‡‡‡	3.1372 **	3.0821 ***	2.8744 ***
	± 0.0610 §§§	± 0.0521	± 0.0610	± 0.0601
	N=22	N=17	N=23	N=18
Right Epididymis Weight (g)[c]				
	0.5303 ‡‡‡	0.5050	0.4783 **	0.4446 ***
	± 0.0099 §§§	± 0.0107	± 0.0121	± 0.0111
	N=22	N=17	N=23	N=18
Left Epididymis Weight (g)[c]				
	0.5299 ‡‡‡	0.4940	0.4673 ***	0.4330 ***
	± 0.0137 §§§	± 0.0075	± 0.0109	± 0.0115
	N=22	N=17	N=23	N=18
Seminal Vesicles with Coagulating Glands Weight (g)[c]				
	1.1126 ‡‡‡	0.9107 *	0.6834 ***	0.6320 ***
	± 0.0448 §§§	± 0.0603	± 0.0455	± 0.0552
	N=22	N=16[e]	N=23	N=18
Ventral Prostate Weight (g)[c]				
	0.4782 ‡‡‡	0.4411	0.3080 ***	0.2728 ***
	± 0.0257 §§§	± 0.0348	± 0.0165	± 0.0215
	N=22	N=17	N=23	N=18
Dorsolateral Prostate Weight (g)[c]				
	0.4081 ‡‡‡	0.3205 **	0.2569 ***	0.2417 ***
	± 0.0207 §§§	± 0.0156	± 0.0173	± 0.0149
	N=22	N=17	N=23	N=18
Prostate Weight (g)[c]				
	0.8863 ‡‡‡	0.7617 *	0.5650 ***	0.5146 ***
	± 0.0355 §§§	± 0.0453	± 0.0304	± 0.0291
	N=22	N=17	N=23	N=18
Levator Ani plus Bulbcavernosus Muscle Complex Weight (g)[c]				
	1.0431 ‡‡‡	0.9562	0.7736 ***	0.6480 ***
	± 0.0346 §§§	± 0.0442	± 0.0410	± 0.0396
	N=22	N=17	N=23	N=18
Cowper's Gland Weight (g)[c]				
	0.1082 ‡‡‡	0.0961	0.0657 ***	0.0692 ***
	± 0.0068 §§§	± 0.0058	± 0.0046	± 0.0048
	N=22	N=17	N=23	N=18

(continued)

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Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 3 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Adjusted Pituitary Weight (g)[f]				
	0.0110 ± 0.0006 N=22	0.0127 ± 0.0005 N=17	0.0128 ± 0.0004 N=23	0.0123 ± 0.0006 N=17[e]
Adjusted Thyroid Weight (g)[f]				
	0.0297 ± 0.0016 N=22	0.0324 ± 0.0012 N=17	0.0349 ± 0.0011 N=23	0.0346 ± 0.0015 N=18
Adjusted Liver Weight (g)[f]				
	17.4336 **ΩΩ** ± 0.3657 **λλλ** N=22	18.1890 ± 0.2662 N=17	19.0218 **φφ** ± 0.2493 N=23	19.6434 **φφ** ± 0.3292 N=18
Adjusted Paired Adrenal Gland Weight (g)[f]				
	0.0543 **ΩΩΩ** ± 0.0038 **λλλ** N=22	0.0642 ± 0.0028 N=17	0.0695 **φ** ± 0.0026 N=23	0.0803 **φφφ** ± 0.0034 N=18
Adjusted Paired Kidney Weight (g)[f]				
	2.8805 **ΩΩ** ± 0.0821 N=22	3.2601 **φφ** ± 0.0598 N=17	3.3123 **φφφ** ± 0.0560 N=23	3.2343 **φ** ± 0.0739 N=18
Adjusted Glans Penis Weight (g)[f]				
	0.1615 ± 0.0187 N=22	0.1400 ± 0.0136 N=17	0.1561 ± 0.0128 N=23	0.1253 ± 0.0169 N=18
Adjusted Paired Testis Weight (g)[f]				
	3.2253 ± 0.0853 N=22	3.1461 ± 0.0621 N=17	3.1494 ± 0.0582 N=23	3.0122 ± 0.0768 N=18
Adjusted Right Epididymis Weight (g)[f]				
	0.4934 ± 0.0158 N=22	0.5067 ± 0.0115 N=17	0.4914 ± 0.0108 N=23	0.4713 ± 0.0142 N=18
Adjusted Left Epididymis Weight (g)[f]				
	0.4915 ± 0.0164 N=22	0.4958 ± 0.0119 N=17	0.4809 ± 0.0112 N=23	0.4608 ± 0.0147 N=18

(continued)

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Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 4 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Adjusted Seminal Vesicles with Coagulating Glands Weight (g)[f]				
	0.8829 ± 0.0669 N=22	0.9175 ± 0.0502 N=16[e]	0.7663 ± 0.0458 N=23	0.8007 ± 0.0605 N=18
Adjusted Ventral Prostate Weight (g)[f]				
	0.3707 **Ω** ± 0.0332 N=22	0.4461 ± 0.0241 N=17	0.3461 ± 0.0226 N=23	0.3507 ± 0.0299 N=18
Adjusted Dorsolateral Prostate Weight (g)[f]				
	0.3363 ± 0.0245 N=22	0.3239 ± 0.0178 N=17	0.2824 ± 0.0167 N=23	0.2938 ± 0.0221 N=18
Adjusted Prostate Weight (g)[f]				
	0.7070 **Ω** ± 0.0452 N=22	0.7700 ± 0.0329 N=17	0.6285 ± 0.0308 N=23	0.6446 ± 0.0407 N=18
Adjusted Levator Ani plus Bulbcavernosus Muscle Complex Weight (g)[f]				
	0.8368 **Ω** ± 0.0513 N=22	0.9658 ± 0.0373 N=17	0.8467 ± 0.0350 N=23	0.7977 ± 0.0462 N=18
Adjusted Cowper's Gland Weight (g)[f]				
	0.0822 **Ω** ± 0.0075 N=22	0.0973 ± 0.0055 N=17	0.0749 ± 0.0051 N=23	0.0881 ± 0.0068 N=18
Adjusted Pituitary Weight (g)[g]				
	0.0130 **ΩΩ** ± 0.0005 **λλλ** N=22	0.0127 ± 0.0005 N=17	0.0120 ± 0.0004 N=23	0.0107 **φφ** ± 0.0005 N=17[e]
Adjusted Thyroid Weight (g)[g]				
	0.0331 ± 0.0011 N=22	0.0323 ± 0.0012 N=17	0.0335 ± 0.0011 N=23	0.0323 ± 0.0012 N=18

(continued)

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Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 5 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Adjusted Liver Weight (g)[g]				
	22.7401 **ΩΩΩ**	18.0064 **φφφ**	17.0517 **φφφ**	15.8474 **φφφ**
	± 0.5618 **λλλ**	± 0.6375	± 0.5482	± 0.6227
	N=22	N=17	N=23	N=18
Adjusted Paired Adrenal Gland Weight (g)[g]				
	0.0640	0.0638	0.0660	0.0733
	± 0.0026 **λ**	± 0.0030	± 0.0025	± 0.0029
	N=22	N=17	N=23	N=18
Adjusted Paired Kidney Weight (g)[g]				
	3.7163 **ΩΩΩ**	3.2347 **φφ**	2.9973 **φφφ**	2.6392 **φφφ**
	± 0.0955 **λλλ**	± 0.1084	± 0.0932	± 0.1059
	N=22	N=17	N=23	N=18
Adjusted Glans Penis Weight (g)[g]				
	0.1549	0.1406	0.1581	0.1304
	± 0.0120	± 0.0137	± 0.0117	± 0.0133
	N=22	N=17	N=23	N=18
Adjusted Paired Testis Weight (g)[g]				
	3.3968 **ΩΩΩ**	3.1523 **φ**	3.0689 **φφφ**	2.8996 **φφφ**
	± 0.0536 **λλλ**	± 0.0609	± 0.0523	± 0.0594
	N=22	N=17	N=23	N=18
Adjusted Right Epididymis Weight (g)[g]				
	0.5275 **ΩΩΩ**	0.5072	0.4763 **φφ**	0.4483 **φφφ**
	± 0.0102 **λλλ**	± 0.0116	± 0.0100	± 0.0114
	N=22	N=17	N=23	N=18
Adjusted Left Epididymis Weight (g)[g]				
	0.5263 **ΩΩΩ**	0.4969	0.4647 **φφφ**	0.4379 **φφφ**
	± 0.0103 **λλλ**	± 0.0117	± 0.0101	± 0.0114
	N=22	N=17	N=23	N=18
Adjusted Seminal Vesicles with Coagulating Glands Weight (g)[g]				
	1.1074 **ΩΩΩ**	0.9157 **φ**	0.6796 **φφφ**	0.6387 **φφφ**
	± 0.0481 **λλλ**	± 0.0563	± 0.0469	± 0.0533
	N=22	N=16[e]	N=23	N=18
Adjusted Ventral Prostate Weight (g)[g]				
	0.4752 **ΩΩΩ**	0.4436	0.3059 **φφφ**	0.2769 **φφφ**
	± 0.0234 **λλλ**	± 0.0266	± 0.0229	± 0.0260
	N=22	N=17	N=23	N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 6 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Adjusted Dorsolateral Prostate Weight (g)[g]				
	0.4076 **ΩΩΩ** ± 0.0172 **λλλ** N=22	0.3209 **φφ** ± 0.0195 N=17	0.2566 **φφφ** ± 0.0168 N=23	0.2424 **φφφ** ± 0.0191 N=18
Adjusted Prostate Weight (g)[g]				
	0.8828 **ΩΩΩ** ± 0.0336 **λλλ** N=22	0.7645 ± 0.0381 N=17	0.5625 **φφφ** ± 0.0327 N=23	0.5193 **φφφ** ± 0.0372 N=18
Adjusted Levator Ani plus Bulbcavernosus Muscle Complex Weight (g)[g]				
	1.0405 **ΩΩΩ** ± 0.0383 **λλλ** N=22	0.9583 ± 0.0435 N=17	0.7717 **φφφ** ± 0.0374 N=23	0.6516 **φφφ** ± 0.0425 N=18
Adjusted Cowper's Gland Weight (g)[g]				
	0.1074 **ΩΩΩ** ± 0.0054 **λλλ** N=22	0.0968 ± 0.0061 N=17	0.0651 **φφφ** ± 0.0052 N=23	0.0703 **φφφ** ± 0.0059 N=18
Percent Motile Sperm[a,c,h]				
	61.8 ± 3.0 N=22			59.5 ± 3.3 N=18
Percent Progressively Motile Sperm[a,c,h]				
	53.1 ± 2.9 N=22			51.3 ± 3.1 N=18
Epididymal Sperm Concentration (10^6/g)[a,c,h]				
	408.04 **ΔΔ** ± 10.80 N=22			356.53 ± 12.00 N=18
Spermatid Head Concentration (10^6/g)[a,c,h]				
	87.74 ± 4.93 N=22			83.36 ± 3.64 N=18

(continued)

US EPA ARCHIVE DOCUMENT

Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 7 of 8)

	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Daily Sperm Production per Testis (10^6/testis/day)[a,c,h]				
	32.22 **ΔΔ** ± 1.41 N=22			25.87 ± 1.08 N=18
Efficiency of Daily Sperm Production (10^6/g. testis/day)[a,c,h]				
	19.03 ± 1.07 N=22			18.08 ± 0.79 N=18
Thyroxine Hormone (T4) (ug/dL)[c]				
#	5.68 **††** ± 0.18 N=22	5.98 ± 0.24 N=17	6.55 **ÞÞÞ** ± 0.16 N=23	5.93 ± 0.28 N=18
Triiodothyronine Hormone (T3) (ng/ml)[c]				
	69.67 ± 3.41 N=22	59.36 ± 3.52 N=17	64.26 ± 3.05 N=23	66.18 ± 3.86 N=18
Thyroid Stimulating Hormone (TSH) (ng/ml)[c]				
#	11.11 ± 0.78 N=22	14.39 ± 1.42 N=17	10.81 ± 0.56 N=23	11.40 ± 0.88 N=18

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Table 42. Summary and Statistical Analysis of the F_1 Dosed Pubertal Male Number of Nipples, Organ Weights, Sperm Analysis and Hormone Data (page 8 of 8)

[a]Decrease in N is due to male 100 being found dead on postnatal day 24 prior to dosing.
[b]Decrease in N is due to male 472 being found dead on postnatal day 26 prior to dosing (misdirected dose).
[c]Reported as the mean ± S.E.M.
[d]Decrease in N is due to one nipple count inadvertently not being recorded.
[e]Decrease in N is due to one weight being a statistical outlier and therefore it was excluded.
[f]Reported as the adjusted mean ± S.E.M. (sacrifice weight as covariate).
[g]Reported as the adjusted mean ± S.E.M. (postnatal day 21 as covariate).
[h]The control and high dose groups only were statistically analyzed for this endpoint.
[#]Levene's test for homogeneity of variances was significant (p<0.05), therefore robust regression methods were used to test all treatment effects.
[‡‡]p<0.01; ANOVA Test.
[‡‡‡]p<0.001; ANOVA Test.
[§]p<0.05; Test for Linear Trend.
[§§§]p<0.001; Test for Linear Trend.
[*]p<0.05; Dunnett's Test.
[**]p<0.01; Dunnett's Test.
[***]p<0.001; Dunnett's Test.
[Ω]p<0.05; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[ΩΩ]p<0.01; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[ΩΩΩ]p<0.001; Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[λ]p<0.05; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[λλλ]p<0.001; Linear Trend Analysis of Covariance with body weight at sacrifice or on postnatal day 21 as the covariate.
[φ]p<0.05; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
[φφ]p<0.01; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
[φφφ]p<0.001; Dunnett's Test with body weight at sacrifice or on postnatal day 21 as the covariate.
[††]p<0.01; Wald Chi-square Test for overall treatment effect in robust regression model.
[ÞÞÞ]p<0.001; Individual t-test for pairwise comparisons to control in robust regression model.
[ΔΔ]p<0.01; Student's T-test.

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Table 43. Summary of the F_1 Dosed Pubertal Male Gross Necropsy Findings (page 1 of 1)

Scheduled Necropsy

	Methoxychlor (mg/kg/day, po)			
Finding	0	25	50	100
Alopecia: face		1		
limb(s)		1		
Intestines, Large: air present			1	1
Kidney: hydronephrosis, left			1	
hydronephrosis, right	2	2	5	
Levator Ani plus Bulbcavernosus Muscle Complex: reduced in size				2
Prostate, Dorsolateral: reduced in size				1
Prostate, Ventral: reduced in size				1
Prostate: reduced in size			1	3
Seminal Vesicles: reduced size			1	4
Testis: undescended, bilateral	1			
undescended, left				1

Unscheduled Necropsy

	Methoxychlor (mg/kg/day, po)			
Finding	0	25	50	100
Esophagus: hole; Dosing solution present in the thoracic cavity, misdirected dose			1	
Intestines, Small and Large: no ingesta or feces present	1			
Stomach: no food present	1			
Urinary Bladder: blood present	1			

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RTI INTERNATIONAL

Quality Assurance Statement

Study Title: **Validation of the *In Utero*/ Lactational Exposure Screening Protocol with Methoxychlor**

Sponsor: **Battelle Memorial Institute**

Study Code: **Rt02-ED04**

Protocol Number: **RTI-839**

This study was audited by the Sciences and Engineering – Quality Assurance Unit and the results of the inspections and audits were reported to the task leader/ study director and management as identified below. To the best of our knowledge, the reported results accurately describe the study methods and procedures used, and the reported results accurately reflect the raw data.

Inspections and Audits	Inspection and Audit Date(s)	Date Inspection/Audit Report Sent to Task Leader and Management
Protocol	May 22, 24, 2002	May 24, 2002
Dosing, Body/ Feed Weights, Clinical Observations, Dose Formulation Sample Collection	February 05, 2003	February 12, 2003
Dosing, Body weights, Clinical Observations, Vaginal Patency	February 21, 2003	February 24, 2003
Necropsy	February 24, 2003	March 03, 2003
Male Necropsy	April 15, 2003	April 17, 2003
Sperm Data	July 24-25, 28-29, 2003	October 21, 2003
Individual, Summary Tables and Data	October 23-24, 2003	October 24, 2003
Individual, Summary Tables and Data	October 23-24, 27, 2003	October 29, 2003
Hormone Data	July 29-31; August 04, 08, 17; October 21, 22, 29, 2003	October 30, 2003
Report Results/Discussion	November 22-23, 25-27, 2005	November 28, 2005
Report Abstract, MM	November 22-23, 25-27; December 01, 2005	December 01, 2005

Carrie Ingalls
Quality Assurance Assistant Manager

12/05/2005
Date

Reviewed by:

Debra A. Drissel
Debra Drissel
Quality Assurance Manager

12/05/2005
Date

US EPA ARCHIVE DOCUMENT

APPENDIX I

INDIVIDUAL TABLES

Table of Contents

Page

Table A-1 Individual F0 Female Fate A-1
Table A-2 Individual F0 Female Body Weights (g) During Gestation A-3
Table A-3 Individual F0 Female Feed Consumption (g/day) During Gestation A-5
Table A-4 Individual F0 Female Clinical Observations During Gestation A-7
Table A-5 Individual F0 Female Body Weights (g) During Lactation A-11
Table A-6 Individual F0 Female Feed Consumption (g/day) During Lactation A-13
Table A-7 Individual F0 Female Clinical Observations During Lactation A-15
Table A-8 Individual F0 Reproductive and Lactational Indexes A-24
Table A-9 Individual F1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0 ....A-28
Table A-10 Individual F1 Pup Weight Data During Lactation (g) A-42
Table A-11 Individual F1 Male Nipple Data During Lactation A-58
Table A-12 Individual F1 Pup Clinical Observations for Postnatal Days 0 Through 21 ....A-62
Table A-13 Individual F1 Pup Gross Necropsy Findings for Postnatal Days 0 Through 21 ....A-65
Table A-14 Individual F0 Female Hormone Data at Necropsy A-67
Table A-15 Individual F0 Female Gross Necropsy Findings A-69
Table A-16 Individual F1 Uterotrophic Female Fate A-70
Table A-17 Individual F1 Uterotrophic Female Body Weights (g) During the Post Wean Holding Period A-71
Table A-18 Individual F1 Uterotrophic Female Clinical Observations During the Post Wean Holding Period A-72
Table A-19 Individual F1 Uterotrophic Female Necropsy Weights (g) and Hormone Data A-73
Table A-20 Individual F1 Uterotrophic Female Gross Necropsy Findings A-74
Table A-21 Individual F1 Undosed Pubertal Female Fate A-75

US EPA ARCHIVE DOCUMENT

Table of Contents (continued)

Page

Table A-22 Individual F1 Undosed Pubertal Female Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 30 of the Post Wean Holding Period....A-78

Table A-23 Individual F1 Undosed Pubertal Female Body Weights (g) on Postnatal Days 32 through 42 of the Post Wean Holding Period....A-80

Table A-24 Individual F1 Undosed Pubertal Female Clinical Observations During the Post Wean Holding Period....A-82

Table A-25 Individual F1 Undosed Pubertal Female Vaginal Opening Data....A-84

Table A-26 Individual F1 Undosed Pubertal Female Vaginal Cytology – Evaluation of Vaginal Smears....A-86

Table A-27 Individual F1 Undosed Pubertal Femal Vaginal Cytology – Evaluation of Estrous Cyclicity....A-90

Table A-28 Individual F1 Undosed Pubertal Female Necropsy and Hormone Data....A-94

Table A-29 Individual F1 Undosed Pubertal Female Gross Necropsy Findings....A-98

Table A-30 Individual F1 Dosed Pubertal Female Fate....A-99

Table A-31 Individual F1 Dosed Pubertal Female Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 30 of the Post Wean Holding Period....A-102

Table A-32 Individual F1 Dosed Pubertal Female Body Weights (g) on Postnatal Days 32 through 42 of the Post Wean Holding Period....A-104

Table A-33 Individual F1 Dosed Pubertal Female Clinical Observations During The Post Wean Holding Period....A-106

Table A-34 Individual F1 Dosed Pubertal Female Vaginal Opening Data....A-110

Table A-35 Individual F1 Dosed Pubertal Female Vaginal Cytology – Evaluation of Vaginal Smears....A-112

Table A-36 Individual F1 Dosed Pubertal Female Vaginal Cytotology – Evaluation of Estrous Cyclicity....A-116

Table A-37 Individual F1 Dosed Pubertal Female Necropsy and Hormone Data....A-120

US EPA ARCHIVE DOCUMENT

Table of Contents (continued)

Page

Table A-38 Individual F1 Dosed Pubertal Female Gross Necropsy Findings A-124

Table A-39 Individual F1 Undosed Pubertal Male Fate A-125

Table A-40 Individual F1 Undosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 thorugh 36 of the Post Wean Holding Period .....A- 128

Table A-41 Individual F1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period A-132

Table A-42 Individual F1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period A-136

Table A-43 Individual F1 Undosed Pubertal Male Clinical Observations During the Post Wean Holding Period A-140

Table A-44 Individual F1 Undosed Pubertal Male Preputial Separation Data A-142

Table A-45 Individual F1 Undosed Pubertal Male Reproductive Organ Weights and Measurements A-144

Table A-46 Individual F1 Undosed Pubertal Male Necropsy Weights and Hormone Data A-148

Table A-47 Individual F1 Undosed Pubertal Male Sperm Data A-152

Table A-48 Individual F1 Undosed Pubertal Male Gross Necropsy Findings A-154

Table A-49 Individual F1 Dosed Pubertal Male Fate A-155

Table A-50 Individual F1 Dosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period A-158

Table A-51 Individual F1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period A-162

Table A-52 Individual F1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period A-166

Table A-53 Individual F1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period A-170

US EPA ARCHIVE DOCUMENT

Table of Contents (continued)

Page

Table A-54 Individual F1 Dosed Pubertal Male Preputial Separation Data A-181

Table A-55 Individual F1 Dosed Pubertal Male Reproductive Organ Weights and Measurements A-183

Table A-56 Individual F1 Dosed Pubertal Male Necropsy Weights and Hormone Data A-187

Table A-57 Individual F1 Dosed Pubertal Male Sperm Data A-191

Table A-58 Individual F1 Dosed Pubertal Male Gross Necropsy Findings A-193

US EPA ARCHIVE DOCUMENT

Table A-1. Individual F_0 Female Fate (page 1 of 2)

Dose[a]	Female ID	Fate
0	1	Scheduled Sacrifice on Postnatal Day 21
	8	Scheduled Sacrifice on Postnatal Day 21
	9	Scheduled Sacrifice on Postnatal Day 21
	16	Scheduled Sacrifice on Postnatal Day 21
	23[b]	Scheduled Sacrifice on Gestational Day 26
	24[c]	Removed from Study
	31	Scheduled Sacrifice on Postnatal Day 21
	32	Scheduled Sacrifice on Postnatal Day 21
	39[d]	Removed from Study
	40	Scheduled Sacrifice on Postnatal Day 21
	42	Scheduled Sacrifice on Postnatal Day 21
	49	Scheduled Sacrifice on Postnatal Day 21
	50	Scheduled Sacrifice on Postnatal Day 21
	57	Scheduled Sacrifice on Postnatal Day 21
	58	Scheduled Sacrifice on Postnatal Day 21
25	2	Scheduled Sacrifice on Postnatal Day 21
	7	Scheduled Sacrifice on Postnatal Day 21
	10	Scheduled Sacrifice on Postnatal Day 21
	15[d]	Removed from Study
	17	Scheduled Sacrifice on Postnatal Day 21
	22[d]	Removed from Study
	25	Scheduled Sacrifice on Postnatal Day 21
	30	Scheduled Sacrifice on Postnatal Day 21
	33[b]	Scheduled Sacrifice on Gestational Day 26
	38	Scheduled Sacrifice on Postnatal Day 21
	41[e]	Removed from Study
	43[f]	Removed from Study after Gestation
	48	Scheduled Sacrifice on Postnatal Day 21
	51	Scheduled Sacrifice on Postnatal Day 21
	56[g]	Removed from Study
50	4	Scheduled Sacrifice on Postnatal Day 21
	5	Scheduled Sacrifice on Postnatal Day 21
	12	Scheduled Sacrifice on Postnatal Day 21
	13	Scheduled Sacrifice on Postnatal Day 21
	19	Scheduled Sacrifice on Postnatal Day 21
	20	Scheduled Sacrifice on Postnatal Day 21
	27	Scheduled Sacrifice on Postnatal Day 21
	28	Scheduled Sacrifice on Postnatal Day 21
	35	Scheduled Sacrifice on Postnatal Day 21
	36	Scheduled Sacrifice on Postnatal Day 21

(continued)

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Table A-1. Individual F_0 Female Fate (page 2 of 2)

Dose[a]	Female ID	Fate
50	45	Euthanized Moribund on Postnatal Day 3
	46	Scheduled Sacrifice on Postnatal Day 21
	53	Euthanized Moribund on Postnatal Day 2
	54	Scheduled Sacrifice on Postnatal Day 21
	60	Scheduled Sacrifice on Postnatal Day 21
100	3	Scheduled Sacrifice on Postnatal Day 21
	6[b]	Scheduled Sacrifice on Gestational Day 26
	11	Scheduled Sacrifice on Postnatal Day 21
	14[h]	Found dead on Gestational Day 23
	18	Scheduled Sacrifice on Postnatal Day 21
	21	Scheduled Sacrifice on Postnatal Day 21
	26	Scheduled Sacrifice on Postnatal Day 21
	29	Euthanized Moribund on Postnatal Day 1
	34[f]	Removed from Study after Gestation
	37	Scheduled Sacrifice on Postnatal Day 21
	44	Scheduled Sacrifice on Postnatal Day 21
	47[b]	Scheduled Sacrifice on Gestational Day 26
	52[d]	Removed from Study
	55	Scheduled Sacrifice on Postnatal Day 21
	59	Scheduled Sacrifice on Postnatal Day 21

[a]Mg/kg/day of Methoxychlor.
[b]Animal was not pregnant.
[c]Animal was found dead on gestational day 19 (misdirected dose).
[d]Animal was removed from the study due to a misdirected dose confirmed at necropsy.
[e]Animal was euthanized moribund on gestational day 17 (misdirected dose).
[f]Animal was removed from the study after gestation because the correct postnatal day 0 could not be confirmed.
[g]Animal was euthanized moribund on gestational day 18 (misdirected dose).
[h]Animal was found dead on gestational day 23 while in the process of delivering.

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Table A-2. Individual F_0 Female Body Weights (g) During Gestation (page 1 of 2)

Dose[a]	Female ID	Gestational Day 0	6	9	12	15	18	20
0	1	227.1	273.1	284.9	308.7	319.5	356.0	387.3
	8	239.5	274.8	283.5	307.8	324.5	360.7	394.5
	9	248.0	286.2	285.4	303.4	319.5	351.5	381.3
	16	222.9	262.1	256.9	274.1	288.1	322.1	346.6
	31	239.4	276.5	282.9	310.3	332.0	369.9	399.0
	32	247.1	289.9	305.1	332.1	346.2	380.7	413.1
	40	255.6	280.0	271.3	296.4	307.0	347.2	378.9
	42	224.8	260.0	269.7	286.4	288.1	322.1	291.2
	49	241.8	278.3	293.6	310.0	329.8	369.5	403.3
	50	243.3	281.9	295.6	310.0	328.1	373.1	402.8
	57	250.8	301.1	281.9	314.2	335.6	391.5	431.2
	58	254.2	299.0	315.5	336.3	351.2	395.7	420.9
25	2	226.0	256.2	251.4	266.0	283.2	319.6	348.7
	7	238.8	274.7	266.9	273.4	299.4	332.3	358.7
	10	241.3	285.2	266.0	277.3	272.0	315.7	338.9
	17	229.4	265.9	261.3	282.0	293.0	335.0	366.6
	25	239.8	271.2	269.4	277.7	289.4	334.1	362.2
	30	241.6	265.0	262.8	271.6	294.6	335.0	368.7
	38	254.3	287.6	281.7	290.8	310.6	338.3	364.9
	43	240.2	289.9	298.6	303.0	322.9	361.6	383.0
	48	244.1	277.0	271.9	286.8	299.0	339.4	355.5
	51	246.5	290.8	288.6	300.7	312.8	354.3	378.1
50	4	216.3	276.9	274.1	294.2	315.1	342.7	370.2
	5	236.6	287.3	276.5	285.1	301.1	319.3	344.7
	12	240.4	267.4	258.8	277.8	290.0	332.0	368.3
	13	257.4	291.8	277.5	280.6	317.4	356.4	389.7
	19	226.5	264.2	273.7	288.4	302.4	338.4	365.1
	20	237.5	273.8	280.3	288.2	294.3	316.5	333.4
	27	238.2	266.8	275.2	281.5	296.8	334.0	358.0
	28	245.7	276.9	274.6	299.4	305.7	320.7	336.1
	35	248.2	280.4	267.3	268.7	267.5	322.9	344.5
	36	255.2	294.2	279.8	282.0	270.4	322.7	343.7
	45	235.1	272.8	247.5	264.1	263.9	317.3	323.0
	46	242.9	291.8	292.9	295.0	300.3	334.3	365.3
	53	243.1	284.8	272.6	286.7	300.3	342.9	367.6
	54	247.7	277.1	266.1	265.0	261.3	282.0	295.0
	60	254.5	300.8	306.4	330.6	340.1	383.2	424.2

(continued)

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Table A-2. Individual F_0 Female Body Weights (g) During Gestation (page 2 of 2)

Dose[a]	Female ID	Gestational Day 0	6	9	12	15	18	20
100	3	224.4	267.2	248.9	253.4	255.2	288.5	307.2
	11	246.9	284.7	272.8	292.9	293.1	318.0	353.8
	14	248.3	273.2	269.1	273.9	291.2	324.3	353.8
	18	229.5	257.0	248.8	261.6	272.3	310.5	328.7
	21	237.1	272.2	274.8	275.6	286.2	324.7	341.6
	26	238.9	269.1	251.0	264.2	266.7	309.1	334.1
	29	247.7	272.2	265.8	271.1	283.8	307.4	332.7
	34	251.0	281.3	278.4	277.5	271.7	291.0	304.0
	37	254.9	284.1	275.4	279.5	281.6	316.9	339.4
	44	223.8	245.5	244.7	241.5	241.4	282.8	285.9
	55	249.1	276.0	270.4	280.9	285.1	323.8	340.4
	59	251.5	282.4	274.5	288.1	286.4	319.2	346.9

[a]Mg/kg/day of Methoxychlor.

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Table A-3. Individual F_0 Female Feed Consumption (g/day) During Gestation (page 1 of 2)

Dose[a]	Female ID	Gestational Days 0-6	6-9	9-12	12-15	15-18	18-20	6-20	0-20
0	1	22.3	20.1	22.9	22.2	23.5	21.3	22.0	22.1
	8	21.5	21.2	21.4	21.1	24.2	23.9	22.3	22.0
	9	23.1	18.7	20.3	21.0	22.1	18.7	20.3	21.1
	16	17.9	15.0	12.9	19.7	18.1	18.6	16.8	17.1
	31	21.5	20.3	22.0	23.3	24.6	22.1	22.5	22.2
	32	23.8	24.3	26.0	25.1	23.3	24.1	24.6	24.4
	40	20.2	14.8	16.7	18.6	19.2	20.4	17.8	18.5
	42	21.3	18.5	22.3	17.1	25.1	1.1	18.0	19.0
	49	24.9	.[b]	.[b]	25.0	27.8	26.9	.[c]	.[c]
	50	22.6	.[b]	1.3	25.1	27.6	25.3	.[c]	.[c]
	57	25.0	13.8	18.5	22.4	28.0	27.5	21.7	22.7
	58	26.1	24.5	24.5	25.8	24.2	21.8	24.3	24.9
25	2	18.0	12.3	14.6	18.6	21.3	19.0	17.0	17.3
	7	21.2	13.8	10.6	20.7	19.2	21.2	16.8	18.1
	10	24.5	11.2	12.5	12.8	18.2	.[d]	.[c]	.[c]
	17	20.5	17.3	18.9	21.3	23.7	21.3	20.5	20.5
	25	22.1	15.3	13.6	21.2	24.5	26.2	19.7	20.4
	30	20.6	13.1	11.8	18.8	19.0	19.0	16.1	17.5
	38	23.2	14.2	13.2	20.6	16.9	18.5	16.5	18.5
	43	15.6	21.2	19.9	22.8	23.8	18.4	21.4	19.7
	48	23.8	16.2	18.5	24.7	14.4	14.0	17.8	19.6
	51	26.2	17.8	16.6	20.3	24.2	18.8	19.6	21.6
50	4	23.5	17.0	18.3	19.9	20.7	17.6	18.8	20.2
	5	24.8	15.7	16.2	19.8	17.3	17.0	17.2	19.5
	12	19.7	12.6	15.6	17.5	23.7	23.8	18.3	18.7
	13	22.0	14.8	13.4	22.3	29.6	24.8	20.7	21.1
	19	20.3	17.4	17.2	19.9	18.6	21.2	18.7	19.2
	20	24.5	19.9	19.2	17.3	14.3	15.3	17.3	19.5
	27	21.8	18.5	13.8	19.4	20.3	19.3	18.2	19.2
	28	22.3	15.5	16.4	17.3	14.1	12.2	15.3	17.4
	35	22.2	12.0	13.5	3.3	17.1	19.8	12.7	15.5
	36	22.8	12.8	15.9	3.0	21.7	23.9	14.8	17.2
	45	22.7	7.1	14.2	9.7	20.7	13.6	13.0	15.9
	46	24.7	17.4	13.6	15.2	16.1	20.8	16.3	18.8
	53	24.0	12.0	13.6	21.9	19.4	19.6	17.2	19.2
	54	21.2	10.6	10.6	11.8	14.6	24.1	13.6	15.9
	60	25.4	23.3	22.6	19.0	25.0	25.2	22.9	23.6

(continued)

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Table A-3. Individual F_0 Female Feed Consumption (g/day) During Gestation (page 2 of 2)

Dose[a]	Female ID	Gestational Days 0-6	6-9	9-12	12-15	15-18	18-20	6-20	0-20
100	3	.[e]	.[d]	13.3	13.1	16.6	13.0	.[c]	.[c]
	11	21.5	11.1	15.1	14.6	14.8	17.5	14.4	16.6
	14	20.4	11.8	11.6	16.5	18.4	17.0	14.9	16.6
	18	20.5	12.2	14.4	13.0	14.5	15.1	13.7	15.8
	21	22.2	17.7	14.5	14.8	16.5	17.2	16.1	17.9
	26	19.5	7.1	12.0	11.9	16.3	17.0	12.6	14.7
	29	19.9	11.6	11.4	15.5	12.3	13.1	12.8	14.9
	34	23.4	15.5	9.7	8.0	11.8	12.1	11.4	15.0
	37	24.0	11.0	11.4	12.0	15.8	18.8	13.5	16.6
	44	19.3	12.9	10.8	7.2	15.6	11.7	11.7	14.0
	55	21.8	12.1	14.2	13.9	17.4	20.3	15.2	17.2
	59	24.5	12.3	13.7	16.0	12.4	19.5	14.4	17.5

[a]Mg/kg/day of Methoxychlor.
[b]Feed consumption value was unrealistic (i.e. negative) and therefore it was excluded.
[c]Interim feed consumption value(s) missing and therefore the overall feed consumption value could not be calculated.
[d]Feed consumption value was a statistical outlier and therefore it was excluded.
[e]Female pulled feed into the cage and therefore an accurate feed weight could not be obtained.

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Table A-4. Individual F_0 Female Clinical Observations During Gestation (page 1 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
0	1	16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
			Efflux of the dosing solution
		21	Alopecia: limb(s)
	8	21	Animal received 97.6% of the required dose volume
	16	7	Weight loss[c]: 8.69 g.
		9	Weight loss: 7.56 g.
	32	6	Animal received 96.6% of the required dose volume
		7	Animal received 96.6% of the required dose volume
	40	8	Weight loss: 15.11 g.
		12	Respiration: audible
		13	Respiration: audible
		14	Respiration: audible
		15	Respiration: audible
		16	Respiration: audible
		17	Respiration: audible
		18	Respiration: audible
		19	Respiration: audible
		20	Respiration: audible
		21	Respiration: audible
	42	10	Weight loss: 23.23 g.
		13	Weight loss: 11.25 g.
		19	Weight loss: 29.70 g.
		20	Piloerection
	50	10	Weight loss: 16.38 g.
	57	8	Weight loss: 22.13 g.
	58	13	Efflux of the dosing solution
		14	Animal received 97.1% of the required dose volume
25	2	7	Weight loss: 13.05 g.
		17	Efflux of the dosing solution
	7	7	Weight loss: 8.24 g.
		10	Weight loss: 6.19 g.
		17	Efflux of the dosing solution
	10	7	Weight loss: 13.89 g.
		14	Weight loss: 6.17 g.
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
			Efflux of the dosing solution
		21	Alopecia: limb(s)

(continued)

US EPA ARCHIVE DOCUMENT

Table A-4. Individual F_0 Female Clinical Observations During Gestation (page 2 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
25	17	16	Efflux of the dosing solution
		20	Animal received 97.3% of the required dose volume
	25	7	Weight loss: 7.92 g.
	38	7	Weight loss: 9.19 g.
		16	Weight loss: 5.24 g.
	43	8	Efflux of the dosing solution
		13	Efflux of the dosing solution
	48	7	Weight loss: 8.35 g.
	51	15	Efflux of the dosing solution
		18	Efflux of the dosing solution
50	4	7	Weight loss: 6.67 g.
	5	7	Animal received 103.7% of the required dose volume
			Weight loss: 12.38 g.
		10	Weight loss: 6.31 g.
		18	Alopecia: abdomen
		19	Alopecia: abdomen
		20	Alopecia: abdomen
		21	Alopecia: abdomen
			Piloerection
		22	Alopecia: abdomen
	12	7	Weight loss: 8.03 g.
		13	Efflux of the dosing solution
		14	Weight loss: 5.06 g.
	13	7	Weight loss: 14.16 g.
	20	10	Weight loss: 5.87 g.
	28	7	Weight loss: 5.74 g.
		13	Weight loss: 7.94 g.
		16	Weight loss: 5.36 g.
	35	7	Weight loss: 10.66 g.
		9	Weight loss: 8.57 g.
		12	Rooting: post dosing
		14	Weight loss: 11.97 g.
		15	Piloerection
		16	Piloerection
	36	7	Weight loss: 7.21 g.
		12	Weight loss: 6.92 g.
		14	Piloerection
			Weight loss: 8.50 g.
		15	Piloerection
		16	Piloerection
		17	Piloerection
		19	Piloerection

(continued)

US EPA ARCHIVE DOCUMENT

Table A-4. Individual F_0 Female Clinical Observations During Gestation (page 3 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	45	7	Weight loss: 19.38 g.
		8	Weight loss: 8.94 g.
		13	Piloerection
			Weight loss: 9.75 g.
		14	Piloerection
		18	Piloerection
		19	Piloerection
			Weight loss: 6.75 g.
		21	Piloerection
			Weight loss: 7.56 g.
		22	Piloerection
	46	7	Weight loss: 9.29 g.
		12	Animal received 96.7% of the required dose volume
	53	9	Weight loss: 6.05 g.
		22	Piloerection
			Weight loss: 7.66 g.
	54	7	Weight loss: 7.98 g.
		19	Piloerection
	60	9	Weight loss: 8.63 g.
		13	Weight loss: 12.68 g.
		19	Piloerection
100	3	7	Weight loss: 12.88 g.
		22	Piloerection
	11	7	Weight loss: 10.58 g.
	14	7	Weight loss: 7.17 g.
		13	Efflux of the dosing solution
		23	Found dead
	18	12	Rooting: post dosing
		15	Rooting: post dosing
		17	Rooting: post dosing
	21	12	Efflux of the dosing solution
			Weight loss: 9.57 g.
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		21	Efflux of the dosing solution
	26	7	Weight loss: 21.03 g.
	29	7	Weight loss: 6.89 g.
		12	Rooting: post dosing
		14	Weight loss: 5.37 g.
	34	13	Weight loss: 6.43 g.
		15	Rooting: post dosing

(continued)

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Table A-4. Individual F_0 Female Clinical Observations During Gestation (page 4 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
100	44	11	Efflux of the dosing solution
		12	Weight loss: 7.56 g.
	55	7	Weight loss: 5.37 g.
		13	Weight loss: 6.84 g.
		19	Animal received 97.0% of the required dose volume Efflux of the dosing solution
		22	Weight loss: 7.22 g.
	59	7	Weight loss: 6.39 g.
		15	Weight loss: 5.37 g.

[a]Mg/kg/day of Methoxychlor.
[b]Gestational day.
[c]Clinical weight loss is weight loss $\geq$ 5 gram in any one weigh period.

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Table A-5. Individual F_0 Female Body Weights (g) During Lactation (page 1 of 2)

Dose[a]	Female ID	Postnatal Day 0	4	7	14	21
0	1	306.2	314.3	321.0	339.7	335.4
	8	298.3	313.7	316.5	339.9	317.1
	9	280.1	314.6	318.0	342.1	325.0
	16	265.0	292.4	295.8	299.9	292.5
	31	300.2	337.2	331.5	345.5	306.4
	32	320.7	348.4	356.7	358.6	346.6
	40	277.9	306.2	319.6	337.6	317.2
	42	254.1	268.5	281.1	285.4	278.6
	49	311.6	336.2	339.9	351.3	333.0
	50	324.8	338.5	351.3	354.5	351.3
	57	324.8	343.8	341.2	379.7	346.4
	58	339.3	350.7	355.6	370.1	355.4
25	2	260.3	283.0	280.9	301.1	268.7
	7	261.9	302.8	317.8	329.4	326.8
	10	266.6	280.8	289.4	321.5	312.6
	17	266.4	298.8	295.1	318.5	310.6
	25	292.8	301.1	307.3	328.9	328.2
	30	265.9	294.3	289.6	326.8	322.4
	38	246.1	280.1	304.8	322.5	310.5
	48	267.2	293.5	306.0	317.3	300.9
	51	256.1	289.9	304.9	317.6	314.8
50	4	277.4	295.3	309.7	321.1	317.7
	5	253.4	285.3	275.1	325.7	315.3
	12	273.1	288.3	305.0	341.8	330.1
	13	310.9	310.7	324.1	344.9	326.7
	19	286.2	300.2	307.2	343.5	309.8
	20	248.5	286.2	293.3	313.4	309.7
	27	261.4	286.3	292.1	316.8	289.9
	28	.[b]	268.7	295.3	319.0	323.0
	35	251.8	261.0	284.7	302.2	300.4
	36	283.1	295.4	313.4	331.7	323.1
	45	211.3	.[c]			
	46	272.1	280.7	282.6	328.9	315.4
	53	237.6	.[d]			
	54	258.1	254.9	255.1	267.8	294.8
	60	335.8	335.3	350.4	375.1	357.4

(continued)

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Table A-5. Individual F_0 Female Body Weights (g) During Lactation (page 2 of 2)

Dose[a]	Female ID	Postnatal Day 0	4	7	14	21
100	3	208.2	265.0	268.1	286.0	295.7
	11	265.3	292.2	294.0	326.0	313.4
	18	224.8	268.5	275.7	304.7	292.6
	21	282.7	272.6	309.4	337.5	326.5
	26	238.4	246.3	257.3	295.6	288.4
	29	238.8	.[e]			
	37	248.4	268.5	277.3	312.9	297.3
	44	219.7	254.1	268.1	302.5	288.5
	55	242.9	284.3	294.3	322.3	.[b]
	59	247.1	279.9	289.3	307.5	301.5

[a]Mg/kg/day of Methoxychlor.
[b]Body weight inadvertently not recorded.
[c]Female was euthanized moribund on postnatal day 3.
[d]Female was euthanized moribund on postnatal day 2.
[e]Female was euthanized moribund on postnatal day 1.

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Table A-6. Individual F_0 Female Feed Consumption (g/day) During Lactation (page 1 of 2)

Dose[a]	Female ID	Postnatal Days 0-4	4-7	7-14	14-21	0-21
0	1	.[b]	45.0	60.7	76.2	.[c]
	8	30.6	45.5	58.8	70.6	55.4
	9	35.9	47.8	61.8	71.4	58.1
	16	28.3	39.4	50.2	63.9	49.0
	31	39.0	51.1	63.6	73.0	60.3
	32	39.7	53.8	69.0	84.8	66.5
	40	33.0	46.5	61.0	74.4	58.1
	42	22.0	32.7	40.6	48.2	38.5
	49	37.1	53.0	68.0	74.1	62.0
	50	32.4	52.3	64.2	75.2	60.1
	57	36.2	52.5	64.7	75.7	61.2
	58	25.8	42.3	58.0	67.8	52.9
25	2	28.9	36.6	48.0	57.3	45.8
	7	44.9	51.5	67.1	85.7	66.9
	10	27.4	36.5	53.4	70.6	51.8
	17	36.9	47.5	64.2	76.8	60.8
	25	27.7	38.2	47.3	65.9	48.5
	30	34.7	41.4	56.3	69.8	54.6
	38	34.1	50.1	57.9	78.3	59.0
	48	31.2	44.8	55.6	66.9	53.2
	51	22.9	42.9	51.9	68.9	50.7
50	4	28.9	36.7	53.3	70.3	52.0
	5	32.8	34.1	51.4	73.8	52.8
	12	27.0	37.2	58.7	70.4	53.5
	13	28.7	43.8	59.8	74.6	56.5
	19	34.1	45.8	60.9	68.2	56.1
	20	31.5	52.9	59.5	78.5	59.6
	27	32.6	44.6	56.1	70.8	54.9
	28	24.6	42.2	55.7	70.2	52.7
	35	23.4	48.7	51.6	79.1	55.0
	36	21.7	46.5	57.2	81.4	57.0
	45	.[d]				
	46	29.6	36.1	52.6	70.9	52.0
	53	.[e]				
	54	44.9	17.2	23.4	29.2	28.6
	60	30.1	49.3	57.8	75.7	57.3

(continued)

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Table A-6. Individual F_0 Female Feed Consumption (g/day) During Lactation (page 2 of 2)

Dose[a]	Female ID	Postnatal Days 0-4	4-7	7-14	14-21	0-21
100	3	.[b]	73.9	51.5	70.1	.[c]
	11	.[b]	39.4	54.2	68.3	.[c]
	18	37.0	50.4	56.2	72.1	57.0
	21	25.9	49.7	61.9	72.2	56.7
	26	18.7	31.5	48.5	62.4	45.0
	29	.[f]				
	37	18.4	33.3	48.5	65.9	46.4
	44	42.7	40.3	56.5	68.7	55.6
	55	39.2	48.4	62.9	.[g]	.[c]
	59	26.0	39.9	50.5	66.9	49.8

[a]Mg/kg/day of Methoxychlor.
[b]Female pulled feed into the cage and therefore an accurate feed weight could not be obtained.
[c]Interim feed consumption value(s) missing and therefore the overall feed consumption value could not be calculated.
[d]Female was euthanized moribund on postnatal day 3.
[e]Female was euthanized moribund on postnatal day 2.
[f]Female was euthanized moribund on postnatal day 1.
[g]Feed weight inadvertently not recorded.

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Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 1 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
0	1	3	Alopecia: limb(s)
		4	Alopecia: limb(s)
		5	Alopecia: limb(s)
		6	Alopecia: limb(s)
		7	Alopecia: limb(s)
		8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: multiple areas
		13	Alopecia: multiple areas
		14	Alopecia: multiple areas
		15	Alopecia: multiple areas
		16	Alopecia: multiple areas
		17	Alopecia: multiple areas
		18	Alopecia: multiple areas
		19	Alopecia: multiple areas
		20	Alopecia: multiple areas
		21	Alopecia: multiple areas
	9	15	Feces: soft
	16	21	Feces: soft
	40	0	Respiration: audible
		3	Respiration: audible
		4	Respiration: audible
		5	Respiration: audible
		6	Respiration: audible
		7	Respiration: audible
		8	Respiration: audible
		9	Respiration: audible
		10	Respiration: audible
		11	Respiration: audible
		12	Respiration: audible
		13	Respiration: audible
		14	Respiration: audible
		15	Respiration: audible
		16	Respiration: audible
		17	Respiration: audible
		18	Respiration: audible
		19	Respiration: audible
		20	Respiration: audible
		21	Respiration: audible

(continued)

US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 2 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
0	42	4	Efflux of the dosing solution
			Rooting: post dosing
		5	Mass: under right front leg, ~2 X 2 cm
		6	Mass: under right front leg
		7	Mass: under right front leg
		8	Mass: under right front leg
		9	Mass: under right front leg
		10	Mass: under right front leg
		11	Mass: under right front leg
		12	Mass: under right front leg
		13	Mass: under right front leg
		14	Mass: under right front leg
		15	Mass: under right front leg
		16	Mass: under right front leg
		17	Mass: under right front leg
		18	Mass: under right front leg
		19	Mass: under right front leg
		20	Mass: under right front leg
		21	Mass: under right front leg
	49	4	Piloerection
		7	Alopecia: limb(s)
		8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)
		15	Alopecia: limb(s)
		16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	57	6	Efflux of the dosing solution
25	2	3	Alopecia: limb(s)
		4	Alopecia: limb(s)
			Efflux of the dosing solution
			Rooting: post dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 3 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
25	2	5	Alopecia: limb(s)
		6	Alopecia: limb(s)
		7	Alopecia: limb(s)
		8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)
		15	Alopecia: limb(s)
		16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	7	11	Chromodacryorrhea: eye, left
		12	Chromodacryorrhea: eye, left
		13	Chromodacryorrhea: eye, left
		14	Chromodacryorrhea: eye, left
		15	Chromodacryorrhea: eye, left
		16	Chromodacryorrhea: eye, left
		17	Chromodacryorrhea: eye, left
		18	Chromodacryorrhea: eye, left
		19	Chromodacryorrhea: eye, left
		20	Chromodacryorrhea: eye, left
		21	Chromodacryorrhea: eye, left
	10	0	Alopecia: limb(s)
		1	Alopecia: limb(s)
		2	Alopecia: limb(s)
		3	Alopecia: limb(s)
		4	Alopecia: limb(s)
		5	Alopecia: limb(s)
		6	Alopecia: limb(s)
		7	Alopecia: limb(s)
		8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)
		15	Alopecia: limb(s)

(continued)

US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 4 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
25	10	16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	25	8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)
		15	Alopecia: limb(s)
		16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	30	11	Sore(s): head
		12	Sore(s): head
		13	Sore(s): head, healed
	38	10	Alopecia: abdomen
		11	Alopecia: abdomen
		12	Alopecia: abdomen
		13	Alopecia: abdomen
		14	Alopecia: abdomen
		15	Alopecia: abdomen
		16	Alopecia: abdomen
		17	Alopecia: abdomen
		18	Alopecia: abdomen
		19	Alopecia: abdomen
		20	Alopecia: abdomen
		21	Alopecia: abdomen
50	5	1	Alopecia: abdomen
		2	Alopecia: abdomen
		3	Alopecia: abdomen
		4	Alopecia: abdomen
		5	Alopecia: abdomen
		6	Alopecia: abdomen
		7	Alopecia: abdomen
		8	Alopecia: abdomen

(continued)

US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 5 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	5	9	Alopecia: abdomen
		10	Alopecia: abdomen
		11	Alopecia: abdomen
		12	Alopecia: abdomen
		13	Alopecia: abdomen
			Rooting: post dosing
		14	Alopecia: abdomen
		15	Alopecia: abdomen
		16	Alopecia: abdomen
		17	Alopecia: abdomen
		18	Alopecia: abdomen
		19	Alopecia: abdomen
		20	Alopecia: abdomen
		21	Alopecia: abdomen
	12	19	Efflux of the dosing solution
	13	7	Alopecia: chest
		8	Alopecia: chest
		9	Alopecia: chest
		10	Alopecia: chest
		11	Alopecia: chest
		12	Alopecia: chest
		13	Alopecia: chest
		14	Alopecia: multiple areas
			Salivation: prior to dosing
		15	Alopecia: multiple areas
			Salivation: prior to dosing
		16	Alopecia: multiple areas
			Salivation: prior to dosing
		17	Alopecia: multiple areas
		18	Alopecia: multiple areas
		19	Alopecia: multiple areas
			Salivation: prior to dosing
		20	Alopecia: multiple areas
			Salivation: prior to dosing
		21	Alopecia: multiple areas
	19	6	Alopecia: limb(s)
		7	Alopecia: limb(s)
		8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)

(continued)

US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 6 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	19	15	Alopecia: limb(s)
		16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	20	2	Alopecia: anogenital area
		3	Alopecia: anogenital area
		4	Alopecia: anogenital area
		5	Alopecia: anogenital area
		6	Alopecia: anogenital area
		7	Alopecia: anogenital area
		8	Alopecia: anogenital area
		9	Alopecia: anogenital area
		10	Alopecia: anogenital area
		11	Alopecia: anogenital area
		12	Alopecia: anogenital area
		13	Alopecia: anogenital area
		14	Alopecia: anogenital area
		15	Alopecia: anogenital area
		16	Alopecia: anogenital area
		17	Alopecia: anogenital area
		18	Alopecia: anogenital area
		19	Alopecia: anogenital area
		20	Alopecia: anogenital area
		21	Alopecia: anogenital area
	27	5	Efflux of the dosing solution
			Salivation: prior to dosing
		7	Salivation: prior to dosing
		16	Efflux of the dosing solution
	28	6	Alopecia: chest
		7	Alopecia: chest
		8	Alopecia: chest
		9	Alopecia: chest
		10	Alopecia: chest
		11	Alopecia: chest
		12	Alopecia: chest
		13	Alopecia: chest
		14	Alopecia: chest
		15	Alopecia: multiple areas
		16	Alopecia: multiple areas

(continued)

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Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 7 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	28	17	Alopecia: multiple areas
		18	Alopecia: multiple areas
		19	Alopecia: multiple areas
		20	Alopecia: multiple areas
		21	Alopecia: multiple areas
	35	15	Feces: soft
	36	7	Piloerection
	45	0	Piloerection
		1	Rough coat
		2	Rough coat
		3	Euthanized moribund
			Not nursing pups
			Rough coat
	46	1	Alopecia: abdomen
		2	Alopecia: multiple areas
		3	Alopecia: multiple areas
		4	Alopecia: multiple areas
		5	Alopecia: multiple areas
		6	Alopecia: multiple areas
		7	Alopecia: multiple areas
		8	Alopecia: multiple areas
		9	Alopecia: multiple areas
		10	Alopecia: multiple areas
			Piloerection
		11	Alopecia: multiple areas
		12	Alopecia: multiple areas
		13	Alopecia: multiple areas
		14	Alopecia: multiple areas
		15	Alopecia: multiple areas
		16	Alopecia: multiple areas
		17	Alopecia: multiple areas
		18	Alopecia: multiple areas
		19	Alopecia: multiple areas
		20	Alopecia: multiple areas
	53	2	Euthanized moribund
			Hunched
			Rough coat
	54	4	Piloerection
		5	Piloerection
		6	Piloerection
		8	Piloerection
		9	Piloerection

(continued)

US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 8 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	60	0	Piloerection
		3	Piloerection
		6	Rooting: post dosing
			Salivation: prior to dosing
		10	Piloerection
		14	Rooting: post dosing
100	3	16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	18	0	Piloerection
	21	6	Alopecia: limb(s)
		7	Alopecia: limb(s)
		8	Alopecia: limb(s)
		9	Alopecia: limb(s)
		10	Alopecia: limb(s)
		11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)
			Efflux of the dosing solution
			Struggled during dosing
		15	Alopecia: limb(s)
		16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
		21	Alopecia: limb(s)
	29	0	Piloerection
			Vaginal discharge, clear
		1	Euthanized moribund
			Piloerection
			Vaginal bleeding
	55	11	Alopecia: limb(s)
		12	Alopecia: limb(s)
		13	Alopecia: limb(s)
		14	Alopecia: limb(s)
		15	Alopecia: limb(s)
			Efflux of the dosing solution

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US EPA ARCHIVE DOCUMENT

Table A-7. Individual F_0 Female Clinical Observations During Lactation (page 9 of 9)

Dose[a]	Female ID	Day[b]	Clinical Observations
100	55	16	Alopecia: limb(s)
		17	Alopecia: limb(s)
		18	Alopecia: limb(s)
		19	Alopecia: limb(s)
		20	Alopecia: limb(s)
	59	0	Piloerection
		14	Feces: soft

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

US EPA ARCHIVE DOCUMENT

Table A-8. Individual F_0 Reproductive and Lactational Indexes (page 1 of 4)

Dose[a]	Female ID	Preg-nant	Live Litter	Male ID	Gesta-tional Length	No. Live Day 0	No. Dead Day 0	Total No. Day 0	No. Live Day 4	No. Live Day 7	No. Live Day 14	No. Live Day 21
0	1	Yes	Yes	Z692	22	16	0	16	15	9	9	9
	8	Yes	Yes	Z713	22	16	0	16	15	9	9	9
	9	Yes	Yes	Z754	22	15	0	15	15	9	9	9
	16	Yes	Yes	Z721	22	13	0	13	13	9	9	9
	23	No		Z728								
	31	Yes	Yes	Z740	22	14	0	14	14	9	9	9
	32	Yes	Yes	Z687	22	16	0	16	16	9	9	9
	40	Yes	Yes	Z716	22	16	1	17	16	9	9	9
	42	Yes	Yes	Z742	23	5	1	6	5	5	5	5
	49	Yes	Yes	Z699	22	14	1	15	14	9	9	9
	50	Yes	Yes	Z750	22	15	0	15	15	9	9	9
	57	Yes	Yes	Z691	22	17	1	18	17	9	9	9
	58	Yes	Yes	Z700	22	14	0	14	14	9	9	9

(continued)

US EPA ARCHIVE DOCUMENT

Table A-8. Individual F_0 Reproductive and Lactational Indexes (page 2 of 4)

Dose[a]	Female ID	Preg-nant	Live Litter	Male ID	Gesta-tional Length	No. Live Day 0	No. Dead Day 0	Total No. Day 0	No. Live Day 4	No. Live Day 7	No. Live Day 14	No. Live Day 21
25	2	Yes	Yes	Z738	22	14	0	14	14	8	7	7
	7	Yes	Yes	Z674	23	13	0	13	13	9	9	9
	10	Yes	Yes	Z724	22	8	0	8	8	8	8	8
	17	Yes	Yes	Z679	22	.[b]	.[b]	.[b]	14	8	8	8
	25	Yes	Yes	Z709	22	11	0	11	11	9	9	9
	30	Yes	Yes	Z714	22	17	0	17	17	9	9	9
	33	No		Z770								
	38	Yes	Yes	Z706	23	15	0	15	14	9	9	9
	43	Yes	Yes	Z736	.[c]							
	48	Yes	Yes	Z729	22	14	1	15	14	9	9	9
	51	Yes	Yes	Z744	22	17	1	18	17	9	9	9

(continued)

US EPA ARCHIVE DOCUMENT

Table A-8. Individual F_0 Reproductive and Lactational Indexes (page 3 of 4)

Dose[a]	Female ID	Preg-nant	Live Litter	Male ID	Gesta-tional Length	No. Live Day 0	No. Dead Day 0	Total No. Day 0	No. Live Day 4	No. Live Day 7	No. Live Day 14	No. Live Day 21
50	4	Yes	Yes	Z768	22	15	0	15	15	9	9	9
	5	Yes	Yes	Z669	22	14	0	14	13	8	8	8
	12	Yes	Yes	Z671	22	14	0	14	14	9	8	8
	13	Yes	Yes	Z684	22	10	1	11	10	7	7	7
	19	Yes	Yes	Z733	22	14	0	14	14	9	9	9
	20	Yes	Yes	Z708	22	12	2	14	12	9	9	9
	27	Yes	Yes	Z743	22	15	0	15	15	9	9	8
	28	Yes	Yes	Z756	21	15	0	15	15	9	9	9
	35	Yes	Yes	Z694	23	16	0	16	16	9	9	9
	36	Yes	Yes	Z727	22	9	0	9	9	9	9	9
	45	Yes	Yes	Z730	22	15	3	18	0	.[d]		
	46	Yes	Yes	Z677	22	14	0	14	14	8	8	8
	53	Yes	Yes	Z680	23	16	1	17	0	.[e]		
	54	Yes	Yes	Z723	23	2	0	2	2	2	2	2
	60	Yes	Yes	Z701	22	15	0	15	15	9	9	9

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US EPA ARCHIVE DOCUMENT

Table A-8. Individual F_0 Reproductive and Lactational Indexes (page 4 of 4)

Dose[a]	Female ID	Preg-nant	Live Litter	Male ID	Gesta-tional Length	No. Live Day 0	No. Dead Day 0	Total No. Day 0	No. Live Day 4	No. Live Day 7	No. Live Day 14	No. Live Day 21
100	3	Yes	Yes	Z746	23	12	0	12	12	9	9	9
	6	No		Z741								
	11	Yes	Yes	Z719	23	15	0	15	15	9	9	9
	14	Yes	.[f]	Z688								
	18	Yes	Yes	Z771	23	14	0	14	14	9	9	9
	21	Yes	Yes	Z672	22	8	0	8	8	7	7	7
	26	Yes	Yes	Z703	22	12	1	13	12	9	9	9
	29	Yes	Yes	Z762	23	8	4	12	0	.[g]		
	34	Yes	Yes	Z752	.[c]							
	37	Yes	Yes	Z710	22	11	0	11	11	9	9	9
	44	Yes	Yes	Z673	22	11	0	11	11	7	7	7
	47	No		Z693								
	55	Yes	Yes	Z711	23	13	0	13	13	9	9	9
	59	Yes	Yes	Z748	22	16	0	16	15	9	9	9

[a]Mg/kg/day of Methoxychlor.
[b]Number of live and dead pups inadvertently not recorded.
[c]Female was pregnant but the correct postnatal day 0 could not be determined and therefore this female was removed from the study after gestation and was included here only for the reproductive indexes.
[d]Female was euthanized moribund on postnatal day 3.
[e]Female was euthanized moribund on postnatal day 2.
[f]Female was found dead on gestational day 23 while in the process of delivering. She had one dead pup in the vagina and 15 dead pups in the uterus.
[g]Female was euthanized moribund on postnatal day 1.

US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 1 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
0	1	M	2.5	5.45
			2.4	5.79
			2.2	5.95
			2.5	4.66
			2.0	5.96
			2.1	6.06
		F	1.5	5.08
			1.0	5.37
			1.2	5.26
			1.0	5.22
			1.4	5.59
			1.0	3.99
			1.0	5.74
			0.8	5.92
			1.2	5.61
			1.1	5.71
	8	M	2.1	7.46
			2.0	7.27
			2.0	7.37
			2.1	6.63
			2.6	7.34
			2.5	7.46
		F	0.7	6.48
			0.8	6.79
			1.2	6.91
			1.1	6.57
			1.2	7.33
			1.2	6.84
			1.0	6.19
			1.0	6.34
			1.2	6.47
			1.1	6.78
	9	M	2.5	6.32
			2.1	6.71
			2.0	6.32
			2.0	5.99
			2.5	6.14
			2.2	6.42

(continued)

US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 2 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
0	9	F	1.0	5.86
			1.0	4.75
			1.1	5.46
			1.0	5.87
			1.1	6.17
			1.2	5.71
			1.1	5.96
			1.1	5.67
			1.5	5.60
	16	M	1.5	6.58
			2.4	6.42
			2.0	6.10
			2.0	5.58
			1.5	6.47
			2.0	6.25
			1.8	6.31
		F	1.2	6.44
			1.0	6.41
			1.0	5.78
			1.1	5.85
			1.0	5.62
			1.0	5.80
	31	M	2.2	7.47
			1.9	7.04
			2.0	7.19
			2.3	6.95
			2.6	7.32
			1.9	7.03
			1.8	6.44
			2.4	7.04
		F	1.0	6.83
			1.0	6.75
			1.3	6.81
			1.0	6.54
			1.0	6.71
			1.0	7.04
	32	M	2.1	6.15
			2.2	6.44
			2.0	6.59
			2.0	6.17
			2.1	6.40
			1.8	6.54
			2.0	7.00
			2.0	6.50

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 3 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
0	32	F	1.0	6.02
			1.1	6.61
			1.1	6.14
			1.2	6.11
			1.0	5.43
			1.0	6.63
			1.0	6.03
			1.1	5.90
	40	M	2.0	5.58
			2.2	5.98
			2.2	6.24
			1.5	6.30
			1.7	6.35
			2.0	5.68
			2.2	6.63
			1.5	5.94
			2.5	5.41
		F	1.0	5.74
			1.1	5.87
			1.0	5.68
			1.4	6.05
			1.1	5.24
			1.0	5.61
			1.0	5.45
	42	M	1.8	6.33
			2.0	4.96
		F	1.0	6.02
			0.9	5.90
			1.0	6.44
	49	M	2.0	7.80
			2.1	8.10
			2.2	7.50
			2.0	7.42
			2.0	6.38
			1.9	7.22
		F	1.0	6.45
			0.9	6.38
			0.8	6.17
			0.9	6.50
			1.0	6.99
			0.8	6.49
			0.9	7.28
			0.9	6.40

(continued)

US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 4 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
0	50	M	2.0	7.04
			1.6	6.17
			1.7	6.71
			1.8	6.31
			2.0	6.73
			1.9	6.72
			1.6	5.43
			2.0	6.42
		F	0.9	6.73
			0.9	6.25
			0.7	5.85
			1.0	5.63
			0.7	6.52
			0.9	5.91
			1.0	6.31
	57	M	2.1	6.87
			2.3	6.43
			2.5	7.74
			2.5	7.18
			2.0	7.16
			1.6	7.64
			2.4	7.05
		F	1.0	7.60
			1.0	6.96
			1.0	6.42
			1.0	6.81
			1.1	6.82
			1.1	6.98
			1.2	6.94
			1.0	6.98
			1.1	7.08
			0.9	6.56
	58	M	2.0	6.81
			2.1	6.65
			2.0	6.62
			2.5	6.34
			2.0	6.40
		F	1.1	6.11
			1.0	6.38
			1.0	6.09
			0.9	7.02
			1.1	6.29
			1.0	6.51
			1.1	6.05
			1.1	6.80
			0.9	6.24

(continued)

US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 5 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
25	2	M	2.8	6.28
			2.4	5.89
			2.5	6.85
			2.2	6.17
			2.5	6.39
			2.3	6.11
			2.5	5.91
			2.0	6.68
			2.5	6.37
			2.0	6.25
		F	1.0	5.95
			1.0	5.68
			1.0	5.28
			1.1	5.85
	7	M	2.4	7.80
			2.0	7.60
			2.2	7.90
			2.0	8.05
			2.0	7.87
			2.2	7.95
			2.0	7.37
		F	0.5	6.83
			0.9	7.57
			0.9	7.61
			1.0	7.28
			0.7	7.34
			0.6	7.35
	10	M	2.5	7.66
			2.5	7.85
			2.2	8.35
		F	1.0	7.47
			0.9	7.41
			0.8	7.54
			0.8	7.76
			0.7	7.77
	17[b]			
	25	M	2.0	7.58
			1.9	7.55
			2.0	7.57
			2.0	7.49
		F	1.0	7.45
			0.8	7.12
			1.0	6.31
			1.0	6.65
			1.1	6.68
			0.8	6.75
			0.8	6.41

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 6 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
25	30	M	2.0	6.35
			1.9	5.94
			2.0	5.94
			2.1	5.36
			2.0	5.88
			2.0	5.52
			2.1	5.55
			2.2	5.76
			1.6	5.58
			2.0	6.16
		F	1.1	5.65
			1.0	5.65
			1.0	5.85
			0.8	5.47
			1.0	5.46
			1.0	5.75
			0.7	5.75
	38	M	2.0	5.87
			1.9	6.90
			2.1	5.76
			2.0	6.11
			2.2	6.40
			2.0	5.24
			2.2	6.24
			2.2	6.39
			2.1	7.04
		F	1.0	5.94
			0.9	6.20
			1.1	6.24
			1.0	5.98
			1.3	7.62
			1.0	6.04
	48	M	2.0	5.06
			2.1	5.81
			1.8	4.68
			2.1	5.10
			2.0	5.96
			2.0	4.90
			2.0	5.75
			1.9	5.06
		F	1.0	5.51
			0.8	4.60
			1.0	5.41
			1.0	5.37
			0.7	5.18
			0.8	5.59

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 7 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
25	51	M	2.0	5.56
			1.8	5.34
			2.0	5.70
			1.9	5.67
			2.0	5.69
			1.9	5.58
			1.9	5.10
			2.0	5.19
			1.8	5.20
		F	1.0	4.51
			1.0	5.38
			1.0	5.56
			0.5	4.72
			0.8	5.40
			1.0	5.53
			0.7	5.19
			1.0	5.42
50	4	M	2.5	6.70
			2.5	6.20
			2.6	6.59
			2.0	6.42
			2.7	6.07
			2.0	5.88
			2.5	5.98
			2.5	6.58
		F	1.0	6.43
			1.2	6.03
			1.1	5.88
			0.7	6.23
			1.0	6.28
			1.0	5.21
			1.0	6.14
	5	M	2.0	5.80
			2.0	5.78
			2.1	7.15
			2.0	6.52
			2.2	6.37
			2.6	6.69
			2.1	6.38
			2.2	5.78
			2.0	6.43
			.[c]	

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 8 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
50	5	F	1.0	6.04
			0.7	5.72
			0.8	5.68
			1.0	5.95
	12	M	2.5	7.35
			2.2	6.04
			2.0	6.67
			2.5	6.09
			2.2	6.75
			2.0	6.50
			2.5	6.88
			2.0	6.38
			2.0	6.37
		F	0.9	5.76
			1.0	5.90
			1.0	6.22
			0.8	5.81
			0.7	6.15
	13	M	2.4	7.30
			2.2	7.03
			2.0	6.99
			2.8	6.86
			2.2	6.47
			2.2	6.38
			2.3	6.17
		F	1.2	6.28
			1.0	7.00
			1.2	7.29
	19	M	2.0	6.87
			1.9	6.83
			2.0	6.43
			1.8	6.57
			1.5	7.14
			2.1	6.76
			2.2	6.95
		F	1.1	6.64
			0.6	6.70
			0.8	6.27
			1.0	6.67
			0.8	6.98
			1.0	7.03
			1.2	6.63

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 9 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
50	20	M	1.8	6.19
			1.3	5.63
			1.5	5.98
			1.5	6.08
			1.7	5.78
			1.8	5.40
		F	0.8	5.66
			0.7	5.60
			1.0	5.97
			1.1	5.39
			1.0	5.74
			0.7	6.32
	27	M	2.5	6.21
			2.4	5.89
			2.0	5.23
			2.0	5.48
			1.8	5.81
			1.9	5.77
		F	1.3	5.55
			1.0	5.59
			1.1	5.66
			1.0	5.29
			1.0	5.03
			0.8	5.79
			1.1	5.91
			1.0	5.50
			0.8	6.38
	28	M	2.2	4.89
			2.0	5.41
			1.8	4.90
			1.9	5.38
			2.2	5.06
			2.0	5.51
		F	1.0	4.72
			1.0	5.31
			0.8	5.05
			0.7	5.12
			0.8	5.32
			0.7	4.93
			1.0	4.98
			0.8	4.90
			0.8	4.44

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 10 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
50	35	M	2.0	6.98
			1.8	6.53
			2.0	6.62
			2.0	6.53
			2.2	5.73
			1.8	7.04
			1.8	6.91
		F	1.0	6.55
			0.6	6.20
			1.0	6.28
			0.8	5.79
			0.6	5.80
			0.8	6.35
			1.0	6.25
			0.8	5.79
			0.9	5.57
	36	M	2.1	7.08
			2.1	7.57
			2.0	7.02
			1.9	7.43
		F	1.0	6.75
			1.0	6.68
			1.1	6.96
			1.0	6.53
			1.2	6.95
	45	M	1.5	4.09
			1.9	4.16
			1.8	4.64
			1.6	4.10
			1.5	4.66
			1.8	4.37
			1.9	4.13
		F	0.8	3.93
			0.6	3.48
			0.9	4.00
			0.7	3.91
			0.7	4.16
			0.8	4.01
			0.9	3.77
			0.8	3.82

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 11 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
50	46	M	1.7	5.96
			1.8	6.10
			1.9	5.94
			2.0	6.19
			2.0	5.58
			1.5	6.40
			1.8	6.11
			1.9	5.35
			2.0	5.63
			2.0	5.43
		F	0.8	5.50
			1.1	5.60
			0.8	5.95
			1.0	5.78
	53	M	2.5	5.94
			2.3	6.05
			2.2	5.20
			2.3	5.73
			2.1	4.71
			2.0	5.20
			2.2	4.72
			2.5	6.09
		F	1.1	5.02
			1.0	5.13
			1.2	4.99
			1.0	4.53
			1.0	4.50
			1.0	4.87
			0.9	3.81
			1.1	4.56
	54	M	2.1	9.57
		F	1.0	8.87
	60	M	2.2	6.34
			2.0	7.56
			1.8	7.17
			2.0	6.95
			1.6	6.51
			2.1	6.70
			1.8	6.69
			2.0	7.52

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 12 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
50	60	F	1.0	6.44
			1.0	6.58
			1.0	6.37
			0.9	6.91
			1.0	6.24
			0.6	6.76
			0.6	6.07
100	3	M	1.9	5.38
			2.0	5.39
			2.1	5.29
			2.6	5.88
			2.5	5.26
			2.4	5.59
		F	1.0	4.97
			1.0	4.58
			0.9	5.13
			1.0	5.13
			1.0	5.23
			0.8	5.29
	11	M	1.8	6.01
			2.2	6.18
			2.5	6.87
			2.4	5.91
			2.2	6.40
			1.8	6.20
		F	1.0	5.77
			0.7	6.02
			1.0	6.16
			1.0	6.03
			1.0	5.01
			0.8	4.87
			0.8	6.11
			1.0	6.54
			1.0	6.40
	18	M	2.5	5.19
			2.0	5.32
			1.9	6.51
			2.0	5.85
			2.0	5.61
			2.5	5.59
			2.0	5.30

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 13 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
100	18	F	0.5	5.47
			1.0	5.04
			0.9	5.71
			1.1	5.42
			1.0	5.70
			1.0	5.13
			1.0	5.50
	21	M	2.1	5.16
			1.8	5.66
			2.1	5.64
			2.2	5.40
			1.6	5.62
		F	1.0	5.41
			0.8	5.07
			0.8	4.77
	26	M	1.8	6.55
			2.0	5.95
			2.0	6.47
			1.9	6.19
			1.6	6.70
			1.9	6.08
		F	1.2	5.88
			1.0	5.46
			0.6	5.44
			1.0	5.20
			1.2	5.93
			1.0	6.31
	29	M	2.1	6.24
			1.9	6.28
			2.0	6.50
			2.1	6.37
			2.0	5.62
			2.2	5.91
		F	1.2	5.50
			1.3	6.00
	37	M	1.8	6.37
			2.3	6.12
			2.0	6.13
			1.7	6.11
			2.1	6.37
		F	0.8	5.78
			1.0	6.32
			1.0	6.34
			1.0	5.99
			0.9	5.79
			1.0	6.07

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US EPA ARCHIVE DOCUMENT

Table A-9. Individual F_1 Offspring Anogenital Distance (mm) and Body Weight (g) on Postnatal Day 0
(page 14 of 14)

Dose[a]	Female ID	Pup Sex	Anogenital Distance	Pup Weight
100	44	M	2.0	6.26
			1.9	5.32
			1.8	5.95
			2.0	6.02
			1.7	5.75
			2.0	6.17
			2.1	5.91
		F	1.0	5.85
			1.0	6.12
			1.0	5.92
			0.8	5.44
	55	M	2.2	5.97
			1.9	5.95
			2.3	6.56
			1.8	6.11
			2.0	6.32
			2.2	5.93
			2.0	6.41
			2.4	6.83
		F	1.0	6.75
			1.1	6.61
			0.8	5.82
			0.9	6.17
			0.9	5.48
	59	M	1.7	4.44
			1.8	5.87
			1.5	4.67
			1.7	4.31
			1.8	5.71
			1.7	5.76
			1.8	5.42
			1.9	4.51
			2.0	6.41
		F	0.7	6.09
			0.7	4.87
			0.8	5.01
			0.7	5.83
			0.8	5.55
			1.0	6.00
			0.9	5.12

[a]Mg/kg/day of Methoxychlor.
[b]Anogenital distance and postnatal day 0 body weights were inadvertently not recorded for this litter.
cThe anogenital distance for this pup was excluded because it had anal atresia and therefore anogenital distance could not be determined.

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Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 1 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
0	1	M	5.45	7.27	8.96	15.53	23.34	33.23	40.22	53.12
			5.79	6.93	9.02	15.10	22.69	30.31	39.70	52.09
			5.95	6.56	8.93	14.86	23.06	33.01	39.41	53.47
			4.66	6.74	8.48	14.16	20.88	32.69	37.04	45.86
			5.96	5.54	7.01					
			6.06	7.29	9.00					
		F	5.08	5.72	9.25	14.67	20.48	31.56	36.91	51.27
			5.37	6.35	8.40	12.80	21.68	27.57	38.23	50.60
			5.26	6.21	7.42	12.49	21.47	31.46	34.70	50.47
			5.22	7.16	9.19	13.78	20.02	29.92	35.55	44.30
			5.59	7.01	8.81	14.19	18.67	29.16	33.65	45.15
			3.99	7.02	9.09					
			5.74	6.61	7.49					
			5.92	7.04	8.50					
			5.61	6.44	8.05					
			5.71	.[d]						
	8	M	7.46	8.79	10.98	17.11	24.68	36.78	42.16	56.54
			7.27	8.43	9.90	16.46	23.05	34.95	45.38	61.93
			7.37	7.93	10.77	17.88	24.48	35.07	42.29	56.29
			6.63	8.15	10.08	17.61	25.61	34.74	42.56	55.97
			7.34	8.72	10.71					
			7.46	8.17	10.65					
		F	6.48	7.66	10.48	16.43	23.70	34.67	41.15	53.48
			6.79	7.96	9.63	17.01	24.15	33.20	41.94	54.06
			6.91	8.03	10.35	15.99	22.48	34.71	41.29	57.80
			6.57	7.87	10.64	17.05	24.63	33.85	42.10	55.42
			7.33	8.10	10.15	16.34	25.17	33.64	40.79	57.21
			6.84	8.03	9.79					
			6.19	7.62	9.83					
			6.34	7.67	9.68					
			6.47	7.88	10.26					
			6.78	8.46	.[e]					
	9	M	6.32	7.13	9.95	16.24	25.12	36.17	43.14	56.14
			6.71	7.82	9.83	17.43	24.47	32.90	41.70	57.93
			6.32	7.76	9.84	17.00	23.45	34.15	43.56	52.87
			5.99	7.88	10.27	16.14	23.72	35.20	40.13	58.15
			6.14	7.54	10.65					
			6.42	8.10	9.40					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 2 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
0	9	F	5.86	7.23	9.05	16.97	19.88	33.24	37.49	52.92
			4.75	7.70	7.99	16.93	24.81	34.20	34.62	55.89
			5.46	6.71	10.01	15.43	22.75	34.21	41.23	47.62
			5.87	6.83	9.30	13.85	23.20	29.98	40.72	52.60
			6.17	7.23	8.72	15.44	23.82	32.83	40.37	54.71
			5.71	6.95	10.11					
			5.96	7.63	8.83					
			5.67	7.47	9.19					
			5.60	6.02	9.66					
	16	M	6.58	8.05	10.82	17.72	23.37	32.56	38.04	52.43
			6.42	7.78	11.29	16.83	24.46	33.84	39.62	54.79
			6.10	8.17	9.65	17.50	23.82	30.90	40.49	49.59
			5.58	7.86	11.00	15.07	21.33	32.77	39.79	54.66
			6.47	7.49	9.14					
			6.25	8.22	11.18					
			6.31	8.40	10.76					
		F	6.44	7.88	11.62	16.53	22.83	33.24	39.85	53.74
			6.41	7.40	10.57	17.48	23.33	34.40	40.74	52.22
			5.78	8.28	9.80	16.05	23.48	33.18	39.71	54.17
			5.85	7.31	9.82	16.00	24.00	33.31	39.00	50.30
			5.62	7.36	10.06	18.32	24.93	32.55	37.97	50.63
			5.80	7.04	8.95					
	31	M	7.47	9.13	12.08	21.41	28.41	39.48	45.75	64.03
			7.04	9.38	11.91	20.92	28.92	40.74	48.83	61.08
			7.19	9.42	11.76	19.36	27.16	38.18	46.46	60.38
			6.95	9.00	12.71	19.00	26.09	38.07	46.78	66.49
			7.32	8.99	11.84					
			7.03	8.47	12.93					
			6.44	9.58	12.59					
			7.04	8.62	12.44					
		F	6.83	8.63	11.61	19.12	26.36	38.23	45.91	60.83
			6.75	8.17	11.94	19.50	27.20	36.46	44.77	58.51
			6.81	8.69	12.11	18.74	26.60	37.84	44.56	56.96
			6.54	8.73	11.92	18.94	26.66	38.55	43.28	57.56
			6.71	8.40	11.28	19.56	26.65	36.90	44.93	60.36
			7.04	8.51	12.10					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 3 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
0	32	M	6.15	8.73	11.65	18.59	26.84	36.37	48.17	62.47
			6.44	8.43	10.83	17.93	25.48	37.32	47.41	63.04
			6.59	7.61	10.20	17.87	26.99	39.24	43.60	61.95
			6.17	8.24	11.26	18.52	25.65	39.05	45.70	60.47
			6.40	7.93	10.39					
			6.54	7.84	12.00					
			7.00	7.67	11.12					
			6.50	8.19	11.11					
		F	6.02	7.48	10.99	19.01	24.50	39.61	47.58	64.95
			6.61	8.38	10.12	16.33	28.41	35.30	45.69	56.25
			6.14	7.82	9.93	17.14	23.75	37.08	44.12	60.23
			6.11	6.53	10.73	19.59	27.55	35.13	41.85	61.80
			5.43	7.82	10.19	16.10	25.35	39.00	44.09	58.40
			6.63	8.29	11.37					
			6.03	7.70	11.99					
			5.90	7.25	10.32					
	40	M	5.58	7.68	9.80	13.61	23.16	33.51	43.55	59.65
			5.98	7.22	9.55	17.04	25.59	33.85	40.72	63.92
			6.24	6.73	9.13	16.36	21.04	38.43	46.31	50.50
			6.30	7.62	9.55	15.49	23.91	35.95	40.88	54.97
			6.35	7.05	7.89					
			5.68	8.09	10.33					
			6.63	7.01	9.81					
			5.94	.[f]						
			5.41	.[f]						
		F	5.74	7.06	9.40	14.25	23.84	33.02	42.14	50.40
			5.87	7.29	9.57	16.05	24.07	35.26	43.65	55.50
			5.68	5.95	9.61	16.37	23.36	35.00	42.77	51.05
			6.05	7.15	9.01	16.28	23.24	35.07	38.87	57.05
			5.24	7.17	9.04	15.65	21.25	34.08	41.20	58.35
			5.61	6.89	8.16					
			5.45	7.49	9.42					
				7.59	10.10					
				6.98	10.21					
	42	M	6.33	7.14	10.09	17.46	27.64	36.69	45.34	54.80
			4.96	8.66	11.70	19.63	25.47	38.59	43.54	57.90
		F	6.02	8.88	12.99	20.00	29.50	40.80	47.09	61.73
			5.90	8.24	12.51	15.37	23.22	34.73	47.14	60.80
			6.44	8.95	9.82	21.31	28.38	39.94	41.71	55.92

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 4 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
0	49	M	7.80	9.17	12.80	17.69	28.56	40.10	44.93	59.66
			8.10	9.18	12.82	20.55	26.07	37.26	46.80	56.67
			7.50	8.72	11.25	20.10	27.75	38.33	45.51	64.46
			7.42	8.93	12.16	19.11	28.62	39.07	47.90	67.72
			6.38	9.22	12.00					
			7.22	8.06	12.06					
		F	6.45	7.63	11.30	17.57	25.22	35.93	43.43	53.87
			6.38	7.62	10.89	17.58	25.09	37.58	44.15	56.93
			6.17	8.30	10.30	17.58	29.27	36.52	46.15	60.33
			6.50	9.16	10.65	19.86	25.87	40.59	41.95	59.12
			6.99	7.60	10.16	16.77	26.00	36.58	42.52	57.99
			6.49	8.48	11.34					
			7.28	7.76	12.98					
			6.40	8.13	10.16					
	50	M	7.04	7.68	9.70	17.78	26.62	35.71	47.02	57.16
			6.17	6.63	9.29	16.08	24.28	35.67	43.20	59.11
			6.71	7.80	11.43	16.69	23.23	39.20	43.61	59.40
			6.31	7.50	11.03	14.93	24.20	35.31	44.45	63.96
			6.73	7.58	9.99					
			6.72	7.26	9.67					
			5.43	8.04	10.26					
			6.42	8.38	9.95					
		F	6.73	7.11	9.88	16.19	25.26	35.72	42.71	57.74
			6.25	7.70	10.36	17.02	24.96	36.04	44.00	57.08
			5.85	7.45	9.44	17.55	25.36	36.63	44.41	59.46
			5.63	7.16	10.10	16.96	25.68	36.16	44.18	58.90
			6.52	7.44	10.09	17.27	24.16	34.36	41.31	57.74
			5.91	7.98	10.80					
			6.31	7.78	9.60					
	57	M	6.87	8.06	9.63	17.40	25.00	37.43	42.73	58.46
			6.43	8.59	8.02	18.78	27.25	36.35	45.13	57.53
			7.74	8.11	11.35	16.69	25.16	34.72	43.25	59.82
			7.18	8.94	11.01	18.93	26.82	37.87	45.63	60.48
			7.16	6.38	11.33					
			7.64	8.03	11.62					
			7.05	7.75	10.36					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 5 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
0	57	F	7.60	8.20	10.02	15.62	26.39	33.36	44.52	52.64
			6.96	7.57	11.47	18.97	23.84	36.02	43.62	59.29
			6.42	7.79	11.01	16.43	26.09	37.02	39.14	55.74
			6.81	8.69	10.62	17.57	26.79	32.12	44.45	59.91
			6.82	8.74	9.98	18.94	23.30	37.55	40.52	53.77
			6.98	8.78	9.00					
			6.94	7.60	9.58					
			6.98	7.14	9.42					
			7.08	7.48	11.90					
			6.56	7.78	10.46					
	58	M	6.81	8.49	11.41	17.08	25.30	37.75	41.33	57.63
			6.65	8.77	10.60	15.57	23.34	35.06	45.48	61.37
			6.62	8.48	10.28	17.52	25.17	36.36	44.30	58.87
			6.34	8.05	9.66	17.05	24.68	37.04	45.68	53.76
			6.40	8.31	11.43					
		F	6.11	8.20	10.82	14.69	22.07	34.22	41.21	52.61
			6.38	7.80	10.20	14.48	21.44	34.28	42.06	55.92
			6.09	8.55	10.86	16.42	23.85	33.14	38.76	56.65
			7.02	7.70	10.74	17.09	23.05	31.17	42.54	52.15
			6.29	8.07	11.69	15.87	22.83	33.78	39.24	53.99
			6.51	7.72	10.95					
			6.05	7.68	10.38					
			6.80	7.62	10.10					
			6.24	8.25	9.34					
25	2	M	6.28	7.43	10.65	17.98	24.31	36.16	43.56	58.75
			5.89	7.34	9.99	16.90	24.23	35.89	42.30	58.31
			6.85	8.07	9.36	17.35	24.40	35.33	43.51	59.10
			6.17	7.31	9.96	17.10	24.65	.[g]		
			6.39	7.70	9.99					
			6.11	7.20	9.73					
			5.91	7.67	10.36					
			6.68	7.98	10.20					
			6.37	7.72	10.14					
			6.25	7.65	9.82					
		F	5.95	6.92	9.76	15.11	23.70	33.75	38.67	56.61
			5.68	7.34	8.97	16.86	23.94	31.29	40.31	54.45
			5.28	7.76	10.18	15.29	22.21	33.01	40.78	51.88
			5.85	7.01	9.10	16.35	21.73	33.67	40.79	55.10

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 6 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
25	7	M	7.80	9.88	13.01	21.38	28.94	41.75	50.34	69.05
			7.60	9.32	13.24	19.48	30.03	41.84	50.71	63.91
			7.90	9.30	13.15	19.08	27.85	38.59	46.73	69.35
			8.05	10.22	12.57	20.32	27.50	40.55	48.35	68.12
			7.87	10.00	12.47					
			7.95	10.73	13.18					
			7.37	9.56	13.64					
		F	6.83	9.38	12.69	19.68	27.47	38.03	45.90	61.19
			7.57	9.58	12.94	18.61	27.65	40.03	46.69	66.50
			7.61	8.83	12.83	19.48	28.30	38.93	48.07	66.62
			7.28	9.56	11.50	19.92	26.47	40.89	46.21	65.78
			7.34	9.57	12.65	20.23	27.17	38.60	47.62	66.19
			7.35	8.82	12.00					
	10	M	7.66	10.13	13.39	19.19	26.13	32.27	43.41	55.78
			7.85	10.09	11.71	18.46	26.49	37.46	42.55	62.08
			8.35	8.86	13.82	17.10	23.66	35.54	45.16	61.61
			.[f]	10.46	12.99	19.09	25.07	34.88	39.39	61.22
		F	7.47	9.56	13.46	18.06	24.71	34.81	42.91	58.05
			7.41	10.14	12.35	18.88	25.49	35.96	42.50	60.03
			7.54	9.67	12.46	18.00	25.39	34.60	42.53	61.22
			7.76	9.43	12.11	18.07	24.56	35.54	43.86	57.85
			7.77							
	17	M	.[h]	7.68	10.69	17.13	27.09	37.11	45.16	60.36
			.[h]	8.12	10.31	18.70	24.05	38.60	47.28	65.48
			.[h]	8.05	10.98	17.92	26.98	36.20	44.13	66.11
			.[h]	7.79	10.56	18.54	25.53	38.60	46.66	61.55
			.[h]	7.90	11.14					
			.[h]	8.82	11.52					
			.[h]	7.08	10.73					
			.[h]	8.14	10.77					
			.[h]	8.33	11.11					
			.[h]	8.24	11.13					
		F	.[h]	8.03	10.63	17.71	26.87	36.29	44.66	64.96
			.[h]	7.63	8.23	18.38	24.46	38.70	46.92	59.44
			.[h]	6.01	10.49	13.93	25.84	36.55	44.74	61.19
			.[h]	7.94	10.46	17.91	20.50	32.01	39.63	52.73
	25	M	7.58	8.96	10.19	15.44	21.98	29.47	37.49	51.04
			7.55	8.11	11.64	16.79	21.95	29.35	36.61	52.87
			7.57	8.70	10.53	15.96	20.88	31.36	39.19	50.67
			7.49	9.01	11.14	16.87	21.72	31.20	38.83	53.19

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US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 7 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
25	25	F	7.45	7.41	10.04	15.50	19.96	30.58	37.43	48.92
			7.12	7.70	10.88	13.91	21.02	27.18	37.63	49.81
			6.31	7.64	12.23	16.34	18.85	30.64	34.13	43.34
			6.65	7.88	9.37	16.16	18.95	28.08	34.65	45.11
			6.68	9.08	9.68	13.95	20.82	27.94	34.56	44.78
			6.75	8.18	10.73					
			6.41	8.43	10.10					
	30	M	6.35	7.04	9.43	15.21	21.40	31.62	39.87	56.09
			5.94	6.54	10.37	14.90	23.85	34.20	42.74	50.32
			5.94	8.00	8.53	16.51	23.35	34.46	38.81	56.06
			5.36	7.36	8.90	16.06	21.77	30.89	41.98	48.46
			5.88	7.05	8.49					
			5.52	7.54	9.56					
			5.55	6.36	8.58					
			5.76	6.73	10.52					
			5.58	7.57	9.41					
			6.16	7.06	9.09					
		F	5.65	7.27	9.75	15.80	23.10	31.15	38.09	49.46
			5.65	6.50	8.80	14.48	22.63	32.79	39.00	49.81
			5.85	6.45	8.43	15.86	22.72	30.47	39.14	48.24
			5.47	7.23	9.10	16.14	22.59	33.42	40.28	50.60
			5.46	6.75	9.99	16.34	23.02	31.79	38.13	52.79
			5.75	6.82	8.25					
			5.75	7.14	9.63					
	38	M	5.87	7.07	10.64	19.02	22.37	33.59	40.62	59.92
			6.90	8.22	9.49	15.67	24.88	36.90	41.56	61.36
			5.76	7.62	10.30	16.96	26.79	34.09	42.25	66.59
			6.11	7.00	11.20	16.84	24.56	32.26	45.99	59.74
			6.40	8.61	11.19					
			5.24	7.41	9.60					
			6.24	7.23	10.17					
			6.39	7.28	10.51					
			7.04	7.69	.[e]					
		F	5.94	7.76	10.27	17.78	24.88	33.06	42.96	61.24
			6.20	8.66	10.29	17.46	24.57	35.73	40.66	59.20
			6.24	8.15	10.73	17.59	26.12	34.21	41.74	64.21
			5.98	7.93	10.68	18.35	26.05	34.76	45.03	59.12
			7.62	8.13	11.50	16.74	25.18	35.04	43.26	59.73
			6.04	8.02	10.52					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 8 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
25	48	M	5.06	6.49	10.43	12.17	24.33	30.25	37.66	50.13
			5.81	5.83	7.79	16.41	22.29	35.27	34.52	47.19
			4.68	7.67	8.84	13.38	20.35	27.54	39.04	53.34
			5.10	5.71	7.96	14.20	18.98	31.10	42.34	42.81
			5.96	6.55	8.40					
			4.90	6.27	10.12					
			5.75	7.56	9.68					
			5.06	7.77	8.88					
		F	5.51	6.77	9.90	15.31	22.16	32.42	39.13	51.41
			4.60	7.09	9.15	14.53	23.41	33.01	40.35	51.48
			5.41	6.68	9.41	15.56	23.32	33.38	40.63	51.51
			5.37	5.53	7.73	14.73	22.95	30.67	37.18	52.80
			5.18	6.82	9.30	15.34	23.68	32.92	39.25	53.26
			5.59	6.71	8.78					
	51	M	5.56	6.11	7.41	12.55	20.57	28.83	40.57	50.47
			5.34	5.78	8.24	14.39	18.96	30.74	37.40	48.73
			5.70	6.31	7.66	14.41	19.68	29.73	36.85	52.41
			5.67	6.42	8.22	13.02	20.89	30.95	39.40	52.66
			5.69	5.47	8.48					
			5.58	6.22	7.67					
			5.10	5.97	7.37					
			5.19	5.51	8.50					
			5.20	5.84	8.77					
		F	4.51	6.46	7.60	9.26	18.97	28.83	35.95	48.86
			5.38	5.74	8.68	13.42	20.45	22.17	29.44	47.91
			5.56	6.34	4.78	12.30	19.46	30.08	36.07	38.78
			4.72	6.04	7.20	14.17	14.71	28.83	37.21	48.03
			5.40	5.48	8.43	14.13	18.90	26.96	37.65	49.34
			5.53	4.10	8.48					
			5.19	4.58	7.50					
			5.42	6.21	5.58					
50	4	M	6.70	6.89	8.36	16.35	23.72	29.39	41.11	52.86
			6.20	6.74	10.42	16.82	20.51	34.11	36.64	49.26
			6.59	7.60	9.22	13.84	23.27	32.38	40.20	59.10
			6.42	7.54	9.73	15.18	21.64	30.91	38.69	56.78
			6.07	7.34	9.39					
			5.88	7.08	9.58					
			5.98	7.81	8.74					
			6.58	6.74	10.22					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 9 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
50	4	F	6.43	6.49	9.45	14.90	19.70	28.25	36.66	48.01
			6.03	7.20	9.62	14.82	22.09	31.13	36.44	54.26
			5.88	7.17	9.65	13.53	20.94	30.25	38.40	50.02
			6.23	7.28	9.07	14.37	21.53	31.52	35.18	53.83
			6.28	7.18	9.22	14.30	20.62	30.50	38.98	51.04
			5.71	6.10	7.74					
			6.14	7.09	9.73					
	5	M	5.80	8.50	9.84	16.97	21.40	31.57	39.02	57.43
			5.78	7.93	11.37	17.65	22.44	32.58	40.35	57.41
			7.15	8.11	10.89	15.75	22.90	31.97	41.27	54.29
			6.52	7.44	11.11	17.06	21.97	30.23	39.60	55.60
			6.37	8.14	9.47					
			6.69	8.04	10.72					
			6.38	7.11	10.35					
			5.78	7.27	10.60					
			6.43	8.26	9.44					
			6.23	.[i]						
		F	6.04	6.88	10.33	16.53	20.25	30.97	39.71	56.67
			5.72	7.67	10.05	16.17	21.96	29.68	37.10	56.85
			5.68	7.62	8.87	17.08	22.03	31.59	39.47	52.38
			5.95	7.34	10.16	14.78	22.97	30.94	37.54	53.77
	12	M	7.35	6.66	9.44	16.04	22.69	35.97	44.11	59.22
			6.04	7.57	8.87	14.67	24.73	35.85	43.26	55.90
			6.67	7.29	8.51	14.25	22.15	32.08	44.20	56.91
			6.09	7.48	9.66	14.89	22.88	34.26	41.72	57.52
			6.75	7.32	9.09					
			6.50	7.82	8.62					
			6.88	7.31	7.49					
			6.38	7.78	9.43					
			6.37	7.25	7.34					
		F	5.76	7.15	8.70	13.68	22.67	34.16	40.21	55.33
			5.90	6.97	9.32	14.95	19.76	34.60	38.52	51.61
			6.22	7.19	8.79	14.32	21.94	33.44	41.67	56.94
			5.81	7.15	8.15	14.86	23.26	31.24	41.34	55.35
			6.15	7.41	9.19	12.47	.[j]			
	13	M	7.30	8.22	13.78	21.88	31.22	42.17	49.08	73.37
			7.03	8.96	11.35	18.82	29.37	38.38	51.46	65.76
			6.99	9.90	11.82	20.82	27.47	40.24	53.86	68.68
			6.86	9.55	12.35	19.71	30.95	42.59	51.78	68.19
			6.47	8.60	13.65					
			6.38	9.24	12.89					
			6.17	8.08	12.86					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 10 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
50	13	F	6.28	9.51	12.73	19.01	28.23	43.14	49.65	64.80
			7.00	9.15	12.84	20.56	30.62	39.52	53.00	70.17
			7.29	8.35	11.57	20.63	29.58	41.20	50.76	66.50
	19	M	6.87	8.12	10.49	16.88	23.59	34.00	41.09	56.92
			6.83	7.43	10.40	17.05	23.54	34.22	39.94	55.55
			6.43	8.14	10.20	16.97	23.38	34.01	42.76	57.40
			6.57	8.21	10.30	16.63	23.72	35.09	41.58	56.84
			7.14	7.84	10.42					
			6.76	8.25	9.67					
			6.95	8.19	10.94					
		F	6.64	8.24	10.37	16.93	23.30	32.75	39.32	53.37
			6.70	7.96	10.17	16.97	24.10	34.73	39.14	54.28
			6.27	8.21	10.29	16.56	22.90	32.96	38.40	59.01
			6.67	8.03	10.39	16.34	23.23	33.17	40.51	54.53
			6.98	7.87	10.51	17.20	24.45	35.23	42.81	56.08
			7.03	7.49	10.18					
			6.63	7.74	10.75					
	20	M	6.19	7.09	10.44	18.33	25.74	34.72	44.13	63.45
			5.63	7.05	10.29	18.43	25.49	36.01	42.23	61.64
			5.98	7.84	11.00	17.50	25.33	35.54	42.55	61.08
			6.08	6.64	10.52	17.45	24.17	36.29	42.23	61.30
			5.78	7.55	9.73					
			5.40	.[f]						
		F	5.66	6.45	9.88	17.58	24.82	35.13	43.02	52.49
			5.60	6.98	10.18	17.65	25.59	35.94	39.93	57.37
			5.97	7.61	9.99	17.09	22.23	32.98	41.48	57.15
			5.39	7.22	10.07	17.30	24.82	34.81	43.20	59.96
			5.74	7.04	9.05	15.46	25.09	35.30	41.78	60.23
			6.32	7.03	10.11					
				6.90	11.10					
	27	M	6.21	6.55	9.25	13.62	22.05	30.40	33.65	55.58
			5.89	6.26	8.15	15.72	20.04	31.47	36.07	54.32
			5.23	6.97	9.18	15.14	20.95	30.60	37.67	54.97
			5.48	7.08	9.40	14.46	21.23	28.71	36.73	50.15
			5.81	6.34	8.18					
			5.77	6.62	9.18					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 11 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
50	27	F	5.55	5.70	9.99	15.18	22.50	32.43	37.43	55.63
			5.59	6.25	8.72	16.17	23.06	29.76	38.66	51.87
			5.66	6.88	9.62	13.41	21.08	30.99	36.25	55.59
			5.29	6.05	9.65	14.74	21.32	32.26	37.87	57.89
			5.03	6.96	9.06	16.08	19.24	28.91	.[k]	
			5.79	7.09	7.64					
			5.91	6.92	8.92					
			5.50	6.45	7.91					
			6.38	7.43	7.70					
	28	M	4.89	6.34	8.17	12.40	19.29	28.71	39.04	53.83
			5.41	6.49	7.19	13.95	20.89	32.34	38.85	50.33
			4.90	5.45	8.39	14.33	21.68	31.64	41.72	51.60
			5.38	5.85	7.91	14.47	21.12	32.36	35.20	47.65
			5.06	6.02	8.41					
			5.51	6.16	7.85					
		F	4.72	5.88	7.26	14.12	20.28	31.34	39.40	47.53
			5.31	5.76	6.45	12.96	20.63	30.70	37.93	48.96
			5.05	5.69	7.97	13.54	20.55	30.11	36.80	49.10
			5.12	5.60	7.62	14.03	19.88	30.48	38.57	52.57
			5.32	6.18	7.30	13.60	21.02	31.04	39.22	50.50
			4.93	5.83	7.51					
			4.98	5.43	7.86					
			4.90	5.13	7.73					
			4.44	6.01	7.60					
	35	M	6.98	7.86	9.93	14.33	21.50	31.02	37.73	52.89
			6.53	7.93	8.51	14.22	23.11	28.98	38.95	56.90
			6.62	7.86	9.68	15.83	21.00	31.77	38.12	57.00
			6.53	7.09	8.57	14.93	20.38	30.56	35.62	59.34
			5.73	7.86	10.24					
			7.04	8.56	9.09					
			6.91	8.08	9.65					
		F	6.55	7.19	9.53	13.94	21.34	30.00	36.08	54.61
			6.20	7.16	9.05	14.14	20.61	29.77	36.96	53.76
			6.28	7.63	8.55	14.40	21.37	28.97	36.54	52.38
			5.79	6.88	8.30	14.97	22.50	29.67	38.31	58.03
			5.80	7.75	6.41	15.16	21.52	31.13	34.82	56.08
			6.35	7.70	9.03					
			6.25	7.58	9.33					
			5.79	6.24	8.69					
			5.57	7.13	8.55					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 12 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
50	36	M	7.08	9.31	12.72	18.13	23.20	32.27	40.89	61.80
			7.57	9.69	11.82	18.46	23.57	31.94	39.32	59.94
			7.02	8.91	12.40	17.96	23.76	33.85	39.53	56.50
			7.43	9.78	12.80	18.81	23.20	32.41	40.15	57.45
		F	6.75	8.70	11.61	17.79	23.33	33.46	40.79	60.91
			6.68	8.66	11.51	16.76	23.32	31.58	39.29	55.15
			6.96	9.12	12.44	18.01	22.00	33.29	40.69	55.76
			6.53	8.72	12.22	17.42	22.65	31.65	38.15	58.72
			6.95	8.62	11.72	17.88	22.86	32.60	41.78	59.00
	45	M	4.09	3.46	.[l]					
			4.16	3.77	.[l]					
			4.64	.[d]						
			4.10	.[d]						
			4.66	.[d]						
			4.37	.[d]						
			4.13	.[d]						
		F	3.93	3.43	.[l]					
			3.48	4.06	.[l]					
			4.00	.[d]						
			3.91	.[d]						
			4.16	.[d]						
			4.01	.[d]						
			3.77	.[d]						
			3.82	.[d]						
	46	M	5.96	7.33	9.12	14.73	21.55	32.10	41.06	53.57
			6.10	7.81	9.73	15.88	23.44	32.35	42.09	58.12
			5.94	6.93	10.06	16.35	23.90	31.15	38.83	56.05
			6.19	7.25	8.87	16.22	23.99	33.23	40.77	59.51
			5.58	6.63	10.18					
			6.40	6.59	9.90					
			6.11	7.46	9.60					
			5.35	6.97	8.88					
			5.63	7.30	11.04					
			5.43	7.69	9.53					
		F	5.50	6.81	8.92	16.53	24.37	33.86	42.13	56.80
			5.60	6.79	9.72	15.25	23.76	30.44	39.28	55.52
			5.95	7.26	9.67	16.36	22.37	33.00	40.48	57.00
			5.78	6.86	8.96	14.66	21.43	31.67	40.58	53.42

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 13 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
50	53	M	5.94	4.58	.[m]					
			6.05	4.73	.[m]					
			5.20	4.13	.[m]					
			5.73	.[d]						
			4.71	.[d]						
			5.20	.[d]						
			4.72	.[d]						
			6.09	.[d]						
		F	5.02	3.95	.[m]					
			5.13	4.19	.[m]					
			4.99	4.20	.[m]					
			4.53	4.66	.[m]					
			4.50	4.16	.[m]					
			4.87	3.87	.[m]					
			3.81	.[d]						
			4.56	.[d]						
	54	M	9.57	9.31	10.81	13.33	16.71	23.64	29.79	46.41
		F	8.87	9.67	10.93	13.01	16.24	22.93	28.59	46.07
	60	M	6.34	8.04	11.35	19.49	26.96	37.45	42.41	58.98
			7.56	9.33	11.99	19.51	25.59	35.26	44.36	68.15
			7.17	9.54	11.33	17.76	27.70	35.22	41.41	60.46
			6.95	9.03	11.91	19.25	25.86	37.45	45.21	59.99
			6.51	9.01	10.74					
			6.70	8.40	10.05					
			6.69	9.21	12.38					
			7.52	8.75	10.69					
		F	6.44	8.39	10.64	18.67	24.78	36.29	43.56	56.83
			6.58	8.12	11.04	17.64	24.26	34.54	43.39	61.34
			6.37	8.40	11.11	18.28	26.75	36.68	42.79	57.56
			6.91	8.92	11.42	18.10	24.84	33.96	41.13	59.35
			6.24	8.36	11.17	18.30	25.84	35.57	41.05	58.54
			6.76	8.73	10.92					
			6.07	8.54	12.26					
100	3	M	5.38	6.92	9.34	14.10	21.35	31.63	38.27	55.92
			5.39	6.52	9.97	14.88	20.70	32.16	35.61	56.24
			5.29	6.67	8.89	14.29	22.10	31.54	38.48	54.83
			5.88	7.33	8.90	15.78	22.04	29.60	39.45	55.52
			5.26	6.61	8.99					
			5.59	7.05	9.50					

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 14 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
100	3	F	4.97	6.48	8.31	14.41	20.19	29.11	36.41	53.12
			4.58	6.42	8.23	13.82	20.97	28.82	35.95	53.36
			5.13	6.74	8.82	14.49	19.96	28.70	36.40	50.87
			5.13	6.33	8.73	13.30	20.16	30.02	35.22	51.48
			5.23	6.57	8.98	14.12	21.06	29.79	35.54	50.75
			5.29	5.86	8.38					
	11	M	6.01	7.91	11.31	16.60	22.61	30.32	40.35	49.20
			6.18	8.47	10.60	16.01	23.85	33.12	39.82	56.47
			6.87	8.11	10.30	17.50	24.00	32.70	40.45	57.91
			5.91	8.05	10.80	17.13	24.46	32.78	35.69	57.95
			6.40	7.76	10.07					
			6.20	7.43	10.80					
		F	5.77	7.00	9.38	16.88	24.65	32.37	37.63	53.01
			6.02	7.66	9.73	16.76	22.00	31.94	35.28	49.28
			6.16	7.48	10.61	15.43	22.66	29.98	41.48	50.32
			6.03	7.40	10.32	15.61	23.02	29.81	38.34	58.79
			5.01	7.68	7.81	18.01	22.30	35.24	35.87	54.54
			4.87	6.96	9.09					
			6.11	8.19	11.19					
			6.54	7.34	10.74					
			6.40	5.87	10.45					
	18	M	5.19	7.15	9.83	17.44	25.00	33.32	43.47	59.47
			5.32	7.06	10.13	16.74	24.08	29.86	36.97	51.36
			6.51	7.13	10.11	17.26	21.32	34.70	42.13	58.42
			5.85	7.02	10.45	17.98	24.14	33.57	41.60	58.33
			5.61	8.18	9.89					
			5.59	7.28	11.05					
			5.30	7.16	10.27					
		F	5.47	6.52	10.18	16.23	22.67	30.67	38.56	52.77
			5.04	6.54	9.42	17.19	20.19	27.29	34.84	49.76
			5.71	7.10	9.26	16.87	21.47	32.67	37.20	53.75
			5.42	7.09	10.46	15.28	21.16	32.73	36.72	55.70
			5.70	7.27	9.46	16.77	24.02	31.94	38.66	53.60
			5.13	6.99	9.77					
			5.50	7.32	9.67					
	21	M	5.16	7.39	11.75	16.44	27.88	42.44	52.08	68.85
			5.66	7.92	9.98	18.86	24.31	37.33	49.22	65.20
			5.64	7.47	10.90	17.68	24.67	39.66	46.77	61.83
			5.40	6.81	11.15	16.34	25.75	37.49	45.44	74.77
			5.62	6.89	10.00					
		F	5.41	7.09	10.31	16.87	25.40	38.12	46.30	59.62
			5.07	6.60	9.80	16.10	23.49	37.85	46.13	62.50
			4.77	6.50	10.35	17.34	25.06	35.76	44.39	61.03

(continued)

US EPA ARCHIVE DOCUMENT

Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 15 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
100	26	M	6.55	7.45	9.25	14.63	21.05	30.54	35.68	53.04
			5.95	8.04	8.37	12.74	19.02	29.36	37.59	48.34
			6.47	7.38	9.55	15.19	21.61	28.35	34.76	51.71
			6.19	7.64	8.92	14.24	21.04	30.47	37.44	48.32
			6.70	7.11	9.35					
			6.08	7.70	9.71					
		F	5.88	6.53	9.57	11.63	17.54	26.56	37.46	44.55
			5.46	6.90	9.13	14.70	19.85	28.42	34.31	50.57
			5.44	7.35	8.89	13.34	19.12	30.76	32.25	47.41
			5.20	7.04	7.41	15.28	19.42	28.30	33.89	46.47
			5.93	7.24	8.15	13.26	21.33	27.72	34.98	47.71
			6.31	6.31	8.29					
	29	M	6.24	.[n]						
			6.28	.[n]						
			6.50	.[o]						
			6.37	.[o]						
			5.62	.[o]						
			5.91	.[o]						
		F	5.50	.[n]						
			6.00	.[o]						
	37	M	6.37	7.28	9.92	14.87	19.80	29.29	36.65	50.10
			6.12	7.68	9.45	14.00	19.86	29.41	36.43	48.60
			6.13	7.83	9.21	14.33	20.14	29.64	34.31	51.08
			6.11	7.57	9.74	14.15	20.23	28.39	34.80	50.95
			6.37	7.60	9.89					
		F	5.78	7.45	9.52	13.65	19.78	28.71	35.42	51.66
			6.32	6.93	9.38	13.96	20.20	28.55	35.95	50.46
			6.34	7.41	9.36	14.16	19.67	29.51	34.99	49.68
			5.99	7.29	9.96	14.03	20.26	29.34	35.53	46.88
			5.79	7.72	9.67	14.68	19.07	29.45	36.51	55.55
			6.07	7.34	9.55					
	44	M	6.26	7.28	10.03	16.67	25.30	38.52	46.17	62.37
			5.32	6.67	10.42	16.13	25.59	37.12	47.18	65.56
			5.95	7.82	10.90	18.15	27.23	37.82	48.34	60.25
			6.02	7.13	9.96	16.83	25.35	36.21	48.17	64.75
			5.75	7.18	9.57					
			6.17	7.35	9.90					
			5.91	7.69	11.00					
		F	5.85	7.58	10.17	16.94	24.88	35.74	47.91	67.28
			6.12	7.35	9.85	17.99	25.66	38.48	49.56	62.01
			5.92	7.51	10.93	16.95	27.73	37.23	44.82	57.40
			5.44	6.91	10.40	.[p]				

(continued)

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Table A-10. Individual F_1 Pup Weight Data During Lactation (g)[a] (page 16 of 16)

Dose[b]	Female ID	Pup Sex[c]	Postnatal Day 0	2	4	7	10	14	17	21
100	55	M	5.97	7.90	10.88	18.80	25.31	37.31	45.13	57.02
			5.95	8.37	11.35	16.88	26.34	37.88	44.35	62.59
			6.56	7.23	10.71	17.82	24.75	38.33	45.85	58.04
			6.11	8.33	10.28	17.16	25.10	36.68	43.76	60.49
			6.32	8.47	10.89					
			5.93	7.18	10.82					
			6.41	8.37	10.16					
			6.83	8.53	10.41					
		F	6.75	8.36	11.51	18.54	26.55	37.88	42.04	57.88
			6.61	7.70	9.87	16.38	24.38	35.53	45.50	59.49
			5.82	8.36	11.07	16.69	26.74	39.56	46.51	55.34
			6.17	7.59	11.23	16.36	25.72	35.23	44.39	53.98
			5.48	7.57	9.90	18.26	23.75	38.39	41.80	60.17
	59	M	4.44	6.49	6.42	12.38	18.68	33.05	35.49	52.77
			5.87	6.72	9.57	13.54	22.52	31.43	40.23	46.81
			4.67	7.28	9.11	15.72	20.66	32.09	40.83	53.60
			4.31	6.37	7.29	15.16	22.02	28.36	39.41	56.87
			5.71	5.63	7.78					
			5.76	5.31	7.99					
			5.42	5.58	9.02					
			4.51	5.12	7.10					
			6.41	.[n]						
		F	6.09	6.71	8.64	13.58	20.89	31.42	41.80	56.32
			4.87	6.05	8.10	13.68	23.38	32.94	40.55	51.93
			5.01	5.81	9.28	14.74	20.72	30.89	39.30	55.34
			5.83	5.87	9.37	13.79	20.32	33.32	38.70	52.31
			5.55	6.74	8.13	15.63	21.81	31.44	39.69	51.06
			6.00	6.83	8.22					
			5.12	5.67	8.32					

[a]Pup body weights are not comparable across columns because the pups were not uniquely identified until postnatal day 21. Litters were culled to 9 pups on postnatal day 4 keeping 4 males at most and 5 females at most if possible.
[b]Mg/kg/day of Methoxychlor.
[c]M is male and F is female.
[d]Pup was found dead or was missing and presumed dead on or before postnatal day 2.
[e]Pup was found dead on postnatal day 4.
[f]Pup was missexed.
[g]Pup was found dead on postnatal day 12.
[h]Weight inadvertently not recorded.
[i]Pup was euthanized on postnatal day 0 because it had anal atresia.
[j]Pup was found dead on postnatal day 9.
[k]Pup was found dead on postnatal day 17.
[l]Pup was euthanized moribund on postnatal day 3.
[m]Pup was euthanized moribund on postnatal day 2.
[n]Pup was found dead on postnatal day 1.
[o]Pup was euthanized moribund on postnatal day 1.
[p]Pup was found dead on postnatal day 7.

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Table A-11. Individual F_1 Male Nipple Data during Lactation[a] (page 1 of 4)

Dose[b]	Female ID	No. Nipples	No. Areolae
0	1	0	0
		0	0
		0	0
		0	0
	8	0	0
		0	0
		0	0
		0	0
	9	0	0
		0	0
		0	0
		0	0
	16	0	0
		0	0
		0	0
		0	0
	31	0	0
		0	0
		0	0
		0	0
	32	0	0
		0	0
		0	0
		0	0
	40	0	0
		0	0
		0	0
		0	0
	42	0	0
		0	0
	49	0	0
		0	0
		0	0
		0	0
	50	0	2
		0	0
		0	0
		0	0
	57	0	2
		0	0
		0	0
		0	0
	58	0	0
		0	0
		0	0
		0	0

(continued)

US EPA ARCHIVE DOCUMENT

Table A-11. Individual F_1 Male Nipple Data during Lactation[a] (page 2 of 4)

Dose[b]	Female ID	No. Nipples	No. Areolae
25	2	1	1
		0	0
		0	0
		0	0
	7	0	0
		0	0
		0	0
		0	0
	10	2	2
		0	0
		0	0
		0	0
	17	0	2
		0	0
		0	0
		0	0
	25	0	0
		0	0
		0	0
		0	0
	30	0	0
		0	0
		0	0
		0	0
	38	0	1
		0	0
		0	0
		0	0
	48	0	0
		0	0
		0	0
		0	0
	51	0	0
		0	0
		0	0
		0	0
50	4	0	0
		0	0
		0	0
		0	0
	5	0	1
		0	0
		0	0
		0	0

(continued)

US EPA ARCHIVE DOCUMENT

Table A-11. Individual F_1 Male Nipple Data during Lactation[a] (page 3 of 4)

Dose[b]	Female ID	No. Nipples	No. Areolae
50	12	0	0
		0	0
		0	0
		0	0
	13	0	0
		0	0
		0	0
		0	0
	19	0	0
		0	0
		0	0
		0	0
	20	0	1
		0	0
		0	0
		0	0
	27	0	0
		0	0
		0	0
		0	0
	28	0	2
		0	0
		0	0
		0	0
	35	0	0
		0	0
		0	0
		0	0
	36	0	3
		0	0
		0	0
		0	0
	46	0	0
		0	0
		0	0
		0	0
	54	0	0
	60	0	0
		0	0
		0	0
		0	0
100	3	0	0
		0	0
		0	0
		0	0

(continued)

US EPA ARCHIVE DOCUMENT

Table A-11. Individual F_1 Male Nipple Data during Lactation[a] (page 4 of 4)

Dose[b]	Female ID	No. Nipples	No. Areolae
100	11	0	0
		0	0
		0	0
		0	0
	18	0	0
		0	0
		0	0
		0	0
	21	0	0
		0	0
		0	0
		0	0
	26	0	0
		0	0
		0	0
		0	0
	37	0	0
		0	0
		0	0
		0	0
	44	0	2
		0	0
		0	0
		0	2
	55	0	0
		0	0
		0	0
		0	0
	59	0	0
		0	0
		0	2
		0	0

[a]Measurement was made one time on postnatal day 11 or 12.
[b]Mg/kg/day of Methoxychlor.

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Table A-12. Individual F_1 Pup Clinical Observations for Postnatal Days 0 Through 21 (page 1 of 3)

Dose[a]	Female ID	Day[b]	Sex[c]	Observation
0	1	2	F	Missing and presumed dead
	8	4	F	Found dead
	40	0	F	Found dead
	42	0	F	Found dead
		4	F	Bite mark on left side
		10	F	Bite mark on left side is scabbed over and healing
		11	F	Umbilical hernia; Bite mark on left side
		14	F	Back: sore and bump; Umbilical hernia
	49	0	M	Found dead
	57	0	F	Found dead
25	2	12	M	Found dead after tail tattooing
	10	14	F	Alopecia: rump
				Alopecia: rump
				Alopecia: rump
				Alopecia: rump
			M	Alopecia: rump
				Alopecia: rump
				Alopecia: rump
				Alopecia: rump
		17	F	Alopecia: rump
				Alopecia: rump
				Alopecia: rump
				Alopecia: rump
			M	Alopecia: rump
				Alopecia: rump
				Alopecia: rump
				Alopecia: rump
	38	4	M	Found dead
	48	0	F	Found dead
	51	0	M	Found dead
50	5	0	F	Anal atresia; String like tail; Euthanized moribund
	12	9	F	Found dead
	13	0	F	Found dead
	20	0	F	Found dead
				Found dead
	27	17	F	Found dead

(continued)

US EPA ARCHIVE DOCUMENT

Table A-12. Individual F_1 Pup Clinical Observations for Postnatal Days 0 Through 21 (page 2 of 3)

Dose[a]	Female ID	Day[b]	Sex[c]	Observation
50	45	0	F	Found dead
				Found dead
			M	Found dead
		1	F	Found dead
				Found dead
				Found dead
				Found dead
			M	Found dead
		2	F	Missing and presumed dead
				Missing and presumed dead
			M	Missing and presumed dead
				Missing and presumed dead
				Missing and presumed dead
				Missing and presumed dead
		3	F	No milk band; Euthanized moribund
			M	No milk band; Euthanized moribund
				No milk band; Euthanized moribund
				No milk band; Euthanized moribund
	53	0	F	Found dead
		2	F	Found dead
				Found dead
				Found dead
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
			M	Found dead
				Found dead
				Found dead
				Found dead
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
				No milk band; Barely alive; Euthanized moribund
100	26	0	F	Found dead
	29	0	F	Found dead
				Found dead
			M	Found dead
				Found dead

(continued)

US EPA ARCHIVE DOCUMENT

Table A-12. Individual F_1 Pup Clinical Observations for Postnatal Days 0 Through 21 (page 3 of 3)

Dose[a]	Female ID	Day[b]	Sex[c]	Observation
100	29	1	F	Found dead
				No milk band; Cold; Euthanized moribund
			M	Found dead
				Found dead
				No milk band; Cold; Euthanized moribund
				No milk band; Cold; Euthanized moribund
				No milk band; Cold; Euthanized moribund
				No milk band; Cold; Euthanized moribund
	44	7	F	Found dead
	59	1	M	Found dead

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.
[c]Sex is F is female and M is male.

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Table A-13. Individual F_1 Pup Gross Necropsy Findings for Postnatal Days 0 Through 21 (page 1 of 2)

Dose[a]	Female ID	Day[b]	Sex[c]	Gross Necropsy Finding
0	8	4	F	Abdominal organs too autolyzed to evaluate
	40	0	F	Ductus closed; Abdominal organs too autolyzed to evaluate
	42	0	F	Ductus open; No air in lungs
	49	0	M	Ductus open; No air in lungs
	57	0	F	Ductus open; No air in lungs
25	2	12	M	Pup found dead after tail tattooing; No findings
	38	4	M	Too autolyzed to evaluate
	48	0	F	Ductus closed; Air in lungs; No milk in stomach
	51	0	M	Ductus open; Air in lungs; No milk in stomach
50	5	0	F	Euthanized moribund; Anal atresia; String like tail; Ductus closed; Milk in stomach; Large intestines ended with no attachment to an external orifice
	12	9	F	Abdominal organs too autolyzed to evaluate
	13	0	F	Ductus open; No air in lungs; Abdominal organs too autolyzed to evaluate
	20	0	F	Ductus open; No milk in stomach
				Ductus open; No milk in stomach
	27	17	F	Bite mark on left side of neck and one on back of head
	45	0	F	Ductus open; No air in lungs
				Ductus open; No air in lungs
			M	Ductus open; No air in lungs
		1	F	Abdominal organs too autolyzed to evaluate
				No milk in stomach
				No milk in stomach
				No milk in stomach
			M	No milk in stomach
		3	F	Euthanized moribund; No milk in stomach
			M	Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
	53	0	F	Ductus closed; Air in lungs; No milk in stomach
		2	F	Euthanized moribund; Cannibalized, unable to evaluate
				Euthanized moribund; Cannibalized, unable to evaluate
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				No milk in stomach
				No milk in stomach
				No milk in stomach

(continued)

US EPA ARCHIVE DOCUMENT

Table A-13. Individual F_1 Pup Gross Necropsy Findings for Postnatal Days 0 Through 21 (page 2 of 2)

Dose[a]	Female ID	Day[b]	Sex[c]	Gross Necropsy Finding
50	53		M	Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				No milk in stomach
				No milk in stomach
				No milk in stomach
				No milk in stomach
100	26	0	F	Ductus open; No air in lungs; No milk in stomach
	29	0	F	Ductus open; No air in lungs
				Ductus open; No air in lungs
			M	Ductus open; No air in lungs
				Ductus open; No air in lungs
		1	F	Euthanized moribund; No milk in stomach
				No milk in stomach
			M	Ductus open; No milk in stomach
				Ductus open; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
				Euthanized moribund; No milk in stomach
	44	7	F	Bedding in mouth; Abdominal organs too autolyzed to evaluate
	59	1	M	Abdominal organs too autolyzed to evaluate

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.
[c]Sex is F is female and M is male.

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Table A-14. Individual F_0 Female Hormone Data at Necropsy (page 1 of 2)

Dose[a]	Female ID	Thyroxine Hormone (ug/dL)	Thyroid Stimulating Hormone (ng/ml)
0	1	3.23	14.53
	8	4.32	9.54
	9	3.84	10.27
	16	5.00	22.21
	31	3.06	11.00
	32	2.50	12.59
	40	2.99	8.35
	42	5.01	16.73
	49	4.07	19.57
	50	4.29	13.31
	57	4.91	17.38
	58	4.49	12.05
25	2	4.25	10.22
	7	2.76	14.03
	10	1.73	8.89
	17	3.52	8.68
	25	3.38	14.73
	30	2.92	12.97
	38	4.37	15.52
	48	4.93	9.98
	51	5.09	14.35
50	4	2.03	12.79
	5	3.40	9.77
	12	2.56	9.69
	13	2.64	6.71
	19	4.05	22.79
	20	3.59	9.77
	27	4.63	12.64
	28	3.47	8.28
	35	5.54	15.61
	36	3.86	6.78
	46	3.91	6.67
	54	5.21	11.06
	60	4.82	11.18

(continued)

US EPA ARCHIVE DOCUMENT

Table A-14. Individual F_0 Female Hormone Data at Necropsy (page 2 of 2)

Dose[a]	Female ID	Thyroxine Hormone (ug/dL)	Thyroid Stimulating Hormone (ng/ml)
100	3	3.24	9.30
	11	4.50	18.87
	18	3.21	12.34
	21	2.67	11.08
	26	3.35	14.47
	37	4.30	20.81
	44	5.62	12.93
	55	3.52	8.24
	59	3.73	13.13

[a]Mg/kg/day of Methoxychlor.

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Table A-15. Individual F_0 Female Gross Necropsy Findings (page 1 of 1)

Dose[a]	Female ID	Finding
Scheduled Necropsy:		
0	1	Alopecia: multiple areas
25	2	Alopecia: limb(s)
	10	Alopecia: limb(s)
50	5	Alopecia: abdomen
	13	Alopecia: multiple areas
	28	Alopecia: chest
Unscheduled Necropsy - Gestation:		
100	14	Chromodacryorrhea: front paws, mouth and nose Uterus and Vagina: 7 pups in each horn and one in vagina
Unscheduled Necropsy - Lactation:		
100	29	Fur in anogenital area stained with old and fresh blood Rust colored fur: limb(s) and nose Uterus: 3 retained middle resorptions in right horn and 2 retained middle resorptions in left horn

[a]Mg/kg/day of Methoxychlor.

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Table A-16. Individual F_1 Uterotrophic Female Fate (page 1 of 1)

Dose[a]	Female ID	Fate
0	108	Scheduled Sacrifice on Postnatal Day 24
	117	Scheduled Sacrifice on Postnatal Day 24
	126	Scheduled Sacrifice on Postnatal Day 24
	199	Scheduled Sacrifice on Postnatal Day 24
	208	Scheduled Sacrifice on Postnatal Day 24
	217	Scheduled Sacrifice on Postnatal Day 24
	226	Removed from Study because Dam was Removed
	235	Scheduled Sacrifice on Postnatal Day 24
	359	Scheduled Sacrifice on Postnatal Day 24
	368	Scheduled Sacrifice on Postnatal Day 24
	377	Scheduled Sacrifice on Postnatal Day 24
	386	Scheduled Sacrifice on Postnatal Day 24
	493	Scheduled Sacrifice on Postnatal Day 24
25	149	Removed from Study because Dam was Removed
	244	Scheduled Sacrifice on Postnatal Day 24
	261	Scheduled Sacrifice on Postnatal Day 24
	270	Scheduled Sacrifice on Postnatal Day 24
	399	Scheduled Sacrifice on Postnatal Day 24
	408	Scheduled Sacrifice on Postnatal Day 24
	417	Scheduled Sacrifice on Postnatal Day 24
	426	Removed from Study because Dam was Removed
50	158	Scheduled Sacrifice on Postnatal Day 24
	181	Scheduled Sacrifice on Postnatal Day 24
	190	Scheduled Sacrifice on Postnatal Day 24
	324	Scheduled Sacrifice on Postnatal Day 24
	333	Scheduled Sacrifice on Postnatal Day 24
	350	Scheduled Sacrifice on Postnatal Day 24
	471	Scheduled Sacrifice on Postnatal Day 24
	480	Scheduled Sacrifice on Postnatal Day 24
100	279	Scheduled Sacrifice on Postnatal Day 24
	288	Scheduled Sacrifice on Postnatal Day 24
	295	Scheduled Sacrifice on Postnatal Day 24
	306	Scheduled Sacrifice on Postnatal Day 24
	315	Scheduled Sacrifice on Postnatal Day 24
	435	Scheduled Sacrifice on Postnatal Day 24
	442	Scheduled Sacrifice on Postnatal Day 24
	449	Removed from Study because Dam was Removed
	462	Scheduled Sacrifice on Postnatal Day 24
	502	Scheduled Sacrifice on Postnatal Day 24

[a]Mg/kg/day of Methoxychlor.

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Table A-17. Individual F_1 Uterotrophic Female Body Weights (g) During the Post Wean Holding Period (page 1 of 1)

Dose[a]	Female ID	Postnatal Day 21	22	23	24
0	108	51.27	51.92	57.95	61.45
	117	53.48	58.59	62.31	67.77
	126	52.92	57.97	62.14	66.10
	199	53.71	58.75	63.10	68.10
	208	60.83	67.41	74.02	80.30
	217	64.95	68.42	76.30	83.30
	235	50.40	63.25	69.18	75.00
	359	53.87	58.33	65.07	71.79
	368	57.74	58.04	60.50	66.22
	377	52.64	56.53	62.61	68.88
	386	52.61	55.25	58.56	65.69
	493	61.73	64.90	71.11	76.46
25	244	61.19	62.80	69.10	73.66
	261	48.92	49.36	54.33	60.06
	270	49.46	52.28	57.13	64.02
	399	61.24	64.51	71.84	77.55
	408	51.41	52.16	58.36	64.66
	417	48.86	51.75	56.76	63.77
50	158	48.01	50.83	55.19	60.67
	181	64.80	68.33	73.20	78.79
	190	47.53	50.81	55.98	63.51
	324	53.37	54.88	60.05	65.11
	333	52.49	55.75	60.42	66.95
	350	60.91	62.37	67.31	73.66
	471	56.83	59.77	65.77	72.50
	480	54.61	54.48	59.83	65.31
100	279	53.12	56.17	59.90	67.92
	288	53.01	56.69	60.58	65.66
	295	59.62	59.63	64.34	68.82
	306	44.55	43.45	46.04	51.12
	315	51.66	52.10	58.60	63.87
	435	52.77	54.56	58.15	64.88
	442	67.28	68.54	69.76	73.37
	462	56.32	56.76	60.80	67.21
	502	57.88	60.55	66.44	74.14

[a]Mg/kg/day of Methoxychlor.

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Table A-18. Individual F_1 Uterotrophic Female Clinical Observations During the Post Wean Holding Period (page 1 of 1)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	190	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
	324	21	Vaginal Opening: pin hole only
		22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
	333	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
	350	21	Vaginal Opening: pin hole only
		22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
	471	21	Vaginal Opening: pin hole only
		22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
	480	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
100	279	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
	315	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

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Table A-19. Individual F_1 Uterotrophic Female Necropsy Weights (g) and Hormone Data (page 1 of 1)

Dose[a]	Female ID	Sacrifice Weight	Paired Ovary Weight	Uterus Weight[b]	Estradiol Hormone (pg/ml)	Thyroxine Hormone (ug/dL)	Thyroid Stimulating Hormone (ng/ml)
0	108	63.21	0.0474	0.1379	38.39	2.93	5.71
	117	66.97	.[c]	0.0990	26.52	3.05	6.23
	126	67.19	0.0410	0.1734	27.74	3.56	5.12
	199	69.74	0.0313	0.1281	37.81	3.97	4.22
	208	80.14	0.0458	0.1117	35.03	3.37	5.28
	217	82.92	0.0452	0.1423	36.86	3.34	5.64
	235	75.49	0.0426	0.1218	24.81	4.01	4.76
	359	71.07	0.0368	0.1117	23.33	3.05	5.80
	368	67.12	0.0425	0.1259	28.06	3.74	5.73
	377	67.39	0.0412	0.1127	22.49	2.98	5.37
	386	.[d]	0.0430	0.0981	27.87	3.39	5.04
	493	76.63	0.0413	0.0693	28.92	2.01	4.51
25	244	72.59	0.0385	0.1312	28.33	3.39	6.94
	261	59.84	0.0398	0.1158	30.28	4.05	5.52
	270	62.94	0.0345	0.1241	36.12	2.63	8.48
	399	76.60	0.0433	0.0880	24.31	2.67	5.57
	408	66.15	0.0319	0.0862	38.55	3.83	7.02
	417	64.00	0.0371	0.0966	31.47	3.96	11.22
50	158	61.04	0.0310	0.1099	37.79	3.74	6.39
	181	76.76	0.0389	0.1509	29.64	4.62	5.86
	190	63.87	0.0318	0.0852	28.49	4.01	5.65
	324	66.36	0.0271	0.0911	30.25	3.30	5.26
	333	66.46	0.0280	0.0923	34.59	3.65	5.98
	350	72.99	0.0219	0.0853	30.36	3.47	6.19
	471	74.52	0.0271	0.1209	28.07	3.71	5.65
	480	65.33	0.0261	0.0810	25.96	3.47	6.53
100	279	67.03	0.0376	0.0952	36.86	3.15	7.13
	288	64.79	0.0461	0.1138	36.19	4.23	4.76
	295	68.69	0.0348	0.0821	27.18	3.62	6.01
	306	52.14	0.0299	0.0741	20.53	3.03	6.34
	315	63.78	0.0280	0.0733	32.14	3.03	8.86
	435	62.39	0.0308	0.1221	20.75	1.74	5.71
	442	75.09	0.0313	0.1085	27.50	2.50	5.70
	462	68.31	0.0264	0.1240	28.00	2.79	6.79
	502	73.93	0.0281	0.1064	25.47	2.89	5.23

[a]Mg/kg/day of Methoxychlor.
[b]Uterus with fluid weight.
[c]Paired ovary weight was a statistical outlier and therefore excluded.
[d]Sacrifice weight inadvertently not recorded prior to bleeding.

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Table A-20. Individual F_1 Uterotrophic Female Gross Necropsy Findings (page 1 of 1)

Dose[a]	Female ID	Finding
Scheduled Necropsy:		
0		No findings
25		No findings
50		No findings
100		No findings

[a]Mg/kg/day of Methoxychlor.

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Table A-21. Individual F_1 Undosed Pubertal Female Fate (page 1 of 3)

Dose[a]	Female ID	Fate
0	106	Scheduled Sacrifice on Postnatal Day 42
	107	Scheduled Sacrifice on Postnatal Day 42
	115	Scheduled Sacrifice on Postnatal Day 42
	116	Scheduled Sacrifice on Postnatal Day 42
	124	Scheduled Sacrifice on Postnatal Day 42
	125	Scheduled Sacrifice on Postnatal Day 42
	197	Scheduled Sacrifice on Postnatal Day 42
	198	Scheduled Sacrifice on Postnatal Day 42
	206	Scheduled Sacrifice on Postnatal Day 42
	207	Scheduled Sacrifice on Postnatal Day 42
	215	Scheduled Sacrifice on Postnatal Day 42
	216	Scheduled Sacrifice on Postnatal Day 42
	224	Removed from Study because Dam was Removed
	225	Removed from Study because Dam was Removed
	233	Scheduled Sacrifice on Postnatal Day 42
	234	Scheduled Sacrifice on Postnatal Day 42
	357	Scheduled Sacrifice on Postnatal Day 42
	358	Scheduled Sacrifice on Postnatal Day 42
	366	Scheduled Sacrifice on Postnatal Day 42
	367	Scheduled Sacrifice on Postnatal Day 42
	375	Scheduled Sacrifice on Postnatal Day 42
	376	Scheduled Sacrifice on Postnatal Day 42
	384	Scheduled Sacrifice on Postnatal Day 42
	385	Scheduled Sacrifice on Postnatal Day 42
	492	Scheduled Sacrifice on Postnatal Day 42
25	131	Scheduled Sacrifice on Postnatal Day 42
	132	Scheduled Sacrifice on Postnatal Day 42
	139	Scheduled Sacrifice on Postnatal Day 42
	140	Scheduled Sacrifice on Postnatal Day 42
	147	Removed from Study because Dam was Removed
	148	Removed from Study because Dam was Removed
	242	Scheduled Sacrifice on Postnatal Day 42
	243	Scheduled Sacrifice on Postnatal Day 42
	251	Scheduled Sacrifice on Postnatal Day 42
	252	Scheduled Sacrifice on Postnatal Day 42
	259	Scheduled Sacrifice on Postnatal Day 42
	260	Scheduled Sacrifice on Postnatal Day 42
	268	Scheduled Sacrifice on Postnatal Day 42
	269	Scheduled Sacrifice on Postnatal Day 42
	390	Removed from Study because Dam was Removed
	397	Scheduled Sacrifice on Postnatal Day 42
	398	Scheduled Sacrifice on Postnatal Day 42

(continued)

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Table A-21. Individual F_1 Undosed Pubertal Female Fate (page 2 of 3)

Dose[a]	Female ID	Fate
25	406	Scheduled Sacrifice on Postnatal Day 42
	407	Scheduled Sacrifice on Postnatal Day 42
	415	Scheduled Sacrifice on Postnatal Day 42
	416	Scheduled Sacrifice on Postnatal Day 42
	424	Removed from Study because Dam was Removed
	425	Removed from Study because Dam was Removed
50	156	Scheduled Sacrifice on Postnatal Day 42
	157	Scheduled Sacrifice on Postnatal Day 42
	165	Scheduled Sacrifice on Postnatal Day 42
	166	Scheduled Sacrifice on Postnatal Day 42
	173	Scheduled Sacrifice on Postnatal Day 42
	174	Scheduled Sacrifice on Postnatal Day 42
	180	Scheduled Sacrifice on Postnatal Day 42
	188	Scheduled Sacrifice on Postnatal Day 42
	189	Scheduled Sacrifice on Postnatal Day 42
	322	Scheduled Sacrifice on Postnatal Day 42
	323	Scheduled Sacrifice on Postnatal Day 42
	331	Scheduled Sacrifice on Postnatal Day 42
	332	Scheduled Sacrifice on Postnatal Day 42
	340	Scheduled Sacrifice on Postnatal Day 42
	341	Scheduled Sacrifice on Postnatal Day 42
	348	Scheduled Sacrifice on Postnatal Day 42
	349	Scheduled Sacrifice on Postnatal Day 42
	469	Scheduled Sacrifice on Postnatal Day 42
	470	Scheduled Sacrifice on Postnatal Day 42
	478	Scheduled Sacrifice on Postnatal Day 42
	479	Scheduled Sacrifice on Postnatal Day 42
	487	Scheduled Sacrifice on Postnatal Day 42
	488	Scheduled Sacrifice on Postnatal Day 42
100	277	Scheduled Sacrifice on Postnatal Day 42
	278	Scheduled Sacrifice on Postnatal Day 42
	286	Scheduled Sacrifice on Postnatal Day 42
	287	Scheduled Sacrifice on Postnatal Day 42
	294	Scheduled Sacrifice on Postnatal Day 42
	304	Scheduled Sacrifice on Postnatal Day 42
	305	Scheduled Sacrifice on Postnatal Day 42
	313	Scheduled Sacrifice on Postnatal Day 42
	314	Scheduled Sacrifice on Postnatal Day 42
	433	Scheduled Sacrifice on Postnatal Day 42
	434	Scheduled Sacrifice on Postnatal Day 42

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Table A-21. Individual F_1 Undosed Pubertal Female Fate (page 3 of 3)

Dose[a]	Female ID	Fate
100	441	Scheduled Sacrifice on Postnatal Day 42
	447	Removed from Study because Dam was Removed
	448	Removed from Study because Dam was Removed
	452	Removed from Study because Dam was Removed
	453	Removed from Study because Dam was Removed
	460	Scheduled Sacrifice on Postnatal Day 42
	461	Scheduled Sacrifice on Postnatal Day 42
	500	Scheduled Sacrifice on Postnatal Day 42
	501	Scheduled Sacrifice on Postnatal Day 42

[a]Mg/kg/day of Methoxychlor.

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Table A-22. Individual F_1 Undosed Pubertal Female Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 30 of the Post Wean Holding Period (page 1 of 2)

Dose[a]	Female ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30
0	106	8.83	44.30	46.03	57.21	67.63	76.84	88.72
	107	9.26	45.15	48.77	58.71	68.54	80.79	90.80
	115	10.63	55.42	60.04	72.94	83.34	96.36	109.24
	116	10.85	57.21	61.67	74.02	83.06	95.76	111.14
	124	11.22	52.60	56.14	65.67	74.58	85.08	96.01
	125	10.13	54.71	59.80	72.06	83.56	96.44	110.54
	197	7.53	50.30	56.42	66.85	75.47	91.40	98.67
	198	7.28	50.63	55.97	67.42	77.15	86.56	101.54
	206	10.16	57.56	61.81	72.57	87.33	98.75	113.75
	207	10.33	60.36	64.99	75.25	90.38	103.08	119.91
	215	8.87	61.80	66.67	77.67	88.16	101.33	113.57
	216	8.18	58.40	61.70	71.88	80.68	93.34	101.63
	233	10.16	57.05	62.14	71.42	81.41	92.78	105.30
	234	10.40	58.35	63.10	73.21	84.33	94.05	104.56
	357	11.23	59.12	65.59	75.88	89.05	103.15	118.52
	358	11.38	57.99	64.28	75.53	89.62	102.51	117.11
	366	11.88	58.90	63.56	76.71	89.31	103.03	118.33
	367	11.47	57.74	61.37	73.44	83.45	95.55	108.52
	375	11.59	59.91	64.61	75.73	86.47	96.49	112.49
	376	8.96	53.72	59.88	69.80	80.61	92.17	104.78
	384	10.52	52.15	57.49	68.98	81.29	91.51	104.65
	385	10.03	53.99	61.06	69.76	82.61	95.50	110.23
	492	9.97	55.92	61.58	74.12	85.75	99.73	114.58
25	131	10.32	51.88	55.03	64.75	76.18	88.49	99.59
	132	11.32	55.10	58.27	67.38	77.29	88.09	98.10
	139	12.36	61.22	64.38	79.11	93.55	108.97	123.82
	140	12.69	57.85	61.43	74.60	85.18	98.32	112.63
	242	10.66	65.78	69.80	82.49	93.68	108.37	121.15
	243	10.21	66.19	69.77	81.46	94.56	107.10	122.29
	251	11.66	61.19	67.66	80.49	93.57	105.97	121.81
	252	10.01	52.73	57.54	66.58	78.29	89.91	105.06
	259	8.52	45.11	49.86	61.96	75.76	87.30	100.29
	260	9.01	44.78	48.95	59.59	71.79	81.98	96.29
	268	8.11	50.60	56.12	67.65	78.28	91.76	104.68
	269	8.18	52.79	57.14	66.33	76.62	88.67	101.57
	397	11.01	59.12	64.82	76.83	86.52	97.28	112.27
	398	11.02	59.73	63.10	73.33	84.10	94.78	107.74
	406	9.55	52.80	58.79	70.84	82.49	94.28	109.23
	407	9.42	53.26	58.10	69.90	81.85	94.16	110.55
	415	8.18	48.03	50.01	58.93	69.13	77.41	92.09
	416	8.76	49.34	53.36	63.94	74.40	84.46	99.18

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Table A-22. Individual F_1 Undosed Pubertal Female Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 30 of the Post Wean Holding Period (page 2 of 2)

Dose[a]	Female ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30
50	156	12.58	53.83	56.80	69.27	80.40	94.64	109.60
	157	.[b]	51.04	55.38	68.83	81.60	97.08	111.92
	165	8.61	52.38	56.69	67.11	76.13	89.51	100.63
	166	8.69	53.77	56.79	68.03	80.27	92.67	106.37
	173	9.75	56.94	60.31	72.08	84.46	96.63	109.23
	174	12.25	55.35	57.41	69.97	81.33	91.74	104.30
	180	11.99	66.50	67.97	80.22	95.43	110.84	124.26
	188	11.07	52.57	56.34	69.21	80.36	95.49	109.02
	189	10.53	50.50	52.29	65.55	77.60	89.22	105.67
	322	10.42	54.53	56.54	66.34	78.71	90.07	105.39
	323	9.76	56.08	59.45	69.48	82.21	95.10	113.86
	331	9.27	59.96	64.49	79.55	95.02	110.17	125.90
	332	10.11	60.23	64.86	76.54	89.23	101.68	115.08
	340	8.84	55.59	60.08	71.40	80.93	92.37	106.01
	341	11.10	57.89	62.57	72.76	83.75	96.05	108.45
	348	9.88	58.72	63.56	71.64	82.41	93.65	107.95
	349	9.98	59.00	62.32	72.23	82.64	96.38	109.95
	469	8.23	59.35	64.77	77.43	89.93	104.27	123.93
	470	9.37	58.54	63.52	76.15	86.87	100.50	118.83
	478	9.90	58.03	62.80	73.50	84.20	93.43	108.92
	479	11.13	56.08	61.26	72.94	84.42	96.35	111.55
	487	9.37	57.00	60.70	73.16	86.17	99.53	117.08
	488	10.08	53.42	56.03	66.18	76.09	85.31	97.73
100	277	10.04	51.48	44.07	64.12	74.28	85.45	101.92
	278	9.18	50.75	53.80	63.22	74.10	85.57	100.60
	286	11.32	58.79	63.85	74.38	85.39	99.27	112.59
	287	9.34	54.54	59.02	71.15	82.75	97.06	110.67
	294	10.46	61.03	63.35	76.13	88.02	100.60	114.47
	304	8.19	46.47	48.61	57.04	64.62	73.72	85.46
	305	9.84	47.71	50.32	58.74	67.90	77.28	88.20
	313	9.23	46.88	51.15	63.08	76.72	90.10	105.93
	314	10.39	55.55	58.46	71.82	84.04	98.43	113.98
	433	9.22	55.70	61.99	74.40	86.32	96.73	112.21
	434	10.05	53.60	58.31	69.41	80.92	92.66	105.44
	441	10.24	57.40	62.16	72.23	82.52	91.77	108.32
	460	9.32	52.31	55.42	65.74	78.57	91.91	106.30
	461	8.71	51.06	52.53	63.90	76.65	87.72	104.58
	500	10.08	53.98	60.85	70.50	81.83	94.94	108.66
	501	.[b]	60.17	66.47	77.60	88.54	103.82	115.61

[a]Mg/kg/day of Methoxychlor.
[b]Anogenital distance inadvertently not recorded.

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Table A-23. Individual F_1 Undosed Pubertal Female Body Weights (g) on Postnatal Days 32 through 42 of the Post Wean Holding Period (page 1 of 2)

Dose[a]	Female ID	Postnatal Day 32	34	36	38	40	42
0	106	103.84	115.30	126.27	136.98	149.63	162.66
	107	103.78	114.44	125.06	139.43	152.56	163.47
	115	124.81	137.02	149.24	162.23	170.30	185.79
	116	122.14	137.92	150.10	162.06	172.23	188.56
	124	107.12	122.20	131.05	144.22	156.05	167.03
	125	123.85	138.77	155.03	171.99	185.21	198.50
	197	109.59	121.00	134.70	143.22	156.84	170.68
	198	115.68	127.95	141.50	154.73	162.24	180.06
	206	127.11	141.99	152.08	164.96	175.37	191.06
	207	133.75	146.92	159.55	174.57	185.53	203.34
	215	126.53	136.03	150.74	162.23	172.85	185.50
	216	116.15	127.64	139.42	150.85	158.59	173.83
	233	117.41	130.15	146.27	160.42	168.86	186.79
	234	117.66	131.61	145.84	154.90	163.74	176.75
	357	138.75	154.39	165.14	182.30	194.03	211.42
	358	132.13	148.69	165.72	177.72	191.97	209.02
	366	128.80	142.52	159.56	168.95	175.64	190.00
	367	118.75	129.90	143.42	150.66	160.66	166.37
	375	127.66	144.08	157.48	168.55	177.19	194.52
	376	119.68	133.18	146.03	163.18	174.27	188.30
	384	118.06	130.47	142.02	154.75	166.81	181.19
	385	122.93	135.39	150.74	160.54	176.27	182.86
	492	129.12	145.18	160.53	180.12	187.67	209.50
25	131	113.64	129.51	140.91	157.73	165.11	183.41
	132	111.21	122.95	132.71	147.68	152.10	164.90
	139	142.22	156.33	169.61	181.43	189.63	203.92
	140	127.44	139.18	150.39	160.48	171.85	172.38
	242	135.70	152.62	163.19	178.55	185.00	202.35
	243	136.80	150.24	162.08	180.97	190.11	207.55
	251	136.90	155.68	169.72	183.81	183.98	194.54
	252	120.40	132.32	141.43	152.31	163.06	168.41
	259	113.11	128.29	136.12	150.29	155.70	169.15
	260	111.10	125.32	135.68	149.03	160.63	172.54
	268	118.12	131.57	140.79	154.16	162.52	177.28
	269	114.79	127.78	138.74	151.04	164.11	177.86
	397	126.05	140.70	150.12	161.80	172.10	183.41
	398	122.17	136.90	148.26	161.14	170.61	182.89
	406	121.64	133.42	143.79	157.43	163.84	174.78
	407	123.97	139.77	155.22	169.05	179.31	194.15
	415	104.60	117.51	125.40	137.66	145.90	151.15
	416	115.18	126.97	140.44	152.71	161.96	171.50

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Table A-23. Individual F_1 Undosed Pubertal Female Body Weights (g) on Postnatal Days 32 through 42 of the Post Wean Holding Period (page 2 of 2)

Dose[a]	Female ID	Postnatal Day 32	34	36	38	40	42
50	156	125.88	138.03	150.55	166.38	176.65	195.50
	157	128.75	143.26	152.30	166.80	171.75	184.06
	165	115.65	126.51	140.48	154.62	163.95	176.17
	166	121.51	136.54	148.28	163.16	174.23	194.37
	173	125.75	139.43	153.88	168.46	181.08	197.08
	174	119.62	130.92	145.15	157.10	164.31	179.16
	180	143.43	161.78	177.31	194.76	210.52	229.60
	188	129.89	144.65	160.11	173.60	189.87	203.03
	189	122.48	140.91	156.63	169.48	180.92	192.65
	322	116.53	131.63	147.21	159.31	171.89	197.94
	323	126.61	143.22	158.28	167.13	181.74	183.79
	331	140.03	149.55	167.16	177.42	188.14	200.77
	332	127.34	140.34	151.37	166.83	174.86	182.71
	340	116.22	131.65	143.48	155.79	164.03	177.96
	341	121.69	137.14	151.27	164.62	176.92	191.83
	348	120.25	135.64	145.88	157.60	169.47	184.80
	349	123.14	138.40	150.78	163.22	175.68	186.79
	469	137.96	153.47	167.31	179.59	193.42	208.33
	470	133.09	147.64	158.62	170.08	180.29	194.22
	478	122.47	135.02	148.66	157.09	166.74	177.68
	479	124.57	138.66	148.92	158.07	169.45	181.77
	487	133.18	147.78	166.48	178.64	187.99	198.83
	488	111.98	125.56	138.23	151.52	160.02	171.89
100	277	113.13	124.32	138.82	149.82	160.46	171.60
	278	111.46	121.62	133.26	145.29	155.48	161.63
	286	124.81	140.87	148.87	161.07	169.82	175.27
	287	123.10	139.32	149.27	161.47	168.33	179.34
	294	130.79	144.52	153.88	165.17	174.23	185.39
	304	97.37	110.59	121.76	135.49	145.89	160.39
	305	99.63	111.30	122.87	135.39	147.74	162.42
	313	121.02	139.69	151.29	168.40	180.31	193.74
	314	128.09	145.62	157.14	167.84	179.38	190.87
	433	125.70	139.16	152.90	166.04	176.90	193.90
	434	121.47	136.90	151.24	165.13	181.40	197.46
	441	118.88	132.27	144.63	156.03	164.81	175.45
	460	120.46	136.13	151.59	161.10	175.59	190.14
	461	118.80	131.86	149.42	159.50	175.17	189.92
	500	121.58	134.31	148.05	157.92	166.50	176.91
	501	129.66	145.09	159.22	170.06	184.35	202.41

[a]Mg/kg/day of Methoxychlor.

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Table A-24. Individual F_1 Undosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 1 of 2)

Dose[a]	Female ID	Day[b]	Clinical Observations
0	198	34	Vaginal Opening: pin hole only
	206	31	Vaginal Opening: pin hole only
		32	Vaginal Opening: pin hole only
		33	Vaginal Opening: pin hole only
		34	Vaginal Opening: pin hole only
	375	31	Vaginal Opening: pin hole only
	492	31	Vaginal Opening: pin hole only
		38	Umbilical hernia
		39	Umbilical hernia
		40	Umbilical hernia
		41	Umbilical hernia
		42	Umbilical hernia
25	140	30	Vaginal Opening: pin hole only
	243	32	Chromodacryorrhea: eye, left
		33	Chromodacryorrhea: eye, left
		34	Chromodacryorrhea: eye, left, gone
	398	31	Vaginal Opening: pin hole only
	406	32	Vaginal Opening: vaginal thread
	416	31	Vaginal Opening: pin hole only
50	156	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	157	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	165	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	174	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	180	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	188	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	322	22	Vaginal Opening: pin hole only
	332	22	Vaginal Opening: pin hole only
100	277	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
	287	31	Vaginal Opening: pin hole only
		32	Vaginal Opening: pin hole only
		33	Vaginal Opening: pin hole only
		34	Vaginal Opening: pin hole only

(continued)

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Table A-24. Individual F_1 Undosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 2 of 2)

Dose[a]	Female ID	Day[b]	Clinical Observations
100	313	26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
	461	31	Vaginal Opening: pin hole only
		32	Vaginal Opening: pin hole only
	500	23	Vaginal Opening: pin hole only
	501	24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

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Table A-25. Individual F_1 Undosed Pubertal Female Vaginal Opening Data (page 1 of 2)

Dose[a]	Female ID	Day of Acquisition[b]	Body Weight (g)
0	106	33	109.59
	107	32	103.78
	115	31	114.86
	116	31	113.69
	124	32	107.12
	125	34	138.77
	197	36	134.70
	198	35	133.72
	206	35	149.23
	207	31	124.78
	215	30	113.57
	216	30	101.63
	233	33	125.39
	234	36	145.84
	357	30	118.52
	358	30	117.11
	366	32	128.80
	367	32	118.75
	375	32	127.66
	376	34	133.18
	384	35	143.66
	385	33	128.52
	492	32	129.12
25	131	33	122.41
	132	31	106.02
	139	31	133.07
	140	31	118.41
	242	32	135.70
	243	30	122.29
	251	26	93.57
	252	31	112.22
	259	31	105.98
	260	32	111.10
	268	31	111.65
	269	33	121.89
	397	31	120.61
	398	32	122.17
	406	33	132.88
	407	32	123.97
	415	32	104.60
	416	32	115.18

(continued)

US EPA ARCHIVE DOCUMENT

Table A-25. Individual F_1 Undosed Pubertal Female Vaginal Opening Data (page 2 of 2)

Dose[a]	Female ID	Day of Acquisition[b]	Body Weight (g)
50	156	24	69.27
	157	24	68.83
	165	24	67.11
	166	24	68.03
	173	32	125.75
	174	24	69.97
	180	24	80.22
	188	24	69.21
	189	24	65.55
	322	23	62.14
	323	23	62.74
	331	24	79.55
	332	23	70.52
	340	23	65.83
	341	23	67.09
	348	23	66.87
	349	23	65.90
	469	22	64.77
	470	22	63.52
	478	22	62.80
	479	22	61.26
	487	22	60.70
	488	22	56.03
100	277	24	64.12
	278	23	58.44
	286	30	112.59
	287	35	143.59
	294	31	122.23
	304	31	90.57
	305	32	99.63
	313	29	97.67
	314	30	113.98
	433	31	118.48
	434	29	101.10
	441	31	113.94
	460	31	110.10
	461	33	126.28
	500	24	70.50
	501	28	103.82

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

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Table A-26. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 1 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0	106	E	M	M	M	P	E	M	D	D	E											
	107	E	M	D	M	M	M	M	M	D	M	M										
	115	M	M	M	P	E	E/M	M	D	E	E	M	D									
	116	M	M	M	P	E	M	D	D	D	E	M	D									
	124	E	ND	M	D	E	E	M	M	D	E	M										
	125	E	E	M	D	M	D	M	P	E												
	197	E	M	D	E	D	P	M														
	198	D	E/M	M	E	M	D	M	D													
	206	E	E	M	M	D	E	E	M													
	207	E/M	M	D	P	E	E	M	D	P/E	E	E	M									
	215	M	D	M	D	E	M	M	D	P	E	M	M	M								
	216	E	M	D	M	P	E	D	M	P	E	M	M	D								
	233	E	M	M	D	D	M	D	P	NC	M											
	234	M	M	M	P	E	M	D														
	357	E	M	D	ND	D	E	E	M	M	M	D	E	E/M								
	358	E	M	M	M	D	D	P/E	E	M	M	D	D	E								
	366	E	D	D	M	P	E	M	M	D	E	M										
	367	E	M	D	M	P	E	M	D	D	P	E										
	375	M	M	D	E	E/M	M	M	D	E	M	D										
	376	E	E	M	M	M	D	NC	M	M												
	384	E/M	M	M	D	E	E	M	M													
	385	E	M	E	M	D	E	M	M	P	E											
	492	P	D	E	M	D	P	P	E	E	M	D										

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Table A-26. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 2 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
25	131	D	P/E	E	D	M	D	E	E	M	M											
	132	E	M	D	D	P	E	M	M	D	D	E	M									
	139	E	M	M	P	P/E	E	M	M	D	D	E	M									
	140	E	E	D	M	D	D	E	M	M	M/D	P	E									
	242	M	D	M	D	E	M	D	D	P	E	M										
	243	M	D	D	E	E	M	M	P	E	E	M	D	D								
	251	D	P	E	M	D	D	E	M	D	M	D	D	D	D	P/E	M	M				
	252	P/E	E	M	M	D	E	E	M	M	D	E	M									
	259	E	D	D	E	E	E	M	M	D	P	E	M									
	260	E	M	M	M	E	E/M	M	D	P	E	M										
	268	E	M	D	D	P	E	M	D	D	E	E	M									
	269	M	D	M	D	E	M	M	P	E	M											
	397	E	M	D	M	D	P	M	D	D	P	M	D									
	398	M	M	D	P	E	M	M	M	P	P	M										
	406	D	D	P	P	M	D	E	E	M/D	D											
	407	E	M	M	M	D	P	NC	NC	D	E	M										
	415	E	E	E	NC	M	D	NC	M	P	E	E										
	416	E	M	M	M	P	E	M	M	P	E	E										

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US EPA ARCHIVE DOCUMENT

Table A-26. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 3 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
50	156	M	M	D	D	D	D	P	E	E	E	E	E	E	M	M	M	D	E	E		
	157	M	M	D	D	P	E	E	M	M	D	E	E	D	E	M	E	E	E	E		
	165	M	M	M	M	M	D	D	M	E	E	M	M	M	P/E	E	E	M	M	D		
	166	M	M	M	P	NC	M	D	P	E	E	E	E	E	M	M	M	D	E	E		
	173	D	D	E	M	M	D	M	M	M	M	M										
	174	M	M	M	M	M	M	D	D	D	E	E	E	M	M	D	M	D	P	M		
	180	M	M	D	M	M	M	D	D	D	E	E	E	E	E	M	M	P/E	E	E		
	188	NC	M	D	D	D	D	M	P	P	E	E	E	E	E	E	E	E	E	E		
	189	M	M	D	D	D	D	D	D	D	E	E	M	M	D	E	E	M	E	D		
	322	M	NC	M	M	M	M	D	D	D	P/E	E	E	E	E	E	E/M	M	D	P		
	323	M	M	M	D	P	E	E	E	E	E	M	M	M	D	E	E	M	M	M	E	
	331	M	M	D	D	P	E	M	M	M	D	P/E	NC	M	M	D	M	M	M	M		
	332	M	M	M	M	D	D	P	E	NC	M	M	D	M	M	D	D	E	E	E	E	
	340	D	D	M	M	D	M	D	D	P	E	E	E	E	E	M	M	D/P	E	E	D	
	341	D	M	M	M	M	NC	D	D	D	P	E	E	M	M	D	P	E	E	M	P	
	348	M	M	M	M	NC	D	P	E	E	E	M	M	NC	D	E	E/M	M	D	E	NC	
	349	D	M	M	NC	NC	P	P	E	E	M	E	M	P	E	E	D	D	E	E	M	
	469	E/M	M	NC	M	M	D	M	M	P/E	E	E	M	D	D	E	E	E	E	E	E/M	D
	470	M	M	M	M	D	D	D	P	E	E	M	D	P	E	E	E	E	E	E	E	E
	478	M	M	D	M	D	D	D	P	E	E	E	E	E	E	E	E	E	E	E	E	E
	479	M	M	M	M	D	D	E	D	E	E	E	M	P	E	E	E	M	P	M	M	M
	487	M	M	M	M	M	M	D	E	E	E	E	E	D	M	P	E	E	E	D	E	E
	488	M	M	M	M	D	M	D	M	P	M	D	E	E	E	E	M	M	M	P	E	E

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US EPA ARCHIVE DOCUMENT

Table A-26. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 4 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
100	277	D	D	D	E	M/E	D	D	D/P	E	M	M	P/E	E	E/M	D	D	P/E	E/M	E		
	278	D	D	D	D	D	P	P	P/E	E	E	M	E	E	E	D	D	P	E	M		
	286	D/P	D	D	D/P	D	D/P	P	P	P/E	D	D	D	P								
	287	D/P	P/E	P/E	D	D	E	D	D													
	294	M/E	D	D	D	D	M/E	D	D	D/P	E	D/P	P									
	304	P/E	P	D	D	D	E/M	D	D	D/P	P/E	D	D									
	305	E	D	D	D	D	D	D	D	D	D	D										
	313	P	E	E	E	M	M	M	M	M	M	M	M	M	D							
	314	P/E	E	E	M	D	D	E	E	D	D	D	E	E								
	433	E	M	D	D	D	P	M	D	D	M	M	D									
	434	E	E	M	D	D	D	M	M	D	M	M	M	D	D							
	441	E	M	M	D	E	E	M	M	P	E	M	D									
	460	E	M	D	P	P	E	E/M	D	D	P	E	M									
	461	M	M	M	M	D	D	D	D	D	M											
	500	M	D	D	D	P	E	E	E	D	M	D	E	E	D	D	P	E	E	E		
	501	D	D	E	E	M	M	M	E	E	M	M	D	E	E	M						

[a]The first day of vaginal smears was the day the animal was found positive for vaginal opening and smear continued until the animal was sacrificed, found dead or euthanized moribund. Codes for the smear stages are P is proestrus; E is estrus; M is metestrus; D is diestrus; NC is no cells; ND is could not be determined; NP is smear not present. A "/" between each indicates that cells from both stages were present equally.
[b]Mg/kg/day of Methoxychlor.

US EPA ARCHIVE DOCUMENT

Table A-27. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 1 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
0	106	Yes	0	33	0	33	4	37	No	No
	107	No	0	32	.	.	.	.	No	No
	115	Yes	4	35	3	34	7	38	No	No
	116	Yes	4	35	3	34	8	39	No	No
	124	Yes	0	32	0	32	3	35	No	No
	125	Yes	0	34	0	34	7	41	No	No
	197	Yes	0	36	0	36	2	38	No	No
	198	No	1	36	.	.	.	.	No	No
	206	Yes	0	35	0	35	4	39	No	No
	207	Yes	0	31	0	31	3	34	No	No
	215	Yes	4	34	3	33	6	36	No	No
	216	Yes	0	30	0	30	4	34	No	No
	233	Yes	0	33	0	33	7	40	No	No
	234	Yes	4	40	3	39	6	42	No	No
	357	Yes	0	30	0	30	4	34	No	No
	358	Yes	0	30	0	30	6	36	No	No
	366	Yes	0	32	0	32	4	36	No	No
	367	Yes	0	32	0	32	4	36	No	No
	375	Yes	3	35	2	34	6	38	No	No
	376	No	0	34	.	.	.	.	No	No
	384	Yes	0	35	0	35	3	38	No	No
	385	Yes	0	33	2	35	4	37	No	No
	492	Yes	2	34	1	33	3	35	No	No

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Table A-27. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 2 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
25	131	Yes	1	34	0	33	2	35	No	No
	132	Yes	0	31	0	31	4	35	No	No
	139	Yes	0	31	0	31	3	34	No	No
	140	Yes	0	31	1	32	5	36	No	No
	242	Yes	4	36	2	34	4	36	No	No
	243	Yes	3	33	0	30	4	34	No	No
	251	Yes	2	28	0	26	3	29	No	Yes
	252	Yes	0	31	0	31	4	35	No	No
	259	Yes	0	31	5	36	9	40	Yes	No
	260	Yes	0	32	4	36	8	40	No	No
	268	Yes	0	31	0	31	4	35	No	No
	269	Yes	4	37	2	35	4	37	No	No
	397	Yes	0	31	0	31	5	36	No	No
	398	Yes	4	36	0	32	4	36	No	No
	406	Yes	6	39	4	37	7	40	No	No
	407	Yes	0	32	0	32	5	37	No	No
	415	Yes	0	32	2	34	8	40	Yes	No
	416	Yes	0	32	0	32	4	36	No	No

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US EPA ARCHIVE DOCUMENT

Table A-27. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 3 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
50	156	Yes	7	31	5	29	15	39	Yes	Yes
	157	Yes	5	29	0	24	6	30	Yes	No
	165	Yes	8	32	8	32	13	37	No	No
	166	Yes	8	32	5	29	12	36	Yes	No
	173	Yes	2	34	0	32	4	36	No	No
	174	Yes	9	33	5	29	11	35	Yes	No
	180	Yes	9	33	5	29	13	37	Yes	No
	188	No	9	33	.	.	.	.	Yes	Yes
	189	Yes	9	33	8	32	12	36	No	Yes
	322	Yes	9	32	8	31	16	39	Yes	No
	323	Yes	5	28	2	25	9	32	Yes	No
	331	Yes	5	29	0	24	5	29	No	No
	332	Yes	7	30	3	26	8	31	Yes	No
	340	Yes	9	32	5	28	13	36	Yes	No
	341	Yes	10	33	8	31	13	36	No	No
	348	Yes	7	30	5	28	12	35	Yes	No
	349	Yes	7	30	2	25	8	31	No	No
	469	Yes	0	22	8	30	13	35	Yes	No
	470	Yes	8	30	3	25	9	31	Yes	No
	478	No	8	30	.	.	.	.	Yes	No
	479	Yes	8	30	11	33	15	37	Yes	No
	487	Yes	7	29	5	27	11	33	Yes	No
	488	Yes	11	33	9	31	14	36	Yes	No

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US EPA ARCHIVE DOCUMENT

Table A-27. Individual F_1 Undosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 4 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
100	277	Yes	3	27	0	24	4	28	No	No
	278	Yes	7	30	13	36	16	39	Yes	Yes
	286	Yes	8	38	4	34	8	38	No	No
	287	Yes	1	36	0	35	3	38	No	No
	294	Yes	0	31	0	31	4	35	No	Yes
	304	Yes	0	31	5	36	9	40	No	No
	305	No	0	32	.	.	.	.	No	Yes
	313	Yes	1	30	0	29	13	42	Yes	No
	314	Yes	0	30	0	30	5	35	No	No
	433	Yes	0	31	0	31	5	36	No	No
	434	No	0	29	.	.	.	.	No	No
	441	Yes	0	31	0	31	3	34	No	No
	460	Yes	0	31	0	31	4	35	No	No
	461	No	.	.	.	.	.	.	No	Yes
	500	Yes	5	29	1	25	7	31	Yes	No
	501	Yes	2	30	0	28	6	34	No	No

[a]Mg/kg/day of Methoxychlor.

[b]Number of days since the animal was positive for vaginal opening.

[c]Age in postnatal days.

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Table A-28. Individual F_1 Undosed Pubertal Female Necropsy and Hormone Data (page 1 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
0	106	160.35	9.61	12	12	2.57	0.0100	0.0176	8.366[b]	0.0404	1.5906	0.0996	0.5507	0.5315	4.24	67.58	7.99
	107	161.28	11.23	12	12	1.84	0.0099	0.0202	9.0535	.[c]	1.8425	0.0787	0.2575	0.2458	5.56	90.47	10.97
	115	182.04	9.80	12	12	1.99	0.0111	0.0181	9.6368	0.0470	1.7990	0.1036	0.2835	0.2772	3.96	60.17	8.23
	116	183.72	12.56	12	12	3.01	0.0101	0.0244	9.4675	0.0429	1.8037	0.0925	0.2723	0.2595	3.50	68.47	5.75
	124	163.15	10.47	12	12	2.51	0.0080	0.0166	8.0027	0.0490	1.6122	0.0952	0.2762	0.2679	3.50	73.64	9.19
	125	195.71	11.17	12	12	2.20	0.0116	0.0170	9.3180	0.0508	1.8510	0.1186	0.3968	0.3830	4.66	70.55	6.84
	197	167.67	9.81	12	12	2.73	0.0100	0.0224	8.4086	0.0465	1.7071	0.0852	0.2405	0.1869	3.60	61.77	5.64
	198	175.44	11.38	12	12	2.51	0.0101	0.0199	8.7056	0.0506	1.7694	0.0949	0.3098	0.3058	5.79	65.00	5.17
	206	185.29	11.48	12	12	3.16	0.0125	0.0221	9.6510	0.0441	1.8322	0.1030	0.2613	0.2579	3.07	64.89	6.30
	207	195.82	13.10	12	12	2.23	0.0136	0.0246	11.1352	0.0527	2.1068	0.1347	0.2683	0.2572	3.24	76.71	7.31
	215	183.50	12.61	12	12	2.61	0.0105	0.0220	9.0903	0.0620	1.7439	0.0928	0.3805	0.3652	3.02	53.92	9.08
	216	169.66	12.01	12	12	1.63	0.0129	0.0199	9.0650	0.0478	1.7865	0.0943	0.3611	0.3197	2.69	58.25	10.43
	233	179.27	11.36	12	12	2.85	0.0132	0.0219	9.1785	0.0397	1.8508	0.1044	0.2546	0.2398	4.97	80.31	8.09
	234	168.46	12.59	12	12	2.64	0.0097	0.0176	8.2322	0.0434	1.7716	0.0613	0.2694	0.2531	3.71	79.37	5.10
	357	207.62	13.65	12	12	2.41	0.0122	0.0301	11.5169	0.0629	2.0936	0.1226	0.4049	0.3839	4.33	85.47	6.65
	358	201.14	14.68	12	12	3.57	0.0137	0.0203	10.9608	0.0603	2.0738	0.1396	0.4246	0.3977	3.37	102.94	5.51
	366	187.58	11.74	12	12	2.09	0.0125	0.0189	9.5889	0.0491	2.0365	0.1207	0.2611	0.2544	2.86	78.99	6.34
	367	166.60	11.00	12	12	2.82	.[c]	0.0253	8.5419	0.0473	1.7582	0.0762	0.3089	0.2959	4.31	95.48	6.41
	375	190.65	13.05	12	12	4.39	0.0217	0.0199	10.6398	0.0480	2.0115	0.1027	0.2872	0.2651	3.51	94.87	9.57
	376	183.78	12.75	12	12	3.53	0.0109	0.0182	9.7758	0.0486	1.9399	0.1023	0.2615	0.2352	4.28	83.21	7.73
	384	176.69	13.09	12	12	3.11	0.0079	0.0254	9.6810	0.0424	1.7936	0.0898	0.2088	0.1984	4.84	78.12	6.63
	385	181.22	12.97	12	12	3.47	0.0132	0.0190	9.0933	0.0526	1.9728	0.1051	0.3095	0.2966	5.14	86.06	8.81
	492	205.96	12.44	12	12	1.67	0.0114	0.0238	12.8804	0.0660	2.2766	0.1104	0.3471	0.3381	2.13	74.97	6.18

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Table A-28. Individual F_1 Undosed Pubertal Female Necropsy and Hormone Data (page 2 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
25	131	179.39	9.56	12	12	1.89	0.0194	0.0255	9.9251	0.032[b]	2.0140	0.0813	0.3058	0.2820	3.37	72.04	6.38
	132	162.21	11.07	12	12	2.05	0.0109	0.0177	8.6405	0.0425	1.6464	0.0887	0.2625	0.2459	3.66	58.25	7.17
	139	202.50	11.30	12	12	2.30	0.0120	0.0213	11.3254	0.0424	1.9377	0.1115	0.2977	0.2785	2.88	64.01	6.45
	140	173.71	12.23	12	12	2.87	0.0114	0.0199	9.4992	0.0551	1.8316	0.1046	0.3296	0.3207	2.90	70.22	8.87
	242	197.26	12.56	12	12	2.60	0.0108	0.0185	11.2077	0.0563	1.9905	0.1148	0.3363	0.3174	3.37	65.79	5.56
	243	201.89	12.16	12	12	2.40	0.0131	0.0216	11.7166	0.0477	1.9011	0.0777	0.4049	0.3952	3.11	84.35	9.85
	251	195.63	11.96	12	12	2.44	0.0133	0.0321	10.2188	0.0486	2.1454	0.1163	0.3218	0.3161	5.11	72.23	5.79
	252	170.83	11.98	12	12	2.47	0.0110	0.0210	8.2795	0.0459	1.6795	0.0880	0.2536	0.2496	2.49	50.13	5.68
	259	168.77	11.35	12	12	2.60	0.0107	0.0195	9.0596	0.0288	1.7039	0.0855	0.2476	0.2414	3.04	58.13	9.66
	260	169.86	10.50	12	12	2.50	0.0119	0.0223	9.7017	0.0500	1.8003	0.1195	0.2815	0.2729	3.82	95.65	6.13
	268	168.79	13.11	12	12	1.75	0.0132	0.0148	8.3444	0.0562	1.6889	0.0968	0.2932	0.2848	3.32	85.07	6.85
	269	170.13	12.20	12	12	2.21	0.0142	0.0198	8.9401	0.0512	1.6806	0.1123	0.3298	0.2909	4.07	63.46	10.37
	397	181.92	11.35	12	12	2.50	0.0096	0.0187	10.2396	0.0450	1.6886	0.0997	0.2661	0.2474	3.02	91.61	6.38
	398	181.66	12.05	12	12	2.25	0.0111	0.0211	10.4277	0.0444	1.8506	0.1111	0.3030	0.2938	3.10	86.54	9.86
	406	174.72	10.51	12	12	3.20	.[c]	0.0291	9.6046	0.0440	1.7212	0.0957	0.2719	0.2641	3.20	88.32	9.22
	407	193.17	11.82	12	12	1.84	0.0099	0.0209	11.0704	0.0561	1.9214	0.1158	0.2632	0.2569	3.01	70.16	9.41
	415	150.78	11.24	12	12	2.31	0.0101	0.0229	6.8874	0.0478	1.7044	0.0991	0.3283	0.3236	3.94	92.00	11.36
	416	169.74	11.19	12	12	2.61	0.0120	0.0261	8.3300	0.0473	1.6313	0.1069	0.4079	0.4009	3.94	81.47	11.47

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Table A-28. Individual F_1 Undosed Pubertal Female Necropsy and Hormone Data (page 3 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
50	156	194.34	10.90	12	12	2.12	0.0112	0.0282	11.0797	0.0490	1.9687	0.0505	0.6946	0.5297	5.70	97.13	12.17
	157	180.27	10.52	12	12	2.04	0.0144	0.0292	10.2509	0.0516	2.0448	0.0542	0.3945	0.3776	4.94	95.76	10.67
	165	174.96	12.39	12	12	1.90	0.0113	0.0230	9.9253	0.0469	1.8054	0.0706	0.3493	0.3316	5.92	71.40	11.33
	166	189.54	10.83	12	12	2.55	0.0103	0.0229	10.7739	0.0490	1.9090	0.0547	0.4047	0.3579	5.65	72.50	8.70
	173	192.23	12.56	12	12	2.51	0.0114	0.0192	10.2471	0.0501	1.9334	0.0648	0.2612	0.2508	5.62	91.20	7.83
	174	174.07	10.89	12	12	2.28	0.0104	0.0183	9.1340	0.0459	1.9060	0.0784	0.3024	0.2900	6.10	89.57	9.52
	180	222.05	13.02	12	12	1.92	0.0153	0.0288	10.5311	0.0519	2.4337	0.0708	0.8686	0.4516	6.89	87.52	17.31
	188	199.34	11.79	12	12	1.60	0.0121	0.0266	11.7235	0.0561	2.3450	0.0708	0.4152	0.4128	5.29	81.46	9.74
	189	191.04	12.94	12	12	2.45	0.0121	0.0283	9.2148	0.0432	1.9575	0.0873	0.4282	0.3790	5.28	80.17	8.76
	322	183.59	11.16	12	12	1.91	0.0124	0.0227	10.2224	0.0496	1.8626	0.0695	0.4894	0.4613	4.45	80.03	7.11
	323	194.79	11.80	12	12	1.99	0.0084	0.0227	10.1843	0.0484	2.0356	0.1110	0.4877	0.4750	4.85	61.80	11.05
	331	199.61	11.01	12	12	1.94	0.0123	0.0252	10.1055	0.0494	2.0084	0.1114	0.3504	0.3359	5.06	81.00	9.98
	332	183.88	11.43	12	12	1.30	0.0120	0.0199	8.7644	0.0442	1.8908	0.0584	0.3732	0.3675	3.31	63.33	11.90
	340	173.83	10.26	12	12	1.91	0.0154	0.0224	9.8300	0.0388	1.7379	0.0865	0.2680	0.2550	3.97	59.42	13.96
	341	188.43	12.65	12	12	2.55	0.0139	0.0326	9.6619	0.0427	1.6545	0.0876	0.5920	0.4155	3.63	66.23	15.91
	348	180.80	10.42	12	12	2.02	0.0130	0.0272	9.2969	0.0560	2.1324	0.0965	0.3767	0.3574	4.56	102.49	7.53
	349	182.69	12.19	12	12	2.77	0.0143	0.0268	9.9966	0.0440	2.1980	0.0931	0.3155	0.3088	4.22	86.15	9.03
	469	209.30	13.87	12	12	2.33	0.0120	0.0259	11.5000	0.0435	1.9433	0.0739	0.3563	0.3521	4.35	96.45	8.11
	470	193.18	12.74	12	12	2.55	0.0175	0.0253	9.8321	0.0561	2.1256	0.0819	0.4076	0.3924	3.28	90.13	11.81
	478	175.52	12.31	12	12	2.56	0.0125	0.0185	8.8635	0.0490	1.6529	0.0586	0.3913	0.3714	3.05	69.68	9.24
	479	176.85	12.05	12	12	2.74	0.0093	0.0233	9.6049	0.0424	1.6388	0.0859	0.2570	0.1646	6.11	113.65	6.30
	487	199.07	12.98	12	12	1.84	0.0121	0.0096	11.9934	0.0627	2.1916	0.0726	0.5793	0.4554	3.97	98.18	13.20
	488	169.33	13.71	12	12	2.15	0.0110	0.0283	9.2121	0.0562	1.6607	0.0629	0.3424	0.2953	4.57	111.04	10.24

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Table A-28. Individual F_1 Undosed Pubertal Female Necropsy and Hormone Data (page 4 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
100	277	169.35	10.68	12	12	2.76	0.0125	0.0166	9.0307	.[c]	1.9247	0.0646	0.4278	0.2916	3.86	83.89	9.67
	278	160.02	11.68	12	12	2.21	0.0102	0.0215	8.1125	0.0461	1.7052	0.0592	0.3370	0.3315	5.04	66.83	15.11
	286	175.26	10.96	12	12	2.21	0.0102	0.0256	9.4084	0.0418	1.6273	0.1402	0.3901	0.3802	4.70	97.29	6.82
	287	178.60	11.23	12	12	1.87	.[c]	0.0222	10.1320	0.055[b]	1.8019	0.1479	0.4000	0.3756	2.84	52.06	6.98
	294	182.20	11.99	12	12	1.54	0.0135	0.0231	9.6808	0.0472	1.7819	0.1051	0.3342	0.3096	4.63	92.51	9.20
	304	157.24	10.29	12	12	2.13	0.0147	0.0235	8.6986	0.0352	1.5842	0.0960	0.3050	0.2872	4.88	73.28	12.33
	305	158.44	11.92	12	12	1.92	0.0102	0.0161	7.9442	0.0359	1.7501	0.0739	0.2398	0.2373	4.45	90.99	8.00
	313	188.76	12.33	12	12	2.21	0.0124	0.0186	9.6622	0.0481	2.1101	0.1056	0.6776	0.4715	4.80	100.07	16.83
	314	188.63	12.98	12	12	1.84	0.0138	0.0270	9.8593	0.0598	2.0541	0.0869	0.3772	0.3589	4.63	101.28	8.41
	433	192.10	10.97	12	12	2.61	0.0139	0.0193	11.0128	0.0476	2.0126	0.1023	0.7329	0.5798	3.08	87.97	6.79
	434	193.97	12.42	12	12	2.42	0.0190	0.0215	11.6215	0.0575	1.9551	0.1079	0.4138	0.4036	4.20	93.84	4.57
	441	174.20	11.32	12	12	3.09	0.0088	0.0246	9.2734	0.0404	1.9058	0.0820	0.2169	0.2080	3.24	95.96	7.15
	460	184.34	12.59	12	12	2.67	0.0071	0.0176	10.4257	0.0402	1.9107	0.1206	0.2370	0.2296	3.96	81.37	10.34
	461	184.81	12.88	12	12	2.32	0.0139	0.0209	9.9784	0.0364	1.9092	0.0766	0.3057	0.2810	4.12	95.01	8.83
	500	172.32	12.63	12	12	1.90	0.0132	0.0181	9.5598	0.0605	1.8076	0.0838	0.3515	0.3404	2.73	69.76	9.59
	501	195.30	12.74	12	12	3.05	0.0128	0.0234	10.4369	0.0617	2.1987	0.1045	0.3172	0.3098	2.88	69.00	6.34

[a]Mg/kg/day of Methoxychlor.
[b]Weight inadvertently recorded to only 3 decimal places.
[c]Weight was a statistical outlier and therefore excluded.

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Table A-29. Individual F_1 Undosed Pubertal Female Gross Necropsy Findings (page 1 of 1)

Dose[a]	Female ID	Finding
Scheduled Necropsy:		
0	358	Thymus: enlarged
	492	3 x 3 mm hole in abdominal muscle at umbilicus, no protrusion of visera
25	131	Kidney: hydronephrosis, right
	132	Kidney: hydronephrosis, right
50	156	Kidney: hydronephrosis, bilateral
	166	Uterus: fluid present
	180	Uterus: fluid filled, bilateral
	189	Uterus: fluid filled, bilateral
	322	Uterus: fluid filled
	341	Uterus: fluid filled, bilateral
	487	Uterus: fluid filled, bilateral
100	277	Uterus: fluid present, bilateral
	294	Kidney: hydronephrosis, right
	313	Uterus: fluid filled
	433	Uterus: fluid filled, bilateral

[a]Mg/kg/day of Methoxychlor.

US EPA ARCHIVE DOCUMENT

Table A-30. Individual F_1 Dosed Pubertal Female Fate (page 1 of 3)

Dose[a]	Female ID	Fate
0	104	Scheduled Sacrifice on Postnatal Day 42
	105	Scheduled Sacrifice on Postnatal Day 42
	113	Scheduled Sacrifice on Postnatal Day 42
	114	Scheduled Sacrifice on Postnatal Day 42
	122	Scheduled Sacrifice on Postnatal Day 42
	123	Scheduled Sacrifice on Postnatal Day 42
	195	Scheduled Sacrifice on Postnatal Day 42
	196	Scheduled Sacrifice on Postnatal Day 42
	204	Scheduled Sacrifice on Postnatal Day 42
	205	Scheduled Sacrifice on Postnatal Day 42
	213	Scheduled Sacrifice on Postnatal Day 42
	214	Scheduled Sacrifice on Postnatal Day 42
	222	Removed from Study because Dam was Removed
	223	Removed from Study because Dam was Removed
	231	Scheduled Sacrifice on Postnatal Day 42
	232	Scheduled Sacrifice on Postnatal Day 42
	355	Scheduled Sacrifice on Postnatal Day 42
	356	Scheduled Sacrifice on Postnatal Day 42
	364	Scheduled Sacrifice on Postnatal Day 42
	365	Scheduled Sacrifice on Postnatal Day 42
	373	Scheduled Sacrifice on Postnatal Day 42
	374	Scheduled Sacrifice on Postnatal Day 42
	382	Scheduled Sacrifice on Postnatal Day 42
	383	Scheduled Sacrifice on Postnatal Day 42
	491	Scheduled Sacrifice on Postnatal Day 42
25	129	Scheduled Sacrifice on Postnatal Day 42
	130	Scheduled Sacrifice on Postnatal Day 42
	137	Scheduled Sacrifice on Postnatal Day 42
	138	Scheduled Sacrifice on Postnatal Day 42
	145	Removed from Study because Dam was Removed
	146	Removed from Study because Dam was Removed
	240	Scheduled Sacrifice on Postnatal Day 42
	241	Scheduled Sacrifice on Postnatal Day 42
	249	Scheduled Sacrifice on Postnatal Day 42
	250	Scheduled Sacrifice on Postnatal Day 42
	257	Scheduled Sacrifice on Postnatal Day 42
	258	Scheduled Sacrifice on Postnatal Day 42
	266	Scheduled Sacrifice on Postnatal Day 42
	267	Scheduled Sacrifice on Postnatal Day 42
	389	Removed from Study because Dam was Removed
	395	Scheduled Sacrifice on Postnatal Day 42
	396	Scheduled Sacrifice on Postnatal Day 42

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Table A-30. Individual F_1 Dosed Pubertal Female Fate (page 2 of 3)

Dose[a]	Female ID	Fate
25	404	Scheduled Sacrifice on Postnatal Day 42
	405	Scheduled Sacrifice on Postnatal Day 42
	413	Scheduled Sacrifice on Postnatal Day 42
	414	Scheduled Sacrifice on Postnatal Day 42
	422	Removed from Study because Dam was Removed
	423	Removed from Study because Dam was Removed
50	154	Scheduled Sacrifice on Postnatal Day 42
	155	Scheduled Sacrifice on Postnatal Day 42
	163	Scheduled Sacrifice on Postnatal Day 42
	164	Scheduled Sacrifice on Postnatal Day 42
	171	Scheduled Sacrifice on Postnatal Day 42
	172	Scheduled Sacrifice on Postnatal Day 42
	179	Scheduled Sacrifice on Postnatal Day 42
	186	Scheduled Sacrifice on Postnatal Day 42
	187	Scheduled Sacrifice on Postnatal Day 42
	320	Scheduled Sacrifice on Postnatal Day 42
	321	Scheduled Sacrifice on Postnatal Day 42
	329[b]	Post Wean Holding Period
	330	Scheduled Sacrifice on Postnatal Day 42
	338	Scheduled Sacrifice on Postnatal Day 42
	339	Scheduled Sacrifice on Postnatal Day 42
	346	Scheduled Sacrifice on Postnatal Day 42
	347	Scheduled Sacrifice on Postnatal Day 42
	467	Scheduled Sacrifice on Postnatal Day 42
	468	Scheduled Sacrifice on Postnatal Day 42
	476	Scheduled Sacrifice on Postnatal Day 42
	477	Scheduled Sacrifice on Postnatal Day 42
	485	Scheduled Sacrifice on Postnatal Day 42
	486	Scheduled Sacrifice on Postnatal Day 42
100	275	Scheduled Sacrifice on Postnatal Day 42
	276	Scheduled Sacrifice on Postnatal Day 42
	284	Scheduled Sacrifice on Postnatal Day 42
	285	Scheduled Sacrifice on Postnatal Day 42
	293	Scheduled Sacrifice on Postnatal Day 42
	302	Scheduled Sacrifice on Postnatal Day 42
	303	Scheduled Sacrifice on Postnatal Day 42
	311	Scheduled Sacrifice on Postnatal Day 42
	312	Scheduled Sacrifice on Postnatal Day 42
	431	Scheduled Sacrifice on Postnatal Day 42
	432	Scheduled Sacrifice on Postnatal Day 42

(continued)

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Table A-30. Individual F_1 Dosed Pubertal Female Fate (page 3 of 3)

Dose[a]	Female ID	Fate
100	440	Scheduled Sacrifice on Postnatal Day 42
	445	Removed from Study because Dam was Removed
	446	Removed from Study because Dam was Removed
	450	Removed from Study because Dam was Removed
	451	Removed from Study because Dam was Removed
	458	Scheduled Sacrifice on Postnatal Day 42
	459	Scheduled Sacrifice on Postnatal Day 42
	498	Scheduled Sacrifice on Postnatal Day 42
	499	Scheduled Sacrifice on Postnatal Day 42

[a]Mg/kg/day of Methoxychlor.
[b]Female was found dead on postnatal day 34 after dosing (misdirected dose).

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Table A-31. Individual F_1 Dosed Pubertal Female Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 30 of the Post Wean Holding Period (page 1 of 2)

Dose[a]	Female ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30
0	104	9.41	50.60	53.47	64.10	76.55	87.20	101.22
	105	10.65	50.47	53.65	63.38	75.10	86.28	99.53
	113	10.38	54.06	58.15	70.35	78.50	91.19	102.60
	114	11.02	57.80	63.97	78.12	88.04	100.88	115.20
	122	11.08	55.89	58.62	69.27	78.11	90.73	100.87
	123	9.23	47.62	51.37	59.95	69.60	78.54	89.45
	195	8.06	52.72	57.76	68.86	76.60	87.05	96.68
	196	9.20	54.17	59.11	69.50	78.45	89.11	99.27
	204	.[b]	58.51	63.19	76.32	87.68	103.01	116.92
	205	6.71	56.96	62.24	74.72	85.90	99.36	111.97
	213	8.72	56.25	60.86	71.15	80.38	92.88	106.36
	214	10.74	60.23	64.64	76.11	84.60	96.48	105.67
	231	10.49	55.50	60.16	67.15	78.38	87.60	98.56
	232	9.52	51.05	54.79	64.17	72.79	82.42	93.58
	355	10.18	56.93	60.22	70.57	81.10	91.76	103.24
	356	11.55	60.33	64.65	76.04	87.81	100.33	113.19
	364	10.63	57.08	61.20	71.22	80.28	93.08	103.03
	365	10.06	59.46	63.01	73.15	84.21	97.37	110.92
	373	10.75	59.29	61.83	74.17	84.37	96.18	109.35
	374	11.58	55.74	60.21	73.41	84.31	96.50	109.38
	382	11.36	55.92	60.85	71.20	80.10	91.77	106.22
	383	10.41	56.65	58.62	72.29	84.30	99.14	112.29
	491	10.85	60.80	61.34	71.70	82.23	94.94	103.67
25	129	9.23	56.61	59.22	68.84	79.14	89.74	96.89
	130	10.99	54.45	57.44	69.17	81.80	93.77	108.58
	137	11.18	58.05	60.68	71.86	84.88	99.33	112.10
	138	10.46	60.03	62.58	75.06	86.02	99.00	110.89
	240	11.30	66.50	70.93	81.89	92.03	107.72	119.65
	241	10.15	66.62	70.86	82.89	93.25	104.75	119.78
	249	11.40	64.96	71.75	85.13	98.55	110.38	127.29
	250	10.17	59.44	63.54	73.10	83.35	92.87	105.28
	257	9.24	49.81	54.54	63.90	74.99	86.27	97.82
	258	8.75	43.34	48.28	58.16	66.50	77.69	88.47
	266	10.61	49.81	53.41	67.30	78.23	90.25	102.46
	267	9.47	48.24	52.53	62.62	71.50	81.44	95.45
	395	10.63	59.20	64.80	76.07	88.24	101.05	114.47
	396	11.14	64.21	68.65	82.78	95.54	109.66	124.62
	404	11.53	51.48	55.26	68.49	78.51	92.19	105.46
	405	10.04	51.51	56.53	69.20	81.83	97.36	110.99
	413	9.97	47.91	50.77	61.75	71.76	81.34	91.75
	414	8.53	38.78	41.48	51.15	60.50	68.90	79.58

(continued)

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Table A-31. Individual F_1 Dosed Pubertal Female Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 30 of the Post Wean Holding Period (page 2 of 2)

Dose[a]	Female ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30
50	154	11.40	54.26	57.31	69.29	79.19	91.58	105.50
	155	10.76	50.02	52.99	64.60	74.51	85.70	98.47
	163	10.05	56.67	59.15	72.02	83.46	96.82	110.28
	164	9.13	56.85	58.52	70.60	81.79	93.59	104.79
	171	10.42	55.33	57.03	66.08	76.94	90.33	105.31
	172	10.60	51.61	52.53	62.59	73.93	85.28	97.90
	179	10.42	70.17	73.87	87.62	101.06	116.52	133.38
	186	11.27	48.96	49.83	62.40	71.96	83.10	98.24
	187	11.60	49.10	51.61	64.05	74.07	86.03	101.96
	320	8.62	54.28	55.80	66.83	76.03	86.79	98.18
	321	10.67	59.01	61.21	73.20	82.90	95.14	108.53
	329	9.23	57.37	62.49	71.83	82.35	93.85	107.54
	330	10.45	57.15	61.70	70.99	78.53	88.86	100.10
	338	12.03	55.63	58.16	68.61	79.78	92.05	106.61
	339	8.96	51.87	55.83	63.66	74.31	84.60	97.46
	346	11.06	55.15	59.14	67.02	77.89	88.56	100.43
	347	11.45	55.76	61.96	73.74	86.26	101.75	114.71
	467	10.30	61.34	64.66	78.13	89.91	101.95	118.20
	468	8.38	57.56	61.16	74.96	85.55	97.30	109.20
	476	10.13	53.76	59.04	69.73	81.46	93.79	106.34
	477	11.85	52.38	56.61	65.17	75.10	86.71	100.11
	485	9.75	56.80	60.15	72.26	80.90	97.29	109.87
	486	9.36	55.52	56.36	69.51	78.62	90.39	101.50
100	275	9.20	53.36	56.64	64.90	75.21	82.60	92.41
	276	7.63	50.87	54.42	64.48	74.35	82.20	92.15
	284	9.99	49.28	51.42	58.66	68.46	77.06	88.51
	285	10.89	50.32	55.27	62.57	73.38	79.88	91.91
	293	11.52	62.50	65.66	75.95	85.93	96.09	108.60
	302	11.15	50.57	54.24	63.16	70.75	80.14	89.91
	303	9.04	47.41	50.84	58.67	71.40	77.36	87.74
	311	10.39	50.46	53.11	64.44	76.76	85.13	98.82
	312	9.67	49.68	53.18	62.66	74.25	83.93	96.43
	431	11.38	49.76	53.70	70.73	71.44	81.55	92.50
	432	10.08	53.75	59.79	62.66	80.16	92.23	104.28
	440	9.84	62.01	64.97	70.19	79.53	90.30	99.98
	458	10.25	51.93	53.59	64.11	72.62	80.85	94.06
	459	9.40	55.34	55.95	66.50	72.05	79.65	90.39
	498	.[b]	59.49	65.80	72.10	80.69	87.73	101.09
	499	10.33	55.34	59.56	67.56	77.15	87.71	101.75

[a]Mg/kg/day of Methoxychlor.
[b]Anogenital distance inadvertently not recorded.

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Table A-32. Individual F_1 Dosed Pubertal Female Body Weights (g) on Postnatal Days 32 through 42 of the Post Wean Holding Period (page 1 of 2)

		Postnatal Day					
Dose[a]	Female ID	32	34	36	38	40	42
0	104	113.07	129.07	144.44	155.03	165.24	170.31
	105	110.66	125.11	139.09	149.88	158.94	174.56
	113	114.72	127.50	137.29	147.84	158.66	165.53
	114	128.84	142.30	153.04	165.70	172.62	182.02
	122	112.27	125.92	139.23	147.86	164.34	164.16
	123	97.77	106.21	117.38	127.56	139.13	151.91
	195	113.33	118.30	131.34	144.70	159.10	171.05
	196	108.47	126.17	141.18	151.13	165.45	174.11
	204	130.11	143.60	157.96	172.21	182.27	182.12
	205	123.26	140.56	153.93	167.31	178.98	185.43
	213	123.14	134.47	152.02	167.83	185.53	198.27
	214	119.05	127.68	138.74	155.31	157.02	170.60
	231	109.65	122.42	132.41	143.58	150.53	164.98
	232	105.51	118.12	129.17	137.40	147.91	157.79
	355	117.89	129.65	142.70	158.41	168.77	184.92
	356	128.25	141.10	156.72	166.87	178.50	183.11
	364	115.02	129.09	140.22	153.09	161.12	166.59
	365	124.37	139.72	149.77	163.77	174.80	179.60
	373	124.25	139.00	152.32	169.43	173.54	187.58
	374	123.49	134.75	146.90	160.97	174.92	181.34
	382	120.59	138.76	153.45	171.23	185.23	194.23
	383	130.18	147.23	162.98	183.84	200.03	211.41
	491	117.33	133.71	144.50	162.48	171.07	182.21
25	129	107.79	115.13	125.51	169.11	143.08	150.61
	130	120.69	136.79	151.19	133.89	174.04	182.97
	137	125.04	136.59	146.75	158.55	167.68	178.20
	138	125.92	139.05	150.76	159.67	173.73	181.90
	240	132.14	147.01	164.65	180.74	189.11	193.94
	241	131.45	145.88	158.73	164.55	176.36	178.06
	249	143.58	153.94	166.50	167.71	191.03	202.81
	250	117.58	130.21	145.15	153.78	160.32	170.72
	257	110.54	125.07	137.87	148.35	154.33	158.59
	258	100.63	112.84	122.17	132.94	131.23	147.38
	266	117.88	131.38	145.53	157.20	168.72	176.00
	267	107.63	120.81	133.16	142.87	151.88	157.54
	395	128.75	141.05	152.04	167.00	176.32	182.03
	396	143.02	162.13	172.46	189.59	200.14	196.50
	404	121.58	139.13	146.46	165.72	173.60	174.90
	405	128.53	144.51	154.25	173.25	185.99	198.70
	413	104.46	117.19	128.10	139.26	149.19	155.08
	414	92.09	105.52	115.53	130.46	140.37	149.74

(continued)

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Table A-32. Individual F_1 Dosed Pubertal Female Body Weights (g) on Postnatal Days 32 through 42 of the Post Wean Holding Period (page 2 of 2)

		Postnatal Day					
Dose[a]	Female ID	32	34	36	38	40	42
50	154	117.12	130.93	144.54	146.70	165.49	174.20
	155	109.38	123.31	136.34	143.69	158.03	171.56
	163	124.82	140.68	154.00	158.80	175.00	175.03
	164	116.69	129.75	143.13	155.23	163.76	165.54
	171	121.79	136.16	149.94	160.53	172.02	179.43
	172	109.98	123.00	136.46	146.82	155.72	167.20
	179	146.26	161.09	180.91	193.63	201.82	210.77
	186	108.18	124.62	139.68	149.73	165.16	175.44
	187	115.46	127.85	143.56	152.42	168.68	175.92
	320	112.47	125.28	137.08	147.74	158.22	164.23
	321	125.49	137.22	152.36	161.92	174.43	181.17
	329	120.74	133.10	.[b]			
	330	111.45	123.17	136.91	150.78	153.78	166.03
	338	120.20	136.82	151.03	164.40	175.07	183.10
	339	109.03	120.94	133.95	142.58	152.75	159.99
	346	115.65	127.19	140.09	152.00	157.60	168.54
	347	128.13	141.80	155.83	165.67	176.90	187.42
	467	133.42	149.81	162.87	176.92	187.76	195.00
	468	122.13	139.54	148.33	161.77	168.34	175.09
	476	120.90	136.33	145.89	158.80	167.25	182.81
	477	112.04	125.68	138.51	151.28	158.26	167.83
	485	124.93	138.16	152.30	155.11	171.50	173.53
	486	114.63	127.75	140.88	155.91	167.62	177.03
100	275	102.46	116.92	129.26	137.55	149.16	154.11
	276	105.39	116.76	127.62	138.77	148.78	153.81
	284	99.42	111.18	122.09	130.92	141.16	153.38
	285	102.05	113.63	127.48	136.75	149.09	160.18
	293	122.40	132.52	143.95	157.79	163.26	175.95
	302	100.65	112.77	119.91	132.63	140.67	150.92
	303	100.01	110.65	123.40	135.41	140.60	150.53
	311	112.83	127.69	140.60	152.54	157.31	165.02
	312	108.81	121.23	135.13	143.83	151.50	159.99
	431	106.90	119.84	130.49	146.41	154.61	165.99
	432	117.65	135.08	147.69	166.31	171.73	179.49
	440	110.88	125.18	132.98	144.42	150.95	157.50
	458	106.09	117.78	126.97	137.96	143.16	155.17
	459	103.67	113.30	122.83	133.01	140.04	144.55
	498	112.05	123.21	133.79	142.32	150.43	163.23
	499	114.16	127.61	142.22	149.47	161.11	166.47

[a]Mg/kg/day of Methoxychlor.
[b]Female was found dead on postnatal day 34 after dosing (misdirected dose).

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Table A-33. Individual F_1 Dosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 1 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
0	105	34	Vaginal Opening: pin hole only
	113	31	Efflux of the dosing solution
	195	32	Vaginal Opening: pin hole only
		33	Vaginal Opening: pin hole only
	196	30	Efflux of the dosing solution
	204	32	Vaginal Opening: pin hole only
		33	Vaginal Opening: pin hole only
		34	Vaginal Opening: pin hole only
	205	32	Vaginal Opening: pin hole only
	213	30	Vaginal Opening: pin hole only
	214	30	Vaginal Opening: pin hole only
		31	Vaginal Opening: pin hole only
	231	34	Vaginal Opening: pin hole only
	232	34	Vaginal Opening: pin hole only
	355	33	Vaginal Opening: pin hole only
	365	38	Efflux of the dosing solution
	373	31	Vaginal Opening: pin hole only
25	129	29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
	138	29	Vaginal Opening: pin hole only
	240	29	Vaginal Opening: pin hole only
	241	27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
		31	Vaginal Opening: pin hole only
		32	Vaginal Opening: pin hole only
		33	Vaginal Opening: pin hole only
		34	Vaginal Opening: pin hole only
	249	39	Efflux of the dosing solution
			Rooting: post dosing
	250	29	Vaginal Opening: pin hole only
	258	29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
	395	26	Efflux of the dosing solution
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
	396	29	Vaginal Opening: pin hole only
		39	Salivation: prior to dosing
	414	30	Vaginal Opening: pin hole only
		31	Vaginal Opening: pin hole only

(continued)

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Table A-33. Individual F_1 Dosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 2 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	154	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		37	Rooting: post dosing
	155	27	Vaginal Opening: pin hole only
	163	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
	164	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
		31	Efflux of the dosing solution
		32	Efflux of the dosing solution
	171	31	Efflux of the dosing solution
			Rooting: post dosing
		41	Rooting: post dosing
	172	31	Efflux of the dosing solution
			Vaginal Opening: pin hole only
	179	40	Salivation: prior to dosing
	186	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
	187	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
		31	Vaginal Opening: pin hole only
	320	24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
	321	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only

(continued)

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Table A-33. Individual F_1 Dosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 3 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
50	329	30	Efflux of the dosing solution
		34	Found dead after dosing
			Lethargic, post dosing
	330	30	Vaginal Opening: pin hole only
		31	Efflux of the dosing solution
	338	25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		40	Rooting: post dosing
		41	Efflux of the dosing solution
			Rooting: post dosing
	339	30	Efflux of the dosing solution
	347	25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
	467	24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
	468	22	Vaginal Opening: pin hole only
		23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
	476	24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
		28	Vaginal Opening: pin hole only
		29	Vaginal Opening: pin hole only
		30	Vaginal Opening: pin hole only
	477	24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		27	Vaginal Opening: pin hole only
	485	24	Vaginal Opening: pin hole only
		25	Efflux of the dosing solution
			Vaginal Opening: pin hole only
	486	23	Vaginal Opening: pin hole only
		24	Vaginal Opening: pin hole only
		25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only

(continued)

US EPA ARCHIVE DOCUMENT

Table A-33. Individual F_1 Dosed Pubertal Female Clinical Observations During the Post Wean Holding Period (page 4 of 4)

Dose[a]	Female ID	Day[b]	Clinical Observations
100	275	27	Vaginal Opening: pin hole only
		38	Rooting: post dosing
	284	34	Salivation: prior to dosing
		38	Salivation: prior to dosing
		40	Salivation: prior to dosing
		41	Salivation: prior to dosing
	302	26	Vaginal Opening: pin hole only
	303	33	Efflux of the dosing solution
	311	33	Rooting: post dosing
	312	26	Vaginal Opening: pin hole only
		34	Rooting: post dosing
		36	Rooting: post dosing
	431	35	Salivation: prior to dosing
		38	Rooting: post dosing
			Salivation: prior to dosing
		39	Salivation: prior to dosing
		40	Salivation: prior to dosing
		41	Rooting: post dosing
			Salivation: prior to dosing
	432	33	Salivation: prior to dosing
		34	Salivation: prior to dosing
		35	Salivation: prior to dosing
		36	Salivation: prior to dosing
		37	Salivation: prior to dosing
		38	Salivation: prior to dosing
		39	Salivation: prior to dosing
		40	Salivation: prior to dosing
		41	Salivation: prior to dosing
	440	34	Salivation: prior to dosing
	458	29	Efflux of the dosing solution
		34	Rooting: post dosing
		38	Salivation: prior to dosing
		39	Rooting: post dosing
	459	25	Vaginal Opening: pin hole only
		26	Vaginal Opening: pin hole only
		29	Efflux of the dosing solution
		40	Salivation: prior to dosing
		41	Salivation: prior to dosing
	498	36	Rooting: post dosing
		38	Rooting: post dosing
	499	29	Efflux of the dosing solution
			Rooting: post dosing

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

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Table A-34. Individual F_1 Dosed Pubertal Female Vaginal Opening Data (page 1 of 2)

Dose[a]	Female ID	Day of Acquisition[b]	Body Weight (g)
0	104	32	113.07
	105	35	133.40
	113	31	107.61
	114	30	115.20
	122	34	125.92
	123	33	117.40
	195	34	118.30
	196	33	122.58
	204	35	152.90
	205	33	134.95
	213	31	112.55
	214	32	119.05
	231	35	127.57
	232	35	122.21
	355	34	129.65
	356	32	128.25
	364	32	115.02
	365	33	131.91
	373	32	124.25
	374	32	123.49
	382	33	127.35
	383	34	147.23
	491	34	133.71
25	129	31	.[c]
	130	32	120.69
	137	27	92.45
	138	30	110.89
	240	30	119.65
	241	35	151.51
	249	27	105.05
	250	30	105.28
	257	31	105.42
	258	31	93.50
	266	28	90.25
	267	32	107.63
	395	31	.[c]
	396	30	124.62
	404	31	112.73
	405	27	88.86
	413	27	75.71
	414	32	92.09

(continued)

US EPA ARCHIVE DOCUMENT

Table A-34. Individual F_1 Dosed Pubertal Female Vaginal Opening Data (page 2 of 2)

Dose[a]	Female ID	Day of Acquisition[b]	Body Weight (g)
50	154	26	79.19
	155	28	85.70
	163	26	83.46
	164	31	112.30
	171	26	76.94
	172	32	109.98
	179	26	101.06
	186	26	71.96
	187	32	115.46
	320	30	98.18
	321	25	77.51
	329	27	87.86
	330	31	105.54
	338	28	92.05
	339	25	68.66
	346	25	73.09
	347	28	101.75
	467	28	101.95
	468	30	109.20
	476	31	114.75
	477	28	86.71
	485	26	80.90
	486	27	.[c]
100	275	28	82.60
	276	27	77.62
	284	27	73.20
	285	27	76.30
	293	27	91.15
	302	27	72.98
	303	26	71.40
	311	26	76.76
	312	27	77.32
	431	26	71.44
	432	24	62.66
	440	26	79.53
	458	24	64.11
	459	27	76.13
	498	23	70.87
	499	23	64.59

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.
[c]Weight inadvertently not recorded.

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Table A-35. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 1 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
0	104	E	M	D	P	E	M	D	D	P/E	M	D										
	105	M	M	M	D	P	E	M	D													
	113	E	M	D	D	P	P/E	E	M	D	D	P	E									
	114	M	P/E	M	D	D	E	NC	D	D	M	D	E	M								
	122	E/M	D	D	P	E	M	D	D	D												
	123	E	E	M	D	P	E	M	D	D												
	195	E	M	D	D	D	M	M	D	M												
	196	E	M	D	M	P	E	E	M	P												
	204	D	P	P	E	M	D	E	E													
	205	M	D	E/M	D	E	M	D	D	E	M											
	213	M	M	D	E	E/M	M	M	D	D	D	D	D									
	214	NC	D	P	E	M	D	D	P	E	D	D										
	231	M	D	D	M	P	E	D	D													
	232	P/E	E/M	D	E	E	M	M	M													
	355	M	M	D	M	P/E	E	M	D	D												
	356	P/E	M	M	M	P	E	D	D	M	P	E										
	364	E	M	D	D	P	E	M	P/E	E	E	E/M										
	365	M	D	M	P/E	E	M	D	M	D	E											
	373	D	E	P	E	M	M	D	P	E	M	D										
	374	E	M	D	M	P	E	D	D	D	M	D										
	382	E	M	D	D	P	E	M	M	P/E	E											
	383	E	M	D	D	M	M	D	M	D												
	491	E	M	D	D	E	M	M	M	D												

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US EPA ARCHIVE DOCUMENT

Table A-35. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 2 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
25	129	M	D	E	M	D	D	M	D	P/E	M	M	M									
	130	E	D	M	M	D	E	E	D	D	E	M										
	137	D	D	D	D	E	M	D	D	D	E	M	D	D	P	E	M					
	138	P/E	E	M	M	D	E	E	E	D	D	D	E	M								
	240	E	M	NC	D	D	P	M	D	NC	D	NC	E	M								
	241	E	M	D	E	M	D	D	NC													
	249	D	E	M	M	M	D	E	E	M	D	P	E	M	M	D	E					
	250	E	M	D	D	P	E	D	D	D	E	E	M	M								
	257	E	M	D	M	P	E	M	D	D	D	D	E									
	258	E	M	D	M	P	E	D	M	M	M	D	D									
	266	E	E	E	M	D	D	M	P	D	D	M	M	D	M	M						
	267	E	M	D	M	P	E	M	M	D	E	M										
	395	M	D	D	E	D	D	D	M	M	M	D	M									
	396	E/M	D	D	D	M	M	D	M	M	M	D	E	M								
	404	P/E	M	D	P	E	E	P	E	D	M	P	E									
	405	M	D	P	E	ND	M	M	D	D	E	NC	NC	M	M	D	D					
	413	D	D	D	P	M	M	D	D	D	E	E	M	M	D	E	E					
	414	D	P	P	E	E	M	NC	M	M	E	M										

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US EPA ARCHIVE DOCUMENT

Table A-35. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 3 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
50	154	D	D	D	P	E	E	D	E	E	E	E	E	E	D	D	M	D				
	155	D	D	P/E	E	E	E	D	D	D	D	P	E	E	D	D						
	163	D	D	P	P/E	E	E	D	E	E	E	E	E	D	D	D	E	E				
	164	D	P/E	E	E	E	E	E	E	E	E	E	E									
	171	P	E	D	M	D	P	E	E	D	D	E	M	M	D	D	E	E				
	172	D	D	D	D	P	E	P	P	M	M	M										
	179	E	D	D	D	D	D	P/E	E	M	M	P	M	D	D	E	E	M				
	186	D	D	D	P	P	P	E	E	E	E	E	E	E	E	E	E	E				
	187	P	E	E	E	E	D	D	D	E	E	E										
	320	P/E	P/E	E	E	E	E	E	D	D	P/E	E	E									
	321	E	E	E	E	E	D	P/E	P/E	E	E	E	E	E	E	E	E	E	E			
	329	.[c]																				
	330	D	P	E	E/M	P	D	D	D	D	E	M	D									
	338	P	E	E	E	D	P	E	M	D	E	E	M	D	D	D						
	339	D	D	D	M	D	P	P	E	E	E	E	E	D	E	E	E	E	E			
	346	E	E	D	D	D	D	E	D	D	D	D	D	E	E	P	E	E	D			
	347	P	E	E	E	E	E	D	D	P	P/E	E	E	M	P	P						
	467	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E						
	468	P/E	P/E	E	D	D	E	E	E	E	E	D	D	P								
	476	D	E	E	E	P/E	E	E	E	E	E	E	E									
	477	NC	E	E	E	E	E	E	E	E	E	E	E	E	E	E						
	485	D	D	P/E	E	E	E	E	D	D	P/E	P/E	E	E	E	D	D	D				
	486	D	D	P/E	M	D	D	E	E	E	E	E	E	E	D	E	M					

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US EPA ARCHIVE DOCUMENT

Table A-35. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Vaginal Smears (page 4 of 4)

		Smear Day[a]																				
Dose[b]	Female ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
100	275	D	P/E	E	M	D	M	P	E	E	M	M	M	D	E	NC						
	276	E	E/M	M	M	P/E	M	M	E	E	M	NP	D	E	M	M	D					
	284	E/M	E/M	E	E	E/M	E	P	E	M	M	M	D	P	E	D	E					
	285	D	E	M	E	M	M	M	D	D	D	D	P	P	M	D	D					
	293	E	E	E	E	M	D	D	P	E	E	E	D	E	E	E	E					
	302	P	E	E	M	P	E	D	D	P	E	D	D	E	E	D	D					
	303	D	P	D	M	NC	M	M	P	D	M	E	D	D	E	E	M	E				
	311	D	D	M	M/E	E/M	P	P	D	E	E	M	D	D	P	E/M	E	D				
	312	D	P/E	D	P/E	E	E	E	E	P/E	E/M	D	D	E/M	E	E	D	D				
	431	E	M/E	E	M	M	E	E	E	D	D	D	D	P/E	D	D	P	D				
	432	P	P	E	E	E	E	E	E	E	M	M/E	E	P/E	E	ND	E	P	E/M	E		
	440	D	M	P	P	P	P/E	P/E	E	P/E	D	D	P	M/E	M/E	D	E	P				
	458	D	D	P/E	E	E	P	D/P	D	D	P	P	P/E	E	E	E	M	P	P	NC		
	459	M	M/E	M/E	NC	E	P	P/E	E	E	E	M/E	P	P	P/E	M	E					
	498	P	P	E	M	M	P/E	P	E	P/E	M	E	E	E	E	M/E	E	E	P	P	P/E	E
	499	D	D	P	M	M/E	M/E	D	P/E	D	D/P	E/M	M	M/E	E	NP	NP	M	E	P	D	

[a]The first day of vaginal smears was the day the animal was found positive for vaginal opening and smear continued until the animal was sacrificed, found dead or euthanized moribund. Codes for the smear stages are P is proestrus; E is estrus; M is metestrus; D is diestrus; NC is no cells; ND is could not be determined; NP is smear not present. A "/" between each indicates that cells from both stages were present equally.
[b]Mg/kg/day of Methoxychlor.
[c]Female was found dead on postnatal day 34 after dosing (misdirected dose) and therefore her data was excluded.

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Table A-36. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 1 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
0	104	Yes	0	32	0	32	3	35	No	No
	105	Yes	5	40	2	37	5	40	No	No
	113	Yes	0	31	0	31	4	35	No	No
	114	Yes	1	31	1	31	4	34	No	No
	122	Yes	0	34	0	34	3	37	No	No
	123	Yes	0	33	1	34	4	37	No	No
	195	No	0	34	.	.	.	.	No	No
	196	Yes	0	33	0	33	4	37	No	No
	204	Yes	3	38	0	35	4	39	No	No
	205	Yes	2	35	0	33	2	35	No	No
	213	Yes	3	34	1	32	4	35	No	Yes
	214	Yes	3	35	1	33	4	36	No	No
	231	Yes	5	40	3	38	7	42	No	No
	232	Yes	0	35	0	35	3	38	No	No
	355	Yes	4	38	4	38	8	42	No	No
	356	Yes	0	32	4	36	8	40	No	No
	364	Yes	0	32	0	32	4	36	No	No
	365	Yes	3	36	3	36	9	42	No	No
	373	Yes	1	33	2	34	6	38	No	No
	374	Yes	0	32	0	32	4	36	No	No
	382	Yes	0	33	0	33	4	37	No	No
	383	No	0	34	.	.	.	.	No	No
	491	Yes	0	34	0	34	3	37	No	No

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Table A-36. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 2 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
25	129	Yes	2	33	0	31	2	33	No	No
	130	Yes	0	32	3	35	6	38	No	No
	137	Yes	4	31	3	30	5	32	No	Yes
	138	Yes	0	30	0	30	4	34	No	No
	240	Yes	0	30	0	30	5	35	No	No
	241	Yes	0	35	0	35	2	37	No	No
	249	Yes	1	28	0	27	4	31	No	No
	250	Yes	0	30	0	30	4	34	No	No
	257	Yes	0	31	0	31	4	35	No	Yes
	258	Yes	0	31	0	31	4	35	No	No
	266	No	0	28	.	.	.	.	No	No
	267	Yes	0	32	0	32	4	36	No	No
	395	No	3	34	.	.	.	.	No	No
	396	No	0	30	.	.	.	.	No	No
	404	Yes	0	31	0	31	3	34	No	No
	405	Yes	3	30	0	27	4	31	No	No
	413	Yes	9	36	4	31	10	37	No	No
	414	Yes	3	35	0	32	8	40	No	No

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US EPA ARCHIVE DOCUMENT

Table A-36. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 3 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
50	154	Yes	4	30	2	28	12	38	Yes	No
	155	Yes	2	30	0	28	5	33	Yes	Yes
	163	Yes	3	29	0	26	5	31	Yes	No
	164	No	1	32	.	.	.	.	Yes	No
	171	Yes	1	27	0	26	4	30	No	No
	172	No	5	37	.	.	.	.	No	Yes
	179	Yes	0	26	0	26	6	32	No	Yes
	186	No	6	32	.	.	.	.	Yes	No
	187	No	1	33	.	.	.	.	Yes	No
	320	Yes	0	30	1	31	8	38	Yes	No
	321	No	0	25	.	.	.	.	Yes	No
	329	.[d]								
	330	Yes	2	33	0	31	4	35	No	Yes
	338	Yes	1	29	0	28	4	32	Yes	No
	339	Yes	7	32	4	29	11	36	Yes	No
	346	Yes	0	25	0	25	5	30	No	Yes
	347	Yes	1	29	0	28	7	35	Yes	No
	467	No	0	28	.	.	.	.	Yes	No
	468	Yes	0	30	0	30	4	34	Yes	No
	476	No	1	32	.	.	.	.	Yes	No
	477	No	1	29	.	.	.	.	Yes	No
	485	Yes	2	28	2	28	8	34	Yes	No
	486	Yes	2	29	1	28	3	30	Yes	No

(continued)

US EPA ARCHIVE DOCUMENT

Table A-36. Individual F_1 Dosed Pubertal Female Vaginal Cytology - Evaluation of Estrous Cyclicity (page 4 of 4)

Dose[a]	Female ID	Cycling	Day of First Estrus[b]	Age at First Estrus[c]	Day at Start of First Cycle[b]	Age at Start of First Cycle[c]	Day at End of First Cycle[b]	Age at End of First Cycle[c]	Prolonged Estrus	Prolonged Diestrus
100	275	Yes	1	29	1	29	5	33	No	No
	276	Yes	0	27	0	27	4	31	No	No
	284	Yes	0	27	6	33	11	38	No	No
	285	Yes	1	28	3	30	12	39	No	Yes
	293	Yes	0	27	3	30	7	34	Yes	No
	302	Yes	1	28	0	27	3	30	No	No
	303	Yes	10	36	1	27	6	32	No	No
	311	Yes	3	29	8	34	13	39	No	No
	312	Yes	1	28	8	35	11	38	Yes	No
	431	Yes	0	26	7	33	12	38	Yes	Yes
	432	No	2	26	.	.	.	.	Yes	No
	440	Yes	5	31	8	34	12	38	No	No
	458	Yes	2	26	11	35	15	39	Yes	No
	459	Yes	1	28	6	33	10	37	Yes	No
	498	Yes	2	25	0	23	4	27	Yes	No
	499	Yes	4	27	1	24	5	28	No	No

[a]Mg/kg/day of Methoxychlor.
[b]Number of days since the animal was positive for vaginal opening.
[c]Age in postnatal days.
[d]Female was found dead on postnatal day 34 after dosing (misdirected dose) and therefore her data was excluded.

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Table A-37. Individual F_1 Dosed Pubertal Female Necropsy and Hormone Data (page 1 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
0	104	166.23	10.88	12	12	2.18	0.0085	0.0214	8.9879	0.0462	1.6995	0.0972	0.3334	0.3089	3.14	87.84	6.83
	105	170.59	10.80	12	12	2.42	0.0083	0.0176	9.0629	0.0361	1.7826	0.0888	0.1983	0.1910	4.50	74.59	7.54
	113	168.54	9.94	12	12	3.02	0.0104	0.0248	8.4353	0.0447	1.5941	0.1073	0.3650	0.3566	5.12	115.10	7.55
	114	185.02	10.37	12	12	2.30	0.0110	0.0219	10.082[b]	0.0499	1.7232	0.1008	0.3348	0.3206	3.70	54.18	5.60
	122	165.63	10.86	12	12	3.19	0.0104	0.0215	8.1863	0.0532	1.8229	0.1194	0.3836	0.3788	6.03	79.19	7.99
	123	151.50	10.85	12	12	2.61	0.0081	0.0162	7.5769	0.0418	1.5014	0.0790	0.2327	0.2274	4.35	77.89	8.47
	195	168.11	10.71	12	12	2.14	0.0142	0.0163	8.8066	0.0216	1.4974	0.0505	0.2118	0.2012	3.76	64.92	4.64
	196	168.41	10.57	12	12	2.16	0.0083	0.0175	8.3428	0.0334	1.5916	0.0795	0.3600	0.3244	4.37	55.13	6.91
	204	189.14	12.16	12	12	2.15	0.0159	0.0205	9.0075	0.0587	1.8122	0.1296	0.2983	0.2868	4.20	65.41	9.80
	205	188.42	12.15	12	12	2.18	0.0129	0.0237	10.0210	0.0616	1.8075	0.1165	0.3020	0.2908	3.16	88.69	11.02
	213	204.26	13.17	12	12	3.18	.[c]	0.0188	11.3584	0.0397	1.9229	0.0720	0.3280	0.3178	5.45	84.93	14.26
	214	173.81	11.52	12	12	2.59	0.0072	0.0147	8.9285	0.0478	1.7577	0.0955	0.2548	0.2473	4.08	71.00	11.65
	231	162.21	11.78	12	12	2.75	0.0070	0.0199	7.2152	0.0414	1.5596	0.0876	0.2147	0.2044	4.88	83.92	6.29
	232	155.64	11.86	12	12	3.03	0.0077	0.0209	7.3549	0.0485	1.5198	0.0885	0.4665	0.3775	5.19	107.12	7.34
	355	180.25	12.53	12	12	3.12	0.0160	0.0220	9.7925	0.0550	1.8497	0.1200	0.3592	0.3419	3.39	114.19	5.48
	356	182.75	12.58	12	12	2.57	0.0151	0.0211	10.0128	0.0503	1.9015	0.1145	0.4041	0.3918	4.76	92.03	6.91
	364	165.05	10.86	12	12	2.27	0.0136	0.0229	8.8926	0.0443	1.9711	0.0732	0.2417	0.2302	2.34	68.03	7.15
	365	177.61	12.17	12	12	3.16	0.0117	0.0226	9.4746	0.0541	1.8132	0.1101	0.2942	0.2870	6.01	95.88	11.09
	373	190.40	13.03	12	12	3.14	0.0113	0.0182	11.5175	0.0431	2.0496	0.0959	0.2918	0.2783	3.87	109.46	12.69
	374	181.88	11.72	12	12	2.78	0.0109	0.0223	11.1013	0.0493	2.1263	0.0936	0.7143	0.4711	4.05	108.34	10.05
	382	194.00	13.03	12	12	3.55	0.0115	0.0221	10.6445	0.0438	1.9443	0.1109	0.3977	0.3839	5.90	90.52	6.64
	383	204.91	14.68	12	12	3.54	0.0202	0.0255	12.3570	0.0475	2.2486	0.0818	0.2730	0.2576	5.68	91.82	7.38
	491	185.62	12.18	12	12	1.72	0.0102	0.0163	9.2912	0.0479	1.8288	0.1013	0.4701	0.4044	2.60	75.11	6.61

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Table A-37. Individual F_1 Dosed Pubertal Female Necropsy and Hormone Data (page 2 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
25	129	149.63	9.21	12	12	1.95	0.0133	0.0215	7.4897	0.0360	1.4377	0.0658	0.2604	0.2545	2.72	72.54	5.02
	130	183.02	11.64	12	12	1.97	0.0125	0.0205	10.7410	0.0435	1.7766	0.1082	0.3008	0.2827	3.51	63.70	7.17
	137	172.18	8.01	12	12	2.48	0.0102	0.0226	9.5530	0.0557	1.8011	0.1022	0.3111	0.2977	3.60	72.97	7.77
	138	177.04	10.77	12	12	2.28	0.0118	0.0185	9.5635	0.0428	1.6592	0.0715	0.2659	0.2625	3.39	72.61	6.97
	240	190.42	12.40	12	12	2.53	0.0138	0.0205	10.3600	0.0468	1.8587	0.1040	0.2860	0.2642	4.17	82.97	5.74
	241	176.47	11.35	12	12	2.53	0.0200	0.0221	9.4161	0.0617	1.8634	0.1320	0.3980	0.3828	4.45	62.92	9.18
	249	201.68	10.94	12	12	3.29	0.0192	0.0265	10.2677	0.0526	2.0270	0.1088	0.3185	0.2977	4.33	59.09	10.05
	250	168.96	10.61	12	12	2.53	0.0115	0.0173	7.7690	0.0427	1.8012	0.1019	0.2733	0.2665	4.26	84.16	9.65
	257	161.38	12.32	12	12	2.47	0.0110	0.0246	8.8211	0.0467	1.5995	0.0936	0.3813	0.3695	3.91	64.80	16.18
	258	150.98	11.63	12	12	2.30	0.0106	0.0197	8.0817	0.0426	1.4164	0.0881	0.3423	0.3391	4.66	103.97	19.59
	266	172.87	11.58	12	12	3.09	0.0100	0.0217	9.1767	0.0447	1.6120	0.0807	0.2166	0.2123	4.33	89.63	8.26
	267	153.56	11.01	12	12	2.12	0.0096	0.0201	7.1591	0.0333	1.5113	0.0862	0.2324	0.2264	3.34	80.82	6.99
	395	184.12	12.13	12	12	2.10	.[c]	0.0221	9.9221	0.0267	1.5791	0.0653	0.3152	0.2902	4.36	88.86	6.30
	396	202.10	12.51	12	12	2.86	.[c]	0.0233	11.1546	0.0575	2.0628	0.0829	0.5115	0.4961	4.89	73.49	7.93
	404	179.03	10.37	12	12	3.14	0.0123	0.0233	9.1049	0.0577	1.8037	0.1132	0.4308	0.4234	4.67	109.43	6.42
	405	197.22	12.03	12	12	2.51	0.0108	0.0205	11.6398	0.0504	1.8387	0.0788	0.3370	0.3258	4.57	73.31	10.16
	413	153.03	10.48	12	12	2.78	0.0098	0.0230	7.1849	0.0495	1.5588	0.0971	0.3754	0.3678	5.34	73.73	7.83
	414	145.75	10.71	12	12	2.25	0.0100	0.0210	7.7876	0.0426	1.6030	0.0752	0.2175	0.2069	3.85	85.18	7.27

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Table A-37. Individual F_1 Dosed Pubertal Female Necropsy and Hormone Data (page 3 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
50	154	173.94	10.49	12	12	1.75	0.0082	0.0263	9.479[b]	0.0290	1.8046	0.0728	0.3662	0.3478	5.08	88.53	8.13
	155	166.79	11.00	12	12	2.12	0.0092	0.0233	9.4713	0.0377	1.8144	0.0746	0.2526	0.2440	4.65	86.95	8.50
	163	174.86	8.74	12	12	1.61	0.0117	0.0203	9.2772	0.0634	1.5666	0.0426	0.3713	0.3622	3.97	70.50	10.68
	164	165.64	12.32	12	12	2.48	0.0111	0.0283	8.5919	0.0460	1.5518	0.0632	0.2485	0.2448	3.51	49.54	9.07
	171	180.87	11.05	12	12	2.19	0.0078	0.0198	9.0950	0.0469	1.7773	0.0740	0.3237	0.3141	6.06	85.80	13.08
	172	166.57	10.66	12	12	2.19	.[c]	0.0170	8.4998	0.0271	1.5767	0.0554	0.2079	0.1981	4.94	58.89	9.32
	179	206.72	10.93	12	12	2.52	0.0123	0.0223	10.9516	0.0425	2.0555	0.1024	0.2866	0.2805	5.72	89.59	6.66
	186	175.32	12.06	12	12	2.11	0.0092	0.0251	8.9235	0.0438	1.9125	0.0583	0.2362	0.2319	6.24	80.62	7.80
	187	180.32	11.29	12	12	1.40	0.0093	0.0224	9.1920	0.0380	1.9002	0.0438	0.2723	0.2698	6.11	88.67	7.24
	320	165.30	12.57	12	12	2.16	0.0109	0.0252	8.7571	0.0465	1.5965	0.0525	0.3598	0.3382	3.59	49.98	14.08
	321	181.82	11.33	12	12	1.80	0.0172	0.0245	9.1718	0.0422	1.6503	0.0567	0.3182	0.3113	3.85	53.04	8.68
	329	.[d]															
	330	159.65	11.48	12	12	1.65	0.0058	0.0281	8.3309	0.0359	1.6238	0.0680	0.2806	0.2696	4.27	69.15	6.89
	338	177.96	11.78	12	12	2.32	0.0111	0.0270	9.7541	0.0517	1.5390	0.0916	0.4481	0.4044	5.53	70.44	20.28
	339	155.79	10.90	12	12	2.28	0.0111	0.0237	7.5645	0.0441	1.5243	0.0570	0.4007	0.3622	4.70	86.89	15.37
	346	163.94	11.86	12	12	2.16	0.0101	0.0264	8.0951	0.0433	1.7017	0.0386	0.2164	0.2120	5.80	111.81	9.03
	347	185.49	12.16	12	12	2.11	0.0123	0.0191	10.3018	0.0437	1.9756	0.0746	0.2398	0.2310	5.39	82.38	8.52
	467	195.80	13.23	12	12	2.96	0.0110	0.0246	10.5721	0.0450	1.9118	0.0549	0.2136	0.2060	4.12	87.63	4.90
	468	177.74	12.64	12	12	2.29	0.0056	0.0170	8.6605	0.0548	1.7185	0.0458	0.2297	0.2260	3.45	85.64	6.98
	476	180.23	13.22	12	12	2.13	0.0096	0.0222	8.8063	0.0403	1.5592	0.0649	0.2342	0.2206	4.25	84.57	8.12
	477	165.78	12.70	12	12	2.37	0.0093	0.0210	9.3828	0.0460	1.5546	0.0737	0.3874	0.3691	5.11	104.70	14.32
	485	177.50	12.46	12	12	2.53	0.0116	0.0259	9.8470	0.0479	1.9358	0.0809	0.4007	0.3862	4.11	106.00	10.51
	486	177.57	11.88	12	12	2.51	0.0091	0.0230	9.8423	0.0454	1.7162	0.0668	0.5573	0.3954	4.54	126.87	10.91

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Table A-37. Individual F_1 Dosed Pubertal Female Necropsy and Hormone Data (page 4 of 4)

Dose[a]	Female ID	Sacrifice Weight (g)	Anogen-ital Distance (mm)	Number of Areolae	Number of Nipples	Urethral-Vaginal Distance (mm)	Pituitary Weight (g)	Thyroid Weight (g)	Liver Weight (g)	Paired Adrenal Gland Weight (g)	Paired Kidney Weight (g)	Paired Ovary Weight (g)	Uterus with Fluid Weight (g)	Uterus without Fluid Weight (g)	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
100	275	153.31	10.90	12	12	2.49	0.0116	0.0226	8.4232	0.0560	1.7074	0.0735	0.3711	0.3609	3.98	79.25	11.80
	276	150.63	11.97	12	12	2.15	0.0082	0.0130	7.4112	0.0568	1.3099	0.1005	0.3762	0.3555	4.23	67.00	8.37
	284	150.08	11.77	12	12	2.15	0.0085	0.0176	7.8947	0.0436	1.4990	0.0729	0.2282	0.2165	3.64	78.14	8.28
	285	157.53	12.03	12	12	1.75	0.0064	0.0217	7.3394	0.0419	1.4652	0.0908	0.4169	0.3472	2.91	49.77	6.82
	293	173.36	11.37	12	12	2.13	0.0092	0.0264	9.4683	0.0566	1.7338	0.0674	0.2284	0.2177	4.41	76.59	7.24
	302	149.34	11.47	12	12	2.26	0.0139	0.0183	8.1867	0.0381	1.4190	0.0621	0.2035	0.1951	3.88	71.93	9.51
	303	147.31	10.65	12	12	2.73	0.0089	0.0172	7.5864	0.0425	1.5872	0.0762	0.3837	0.3720	5.45	98.86	15.22
	311	164.41	11.99	12	12	2.16	0.0109	0.0163	8.7776	0.0379	1.6874	0.0776	0.2314	0.2265	3.29	44.07	11.55
	312	157.61	12.22	12	12	2.02	0.0112	0.0168	7.7492	0.0405	1.6032	0.0831	0.3150	0.3095	4.66	89.38	11.07
	431	163.13	12.24	12	12	3.12	0.0123	0.0158	9.5881	0.0453	1.4990	0.0477	0.2840	0.2767	2.98	86.39	5.53
	432	179.12	13.17	12	12	2.66	0.0117	0.0203	9.8942	0.0508	1.8845	0.0676	0.2695	0.2626	2.77	103.42	9.78
	440	154.78	12.41	12	12	2.14	0.0075	0.0184	8.0219	0.0445	1.5302	0.0700	0.3518	0.3372	3.44	84.70	7.68
	458	157.53	11.26	12	12	2.00	0.0075	0.0165	7.7447	0.0369	1.5268	0.0579	0.1915	0.1873	4.05	74.11	10.99
	459	145.81	10.66	12	12	2.32	0.0104	0.0175	7.1639	.[c]	1.4907	0.0476	0.2241	0.2158	4.39	102.82	6.77
	498	160.18	13.27	12	12	1.23	0.0077	0.0166	8.7569	0.0478	1.4797	0.0448	0.2079	0.2061	2.32	51.12	6.64
	499	166.31	13.44	12	12	2.00	0.0092	0.0205	8.8998	0.0462	1.7226	0.0730	0.2200	0.2157	2.90	64.55	7.69

[a]Mg/kg/day of Methoxychlor.
[b]Weight inadvertently recorded to only 3 decimal places.
[c]Weight was a statistical outlier and therefore excluded.
[d]Female was found dead on postnatal day 34 after dosing (misdirected dose).

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Table A-38. Individual F_1 Dosed Pubertal Female Gross Necropsy Findings (page 1 of 1)

Dose[a]	Female ID	Finding
Scheduled Necropsy:		
0	491	Uterus: fluid filled, bilateral
25	266	Kidney: hydronephrosis, right
50	154	Kidney: hydronephrosis, bilateral
	155	Kidney: hydronephrosis, right
	338	Kidney: hydronephrosis, right
	486	Uterus: fluid filled, bilateral
Unscheduled Necropsy:		
50	329	Thoracic cavity: oily solution present, dosing error

[a]Mg/kg/day of Methoxychlor.

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Table A-39. Individual F_1 Undosed Pubertal Male Fate (page 1 of 3)

Dose[a]	Male ID	Fate
0	102	Scheduled Sacrifice on Postnatal Day 75
	103	Scheduled Sacrifice on Postnatal Day 75
	111	Scheduled Sacrifice on Postnatal Day 75
	112	Scheduled Sacrifice on Postnatal Day 75
	120	Scheduled Sacrifice on Postnatal Day 75
	121	Scheduled Sacrifice on Postnatal Day 75
	193	Scheduled Sacrifice on Postnatal Day 75
	194	Scheduled Sacrifice on Postnatal Day 75
	202	Scheduled Sacrifice on Postnatal Day 75
	203	Scheduled Sacrifice on Postnatal Day 75
	211	Scheduled Sacrifice on Postnatal Day 76
	212	Scheduled Sacrifice on Postnatal Day 76
	220	Removed from Study because Dam was Removed
	221	Removed from Study because Dam was Removed
	229	Scheduled Sacrifice on Postnatal Day 76
	230	Scheduled Sacrifice on Postnatal Day 76
	353	Scheduled Sacrifice on Postnatal Day 76
	354	Scheduled Sacrifice on Postnatal Day 76
	362	Scheduled Sacrifice on Postnatal Day 76
	363	Scheduled Sacrifice on Postnatal Day 76
	371	Scheduled Sacrifice on Postnatal Day 76
	372	Scheduled Sacrifice on Postnatal Day 76
	380	Scheduled Sacrifice on Postnatal Day 77
	381	Scheduled Sacrifice on Postnatal Day 77
	490	Scheduled Sacrifice on Postnatal Day 76
25	128	Scheduled Sacrifice on Postnatal Day 75
	135	Scheduled Sacrifice on Postnatal Day 75
	136	Scheduled Sacrifice on Postnatal Day 75
	143	Removed from Study because Dam was Removed
	144	Removed from Study because Dam was Removed
	238	Scheduled Sacrifice on Postnatal Day 75
	239	Scheduled Sacrifice on Postnatal Day 75
	247	Scheduled Sacrifice on Postnatal Day 75
	248	Scheduled Sacrifice on Postnatal Day 75
	255	Scheduled Sacrifice on Postnatal Day 76
	256	Scheduled Sacrifice on Postnatal Day 76
	264	Scheduled Sacrifice on Postnatal Day 76
	265	Scheduled Sacrifice on Postnatal Day 76
	388	Removed from Study because Dam was Removed
	393	Scheduled Sacrifice on Postnatal Day 76
	394	Scheduled Sacrifice on Postnatal Day 76

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Table A-39. Individual F_1 Undosed Pubertal Male Fate (page 2 of 3)

Dose[a]	Male ID	Fate
25	402	Scheduled Sacrifice on Postnatal Day 77
	403	Scheduled Sacrifice on Postnatal Day 77
	411	Scheduled Sacrifice on Postnatal Day 77
	412	Scheduled Sacrifice on Postnatal Day 77
	420	Removed from Study because Dam was Removed
	421	Removed from Study because Dam was Removed
50	152	Scheduled Sacrifice on Postnatal Day 75
	153	Scheduled Sacrifice on Postnatal Day 75
	161	Scheduled Sacrifice on Postnatal Day 75
	162	Scheduled Sacrifice on Postnatal Day 75
	169	Scheduled Sacrifice on Postnatal Day 75
	170	Scheduled Sacrifice on Postnatal Day 75
	177	Scheduled Sacrifice on Postnatal Day 75
	178	Scheduled Sacrifice on Postnatal Day 75
	184	Scheduled Sacrifice on Postnatal Day 76
	185	Scheduled Sacrifice on Postnatal Day 76
	318	Scheduled Sacrifice on Postnatal Day 75
	319	Scheduled Sacrifice on Postnatal Day 75
	327	Scheduled Sacrifice on Postnatal Day 76
	328	Scheduled Sacrifice on Postnatal Day 76
	336	Scheduled Sacrifice on Postnatal Day 76
	337	Scheduled Sacrifice on Postnatal Day 76
	344	Scheduled Sacrifice on Postnatal Day 77
	345	Scheduled Sacrifice on Postnatal Day 77
	465	Scheduled Sacrifice on Postnatal Day 77
	466	Scheduled Sacrifice on Postnatal Day 77
	474	Scheduled Sacrifice on Postnatal Day 76
	475	Scheduled Sacrifice on Postnatal Day 76
	483	Scheduled Sacrifice on Postnatal Day 77
	484	Scheduled Sacrifice on Postnatal Day 77
100	273	Scheduled Sacrifice on Postnatal Day 75
	274	Scheduled Sacrifice on Postnatal Day 75
	282	Scheduled Sacrifice on Postnatal Day 75
	283	Scheduled Sacrifice on Postnatal Day 75
	291	Scheduled Sacrifice on Postnatal Day 75
	292	Scheduled Sacrifice on Postnatal Day 75
	300	Scheduled Sacrifice on Postnatal Day 76
	301	Scheduled Sacrifice on Postnatal Day 76
	309	Scheduled Sacrifice on Postnatal Day 76
	310	Scheduled Sacrifice on Postnatal Day 76

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US EPA ARCHIVE DOCUMENT

Table A-39. Individual F_1 Undosed Pubertal Male Fate (page 3 of 3)

Dose[a]	Male ID	Fate
100	429	Scheduled Sacrifice on Postnatal Day 76
	430	Scheduled Sacrifice on Postnatal Day 76
	438	Scheduled Sacrifice on Postnatal Day 76
	439	Scheduled Sacrifice on Postnatal Day 76
	444	Removed from Study because Dam was Removed
	456	Scheduled Sacrifice on Postnatal Day 77
	457	Scheduled Sacrifice on Postnatal Day 77
	496	Scheduled Sacrifice on Postnatal Day 76
	497	Scheduled Sacrifice on Postnatal Day 76

[a]Mg/kg/day of Methoxychlor.

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Table A-40. Individual F_1 Undosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 1 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
0	102	14.26	53.47	57.47	68.97	81.07	94.80	108.84	126.86	143.76	161.49
	103	13.65	45.86	48.30	60.99	71.16	84.70	99.89	115.69	131.16	144.19
	111	16.12	56.29	60.62	73.42	85.51	96.11	110.67	124.07	142.78	158.25
	112	16.21	55.97	61.15	73.97	85.77	96.05	109.38	125.21	144.40	160.60
	120	16.21	52.87	57.87	69.62	81.48	93.00	108.41	124.38	142.98	161.33
	121	17.12	58.15	63.37	75.04	88.85	102.20	117.74	133.58	153.86	172.90
	193	11.91	49.59	54.16	65.78	76.04	88.83	102.40	117.67	131.82	148.48
	194	13.29	54.66	59.25	74.93	86.92	101.38	117.86	136.29	154.51	170.73
	202	16.85	60.38	65.97	78.60	93.40	109.07	126.58	150.12	168.45	190.17
	203	17.31	66.49	71.97	87.01	102.01	119.25	139.40	165.40	183.17	206.41
	211	15.15	61.95	67.15	80.21	94.80	110.76	128.26	148.15	167.60	186.67
	212	13.47	60.47	65.74	79.16	93.06	107.49	124.40	142.29	160.23	174.41
	229	16.36	50.50	53.73	64.54	77.45	86.50	100.37	116.96	131.82	147.83
	230	14.35	54.97	62.06	75.46	89.87	102.28	118.18	136.24	150.59	166.55
	353	17.57	64.46	70.91	85.02	101.69	117.17	138.45	156.81	176.57	204.16
	354	18.67	67.72	74.42	86.83	104.25	121.53	143.73	163.69	185.83	208.47
	362	15.06	59.40	63.76	76.82	89.32	102.91	119.48	133.94	151.45	169.40
	363	17.54	63.96	69.11	83.11	96.21	113.70	133.52	151.66	171.46	191.87
	371	16.61	59.82	65.51	78.61	91.91	105.70	125.26	143.20	163.44	185.14
	372	16.13	60.48	64.93	77.88	89.01	104.43	121.45	136.69	153.83	173.91
	380	16.74	58.87	66.36	75.97	89.37	106.80	124.38	140.87	161.12	181.63
	381	13.49	53.76	59.72	71.29	83.64	99.17	117.44	132.74	152.60	170.89
	490	15.21	57.90	64.15	75.62	89.88	106.57	121.13	139.12	157.65	182.10

(continued)

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Table A-40. Individual F_1 Undosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 2 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
25	128	14.34	58.31	63.72	77.90	92.35	110.45	128.46	152.85	170.47	188.73
	135	15.83	61.61	65.82	80.24	93.19	110.09	125.70	142.27	167.14	184.46
	136	15.17	61.22	66.44	83.17	98.28	116.40	134.10	153.63	174.26	193.33
	238	17.44	69.35	77.47	92.31	105.59	124.42	140.78	163.47	185.42	204.30
	239	17.80	68.12	74.26	88.88	103.18	119.85	136.63	158.71	180.96	200.76
	247	14.89	66.11	73.11	84.17	98.10	112.81	130.68	145.17	166.13	184.15
	248	16.20	61.55	67.74	79.35	92.60	107.95	124.09	142.10	156.89	174.81
	255	14.38	50.67	55.48	66.88	78.24	91.67	108.29	122.95	140.15	158.46
	256	13.15	53.19	58.09	71.32	84.61	99.05	112.92	131.00	152.64	171.39
	264	15.61	56.06	62.65	73.76	87.45	104.75	121.55	138.21	155.10	170.17
	265	15.13	48.46	53.74	64.59	75.98	88.99	103.14	118.25	134.25	148.72
	393	18.31	66.59	71.71	86.23	98.48	112.69	131.66	150.57	171.83	190.60
	394	15.77	59.74	65.28	79.01	91.47	104.43	123.04	139.36	157.34	173.65
	402	15.15	53.34	60.30	74.34	87.73	102.44	121.65	141.37	159.50	176.43
	403	12.87	42.81	47.05	59.81	71.00	84.45	100.15	115.85	132.37	148.84
	411	15.28	52.41	57.60	71.70	84.13	97.06	116.24	133.46	150.67	169.17
	412	15.18	52.66	57.98	68.85	79.17	90.37	106.15	119.66	134.70	150.58

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Table A-40. Individual F_1 Undosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 3 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
50	152	14.95	59.10	62.68	79.10	92.41	109.10	120.10	145.41	161.60	181.50
	153	12.70	56.78	60.06	76.09	89.53	104.72	118.77	137.32	154.20	171.26
	161	15.35	54.29	58.08	71.15	83.11	101.60	115.32	135.92	150.24	175.06
	162	13.58	55.60	58.47	70.96	81.65	97.45	110.04	130.19	143.67	163.11
	169	15.76	56.91	58.41	75.27	87.01	101.84	118.55	137.43	154.88	174.79
	170	16.27	57.52	60.02	74.81	86.19	99.00	112.60	132.06	147.92	167.75
	177	15.23	68.68	73.53	90.89	106.46	124.32	142.59	164.64	186.15	212.19
	178	14.54	68.19	73.55	90.61	104.55	121.35	138.16	158.90	179.66	203.00
	184	13.59	51.60	54.55	68.65	81.55	96.53	110.05	128.39	145.07	162.68
	185	13.38	47.65	50.12	63.14	75.12	89.46	103.08	124.39	139.16	156.87
	318	16.16	57.40	61.23	72.37	84.93	99.13	116.60	131.19	150.27	166.96
	319	13.66	56.84	60.27	69.29	78.50	89.63	103.02	113.48	127.10	143.76
	327	17.84	61.08	66.43	80.61	94.74	111.18	125.39	142.32	171.77	176.47
	328	14.32	61.30	67.29	81.00	97.20	115.31	133.56	151.80	171.96	191.42
	336	17.62	54.97	59.52	69.74	82.25	94.11	109.98	125.04	140.13	160.05
	337	16.72	50.15	55.23	66.85	77.65	90.80	104.89	120.14	137.41	150.88
	344	16.29	56.50	62.14	76.09	87.74	102.59	118.96	135.01	154.75	170.37
	345	14.58	57.45	62.91	75.20	87.21	101.20	116.93	130.51	146.77	162.63
	465	13.69	60.46	66.49	79.70	95.36	110.25	131.23	148.78	170.90	191.53
	466	13.91	59.99	65.76	75.61	94.93	110.50	132.93	153.10	172.60	192.21
	474	15.37	57.00	61.26	72.45	86.35	98.24	115.15	129.03	147.10	164.57
	475	15.75	59.34	65.11	77.62	93.08	106.87	126.45	142.22	161.55	179.55
	483	13.67	56.05	61.36	72.28	86.30	100.37	118.21	133.82	153.11	167.86
	484	15.06	59.51	65.67	77.50	91.24	106.42	125.38	142.72	158.20	179.50

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Table A-40. Individual F_1 Undosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 4 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
100	273	17.79	54.83	74.89	70.57	86.44	100.50	117.11	132.42	158.28	168.13
	274	17.36	55.52	60.19	71.80	83.27	96.18	114.30	129.51	146.90	168.86
	282	17.61	57.91	63.46	74.54	87.47	101.74	119.81	136.54	152.02	164.86
	283	14.33	57.95	62.49	74.58	86.80	99.80	116.47	131.69	148.05	161.01
	291	17.65	61.83	66.82	79.54	93.20	107.49	120.78	136.44	154.10	172.66
	292	18.20	74.77	80.27	94.84	111.08	131.07	148.78	168.59	190.70	210.25
	300	14.81	51.71	57.12	68.12	78.00	91.12	104.63	120.49	136.30	152.64
	301	15.21	48.32	53.88	64.44	73.76	86.45	100.33	114.54	132.34	145.73
	309	14.67	51.08	56.33	67.65	81.21	93.84	112.18	125.53	144.00	160.81
	310	16.22	50.95	56.37	68.77	80.61	96.20	110.10	126.12	147.93	166.50
	429	16.19	58.42	65.39	76.15	90.93	104.64	122.19	124.64	157.15	173.30
	430	15.47	58.33	63.72	73.14	83.91	95.40	108.69	136.85	142.43	157.74
	438	14.55	60.25	64.57	76.11	85.69	97.07	111.80	124.14	138.41	153.14
	439	14.52	64.75	69.96	82.35	94.72	106.08	123.80	137.25	151.63	167.40
	456	14.90	53.60	58.17	70.56	81.95	93.90	111.55	128.09	144.28	165.52
	457	14.67	56.87	60.75	73.44	87.64	100.82	117.84	133.31	153.20	170.82
	496	15.88	58.04	64.83	77.87	90.35	103.46	121.16	138.77	155.88	173.97
	497	14.41	60.49	65.49	78.25	90.07	102.79	118.19	134.32	148.66	164.91

[a]Mg/kg/day of Methoxychlor.

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Table A-41. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 1 of 4)

		Postnatal Day									
Dose[a]	Male ID	38	40	42	44	46	48	50	52	54	56
0	102	179.26	201.68	218.66	233.34	250.31	270.70	288.45	307.46	332.96	347.33
	103	162.17	180.24	199.42	214.12	231.85	252.61	268.27	288.91	301.89	316.29
	111	175.59	192.78	209.94	229.11	243.02	268.83	285.11	298.48	323.78	338.62
	112	180.71	197.16	214.07	236.15	252.64	276.70	295.16	308.50	330.99	344.37
	120	182.37	199.75	219.23	242.88	258.15	282.39	303.75	317.52	343.88	357.75
	121	192.97	213.10	232.34	248.15	264.48	290.60	313.33	325.17	352.10	370.68
	193	169.19	184.59	202.14	219.44	241.64	258.32	275.65	289.57	312.29	326.76
	194	191.66	207.17	225.36	243.85	265.67	283.72	305.29	314.53	336.03	359.00
	202	212.42	228.21	251.82	269.45	295.12	322.53	345.34	360.79	386.02	400.30
	203	229.30	242.22	269.34	289.88	321.22	350.26	373.12	388.53	415.90	438.10
	211	211.35	227.18	248.18	270.84	296.57	315.69	335.10	352.20	385.34	402.90
	212	193.94	209.74	226.92	247.13	294.88	289.52	316.18	328.80	352.51	370.86
	229	167.70	178.63	197.83	213.17	231.22	245.58	265.29	281.90	303.32	317.06
	230	185.49	201.28	215.95	229.52	254.72	266.38	288.88	299.68	325.52	338.32
	353	220.94	242.57	261.82	284.17	307.23	324.50	348.11	380.32	386.19	413.00
	354	233.29	256.02	278.13	296.41	318.64	341.03	360.80	383.30	399.60	420.30
	362	187.20	204.26	223.40	239.99	262.30	279.44	295.40	316.68	334.30	355.51
	363	214.29	234.81	255.15	273.48	296.46	320.49	335.10	358.44	380.97	400.20
	371	206.02	224.98	249.77	266.95	291.25	307.12	326.10	347.69	368.18	385.55
	372	192.50	210.37	229.53	246.99	268.23	286.14	301.30	326.88	342.46	359.01
	380	197.98	219.99	242.25	259.66	286.35	307.92	322.30	356.00	373.58	396.01
	381	188.63	210.49	226.97	245.17	271.78	291.41	307.80	337.44	351.25	369.57
	490	197.10	215.38	235.32	261.22	284.44	300.66	314.56	335.59	354.01	368.34

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Table A-41. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 2 of 4)

Dose[a]	Male ID	Postnatal Day 38	40	42	44	46	48	50	52	54	56
25	128	207.41	227.83	245.43	261.82	276.53	305.34	320.63	342.00	367.15	387.48
	135	199.54	220.19	239.45	248.62	267.25	287.79	304.11	322.60	344.01	354.54
	136	210.38	230.34	245.13	263.22	283.60	310.90	328.17	346.00	375.02	390.27
	238	226.51	248.21	268.12	289.71	316.29	346.47	369.02	386.04	425.00	439.10
	239	220.10	238.71	262.02	277.69	306.14	328.30	352.04	368.43	397.60	411.30
	247	203.99	220.85	242.05	259.66	277.64	295.94	320.96	333.17	352.98	371.64
	248	195.44	210.24	231.71	246.79	267.47	288.39	307.03	320.47	337.76	352.25
	255	175.74	193.55	212.91	226.87	251.57	270.11	290.04	299.51	318.83	333.05
	256	190.07	210.16	228.53	244.23	267.82	287.58	301.01	316.96	337.47	354.19
	264	192.16	204.72	221.57	241.39	261.95	283.91	299.03	315.15	337.70	350.04
	265	167.71	183.12	197.14	216.32	233.88	250.94	267.32	280.14	303.17	313.32
	393	207.87	227.07	246.18	263.39	284.66	305.32	320.50	345.15	357.31	378.72
	394	191.12	207.01	225.12	239.09	263.38	282.49	298.10	317.40	327.53	344.25
	402	197.44	216.48	230.64	253.11	272.59	293.63	309.00	331.56	345.79	367.98
	403	166.75	183.34	199.20	215.24	236.88	252.26	263.90	287.08	302.66	327.79
	411	190.44	206.13	220.13	246.51	266.12	286.75	308.60	334.58	349.16	373.08
	412	166.66	184.01	199.20	219.78	237.66	255.15	271.10	292.94	309.84	326.10

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Table A-41. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 3 of 4)

Dose[a]	Male ID	Postnatal Day 38	40	42	44	46	48	50	52	54	56
50	152	198.20	216.96	232.11	251.00	267.54	288.46	308.58	319.60	347.97	361.84
	153	191.28	209.06	225.22	245.80	261.83	282.27	308.71	320.90	354.81	375.31
	161	188.10	207.26	222.61	241.19	262.15	285.89	304.94	324.00	349.63	370.21
	162	179.39	198.39	211.29	233.32	247.68	271.77	292.46	305.50	325.72	337.52
	169	195.40	205.51	227.03	250.21	262.36	287.66	301.75	315.90	335.36	345.57
	170	184.20	203.77	219.28	240.19	254.94	275.96	297.25	311.40	332.72	344.47
	177	230.74	252.60	273.86	291.79	311.91	339.57	370.61	382.84	415.80	436.90
	178	219.11	240.25	258.33	277.30	297.89	319.10	343.14	359.04	383.78	407.70
	184	180.43	202.32	218.13	236.28	252.25	274.26	290.97	303.94	326.16	340.16
	185	171.10	191.14	207.56	224.89	241.76	264.13	283.52	298.61	320.85	331.14
	318	186.30	203.39	219.80	237.31	258.24	274.74	296.76	312.26	336.19	346.55
	319	158.53	172.15	187.84	203.29	223.19	239.18	260.70	274.18	294.31	309.17
	327	195.37	210.44	226.04	243.29	260.16	281.43	298.76	314.15	330.69	348.38
	328	213.10	224.96	244.01	261.31	281.50	299.28	318.38	336.13	356.57	376.37
	336	177.30	193.48	213.91	231.21	255.40	271.40	292.13	300.52	324.10	337.99
	337	168.59	182.97	198.09	214.13	234.97	251.08	265.51	276.72	296.91	308.72
	344	189.98	207.18	225.36	240.80	365.24	283.62	298.87	308.21	333.80	347.85
	345	181.52	196.55	211.95	228.55	250.81	269.43	285.01	298.98	320.94	338.39
	465	206.10	227.75	246.50	264.62	288.65	312.98	325.90	357.02	369.81	393.30
	466	211.20	229.41	247.71	266.13	293.79	309.60	326.20	348.30	365.37	385.46
	474	182.08	197.70	214.52	233.81	257.14	270.70	283.05	311.86	332.80	342.12
	475	201.34	216.57	241.54	257.99	288.15	309.42	325.42	357.94	370.00	398.50
	483	187.04	199.23	217.73	234.86	256.54	276.67	286.11	311.44	321.90	350.72
	484	195.23	214.04	232.29	257.16	277.74	297.15	313.81	339.36	358.19	382.81

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US EPA ARCHIVE DOCUMENT

Table A-41. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 4 of 4)

Dose[a]	Male ID	Postnatal Day 38	40	42	44	46	48	50	52	54	56
100	273	187.42	204.23	223.32	238.31	259.52	277.71	299.93	316.50	335.78	352.02
	274	188.36	204.04	226.92	243.37	266.64	288.08	303.42	315.53	339.99	355.31
	282	183.05	201.45	212.32	231.41	246.85	260.83	281.35	292.45	312.46	329.30
	283	180.40	195.95	209.18	227.93	244.85	266.98	280.48	298.44	317.64	334.60
	291	189.23	208.85	222.78	238.30	260.31	280.86	300.59	312.82	336.55	351.79
	292	233.28	251.26	273.64	292.71	315.99	336.30	359.75	375.22	402.20	421.20
	300	171.88	189.81	204.06	217.94	237.56	258.76	272.15	285.80	305.79	316.94
	301	160.94	177.79	191.75	208.71	230.92	254.14	267.11	279.09	302.73	317.58
	309	182.64	195.52	210.75	234.46	257.38	273.80	296.90	309.38	337.93	353.36
	310	180.07	193.96	211.94	230.87	255.20	276.07	297.73	309.06	331.24	349.27
	429	193.68	212.78	231.52	247.28	272.13	291.63	310.40	331.02	351.07	364.76
	430	174.12	192.31	209.37	227.79	252.54	265.38	284.70	306.27	325.25	343.60
	438	170.14	181.06	196.94	211.59	227.08	242.51	253.00	277.44	292.03	310.18
	439	181.28	193.70	210.76	229.36	243.35	261.68	270.50	298.04	313.67	321.45
	456	183.20	199.46	219.24	238.52	261.18	281.74	293.90	320.90	366.86	357.63
	457	185.91	205.95	219.60	235.80	261.08	276.34	294.70	319.37	335.56	352.36
	496	191.11	214.12	227.58	251.70	269.27	290.98	304.14	330.55	345.28	356.97
	497	181.90	199.29	216.95	236.04	249.72	273.51	288.11	309.03	324.83	336.61

[a]Mg/kg/day of Methoxychlor.

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Table A-42. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period (page 1 of 4)

		Postnatal Day									
Dose[a]	Male ID	58	60	62	64	66	68	70	72	74	76
0	102	359.58	365.85	385.04	400.20	406.20	424.10	427.90	444.30	448.60	.[b]
	103	331.07	348.09	360.04	374.57	382.65	400.20	402.50	415.60	425.20	.[b]
	111	353.67	359.50	381.96	397.60	399.70	419.20	421.40	439.70	451.40	.[b]
	112	361.70	369.59	390.43	403.80	404.80	421.90	429.40	446.00	453.50	.[b]
	120	373.66	384.99	403.60	414.10	415.60	437.10	442.60	455.00	460.20	.[b]
	121	386.38	392.03	415.30	427.40	427.20	448.70	459.70	472.00	483.40	.[b]
	193	333.67	355.46	370.28	384.95	385.51	406.50	421.30	428.60	441.40	.[b]
	194	365.74	381.33	399.10	412.90	413.90	433.90	449.60	457.00	464.40	.[b]
	202	420.10	441.50	455.90	473.30	474.60	502.20	507.70	520.30	528.30	.[b]
	203	447.10	473.50	491.40	506.10	512.70	536.00	545.90	561.00	564.30	.[b]
	211	418.20	434.10	449.20	468.50	477.40	501.70	518.20	529.40	540.00	554.90
	212	384.45	402.00	415.50	432.80	440.60	456.30	467.00	475.90	489.60	497.70
	229	328.77	347.59	357.15	372.02	381.81	393.83	414.10	419.30	434.50	431.50
	230	344.74	367.72	385.58	393.40	396.90	417.80	427.10	434.00	438.60	437.70
	353	428.90	445.90	464.10	471.90	496.40	501.50	516.60	527.60	541.90	555.90
	354	430.20	452.30	461.90	465.40	484.80	499.40	512.10	517.30	527.20	535.50
	362	368.23	389.30	405.50	411.90	426.80	428.40	458.90	468.00	479.40	490.10
	363	423.30	445.50	457.10	473.00	498.00	510.00	526.90	538.20	551.30	570.70
	371	398.89	416.10	431.00	439.10	452.30	468.00	483.50	491.10	498.10	510.90
	372	373.44	387.69	400.70	406.00	425.10	438.80	454.70	460.20	473.00	492.80
	380	406.50	428.30	440.10	447.20	476.00	485.10	498.50	509.80	520.70	531.90
	381	379.57	404.40	424.60	425.50	449.30	463.10	477.60	486.00	496.20	511.60
	490	393.60	408.20	422.50	432.20	447.40	456.00	466.00	479.10	486.50	503.90

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Table A-42. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period (page 2 of 4)

		Postnatal Day									
Dose[a]	Male ID	58	60	62	64	66	68	70	72	74	76
25	128	412.40	420.50	443.80	449.00	462.90	487.50	503.70	514.60	527.10	.[b]
	135	378.07	386.93	406.00	410.20	417.50	426.60	438.70	444.90	457.10	.[b]
	136	411.10	422.40	444.00	451.40	463.40	473.80	486.70	501.50	509.20	.[b]
	238	454.30	481.90	499.30	515.30	521.80	546.20	560.80	578.90	590.40	.[b]
	239	426.70	449.60	464.40	478.90	484.90	500.90	518.70	542.20	548.70	.[b]
	247	386.56	401.80	416.10	430.20	436.40	452.30	468.50	478.40	489.30	.[b]
	248	362.60	378.36	386.22	396.72	400.00	415.30	429.50	439.20	442.20	.[b]
	255	343.01	358.76	370.19	385.49	386.94	402.60	412.90	420.90	434.40	439.20
	256	364.70	379.01	391.72	399.30	404.10	413.70	427.30	436.70	443.60	456.20
	264	358.68	379.00	393.20	406.20	409.70	419.70	438.10	440.30	452.30	458.90
	265	329.18	347.14	356.15	363.52	373.32	391.71	400.40	404.50	419.90	422.20
	393	386.86	406.20	421.10	427.90	450.00	449.10	472.60	480.60	485.50	496.90
	394	355.88	367.37	380.96	384.70	407.60	417.80	431.10	438.30	444.90	452.90
	402	381.30	399.70	410.10	422.00	433.90	442.20	454.30	461.60	475.80	478.70
	403	338.68	354.42	373.02	375.61	392.20	401.50	413.00	420.60	430.10	436.50
	411	380.84	407.10	424.00	425.30	442.80	460.10	477.60	489.00	494.00	514.20
	412	334.37	355.81	369.21	376.67	393.45	406.40	423.50	435.40	439.20	450.10

(continued)

US EPA ARCHIVE DOCUMENT

Table A-42. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period (page 3 of 4)

		Postnatal Day									
Dose[a]	Male ID	58	60	62	64	66	68	70	72	74	76
50	152	375.42	385.55	407.70	420.40	426.30	444.60	457.30	469.00	480.00	.[b]
	153	386.60	397.59	425.10	441.00	445.40	462.80	482.00	497.30	507.10	.[b]
	161	381.67	395.29	416.70	430.90	438.80	455.00	465.90	488.20	494.90	.[b]
	162	350.44	358.69	376.07	391.15	393.02	408.90	419.30	427.10	429.60	.[b]
	169	357.91	369.52	376.06	389.05	398.20	408.10	414.40	426.70	432.80	.[b]
	170	362.03	372.82	386.50	400.90	403.80	421.30	424.10	440.50	447.80	.[b]
	177	454.30	466.50	486.60	510.60	519.50	543.50	560.40	575.10	587.90	.[b]
	178	420.50	436.50	457.70	476.30	489.60	515.30	516.30	523.90	538.40	.[b]
	184	358.51	368.93	375.35	394.51	407.00	424.10	431.70	443.00	452.30	.[c]
	185	349.63	362.30	381.28	391.41	399.20	413.50	421.80	437.70	444.70	448.20
	318	355.48	377.00	385.72	399.40	409.00	426.20	432.50	446.30	457.90	.[b]
	319	320.24	337.94	350.17	365.85	370.83	390.17	401.70	406.70	417.20	.[b]
	327	360.65	369.82	386.43	394.50	403.60	417.30	425.20	434.50	441.50	452.60
	328	388.52	400.30	409.60	433.60	437.80	449.40	463.30	473.50	476.30	483.40
	336	348.66	361.11	376.99	389.69	392.73	408.40	421.10	430.20	435.30	447.80
	337	316.07	332.15	344.24	353.39	360.43	374.90	382.79	388.28	398.31	402.30
	344	357.06	376.92	388.69	395.36	400.90	417.00	433.30	437.10	445.50	451.20
	345	344.21	362.85	371.88	393.63	397.60	412.70	428.80	439.50	444.00	449.70
	465	399.63	411.50	434.00	439.30	457.10	469.30	493.10	491.40	504.20	524.20
	466	394.01	412.50	434.30	436.10	458.00	465.70	487.50	491.40	496.10	510.40
	474	360.55	370.70	387.17	402.10	415.10	425.70	440.20	450.20	466.00	475.80
	475	406.30	430.40	447.40	454.10	476.20	497.70	511.60	521.50	530.60	543.90
	483	358.76	380.31	397.65	403.10	424.30	440.70	451.90	465.20	467.80	486.90
	484	394.40	415.60	436.00	439.00	464.30	476.00	487.30	498.10	505.20	520.20

(continued)

US EPA ARCHIVE DOCUMENT

Table A-42. Individual F_1 Undosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period (page 4 of 4)

		Postnatal Day									
Dose[a]	Male ID	58	60	62	64	66	68	70	72	74	76
100	273	361.35	377.40	390.09	397.16	405.00	417.50	430.30	442.30	445.30	.[b]
	274	359.90	379.03	391.08	399.21	403.40	415.90	426.50	435.20	438.30	.[b]
	282	338.59	344.87	363.25	375.46	385.62	391.86	411.90	420.90	430.90	.[b]
	283	350.70	361.67	377.79	396.70	401.60	418.00	429.80	445.10	455.30	.[b]
	291	355.94	382.63	390.60	408.80	411.70	430.90	443.20	447.90	449.80	.[b]
	292	430.90	455.20	470.10	481.60	497.80	516.50	532.20	540.00	557.70	.[b]
	300	331.05	342.80	350.63	364.73	374.23	386.51	400.10	406.00	424.30	429.20
	301	328.82	347.73	357.92	368.63	375.79	391.17	404.10	412.70	423.80	433.60
	309	368.73	386.63	406.20	418.30	429.50	445.00	458.90	466.70	480.70	487.20
	310	365.55	381.33	392.87	408.00	411.30	428.20	442.30	442.50	461.20	473.80
	429	383.30	404.50	413.30	417.20	431.70	446.60	456.70	463.20	475.70	485.90
	430	355.84	376.83	393.18	402.00	415.40	429.50	441.80	448.60	463.60	472.80
	438	316.50	340.07	349.95	358.40	377.73	384.18	396.74	401.90	417.60	420.20
	439	329.19	350.22	364.25	365.21	382.65	397.80	407.60	413.70	421.40	434.70
	456	366.40	384.37	405.80	406.90	408.20	433.10	451.80	469.10	477.00	485.80
	457	366.37	385.95	405.10	407.20	431.80	436.10	452.30	470.20	478.30	483.80
	496	377.40	386.82	406.30	408.90	433.60	446.10	454.00	463.70	470.70	486.30
	497	353.49	369.56	374.11	383.96	405.80	418.70	428.00	439.80	446.90	456.10

[a]Mg/kg/day of Methoxychlor.
[b]Male was necropsied prior to postnatal day 76.
[c]Weight was inadvertently not recorded.

US EPA ARCHIVE DOCUMENT

Table A-43. Individual F_1 Undosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 1 of 2)

Dose[a]	Male ID	Day[b]	Clinical Observations
0	102	70	Alopecia: face
		71	Alopecia: face
		72	Alopecia: face
		73	Alopecia: face
		74	Alopecia: face
		75	Alopecia: face
25	128	65	Alopecia: limb(s)
		66	Alopecia: limb(s)
		67	Alopecia: limb(s)
		68	Alopecia: limb(s)
		69	Alopecia: limb(s)
		70	Alopecia: limb(s)
		71	Alopecia: limb(s)
		72	Alopecia: limb(s)
		73	Alopecia: limb(s)
		74	Alopecia: limb(s)
		75	Alopecia: limb(s)
100	273	66	Alopecia: face
		67	Alopecia: face
		68	Alopecia: face
		69	Alopecia: face
		70	Alopecia: face
		71	Alopecia: face
		72	Alopecia: face
		73	Alopecia: face
		74	Alopecia: face
		75	Alopecia: face
	430	64	Alopecia: face
		65	Alopecia: face
		66	Alopecia: face
		67	Alopecia: face
		68	Alopecia: face
		69	Alopecia: face
		70	Alopecia: face
		71	Alopecia: face
		72	Alopecia: face
		73	Alopecia: face
		74	Alopecia: face
		75	Alopecia: face

(continued)

US EPA ARCHIVE DOCUMENT

Table A-43. Individual F_1 Undosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 2 of 2)

Dose[a]	Male ID	Day[b]	Clinical Observations
100	438	64	Alopecia: face
		65	Alopecia: face
		66	Alopecia: face
		67	Alopecia: face
		68	Alopecia: face
		69	Alopecia: face
		70	Alopecia: face
		71	Alopecia: face
		72	Alopecia: face
		73	Alopecia: face
		74	Alopecia: face
		75	Alopecia: face

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

US EPA ARCHIVE DOCUMENT

Table A-44. Individual F_1 Undosed Pubertal Male Preputial Separation Data (page 1 of 2)

Dose[a]	Male ID	Day of Acquisition[b]	Body Weight (g)
0	102	40	201.68
	103	41	208.51
	111	40	192.78
	112	40	197.16
	120	39	190.91
	121	39	205.65
	193	41	195.99
	194	40	207.17
	202	40	228.21
	203	42	269.34
	211	39	219.88
	212	40	209.74
	229	42	197.83
	230	40	201.28
	353	37	217.20
	354	40	256.02
	362	43	228.74
	363	41	245.62
	371	38	206.02
	372	38	192.50
	380	38	197.98
	381	39	200.34
	490	41	229.16
25	128	40	227.83
	135	40	220.19
	136	43	257.41
	238	39	237.20
	239	39	231.29
	247	39	208.88
	248	39	201.81
	255	39	186.96
	256	39	200.32
	264	39	197.69
	265	41	189.14
	393	40	227.07
	394	38	191.12
	402	44	253.11
	403	42	199.20
	411	40	206.13
	412	40	184.01

(continued)

US EPA ARCHIVE DOCUMENT

Table A-44. Individual F_1 Undosed Pubertal Male Preputial Separation Data (page 2 of 2)

Dose[a]	Male ID	Day of Acquisition[b]	Body Weight (g)
50	152	42	232.11
	153	42	225.22
	161	42	222.61
	162	41	203.24
	169	42	227.03
	170	42	219.28
	177	42	273.86
	178	42	258.33
	184	40	202.32
	185	42	207.56
	318	42	219.80
	319	43	228.65
	327	39	201.75
	328	39	218.20
	336	40	193.48
	337	41	191.09
	344	41	217.74
	345	40	196.55
	465	38	206.10
	466	39	219.34
	474	42	214.52
	475	42	241.54
	483	42	217.73
	484	41	224.31
100	273	40	204.23
	274	38	188.36
	282	40	201.45
	283	39	186.26
	291	40	208.85
	292	39	241.23
	300	39	180.72
	301	41	186.82
	309	40	195.52
	310	39	186.25
	429	37	183.72
	430	38	174.12
	438	45	217.87
	439	39	188.15
	456	40	199.46
	457	43	228.76
	496	42	227.58
	497	39	188.24

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.

US EPA ARCHIVE DOCUMENT

Table A-45. Individual F_1 Undosed Pubertal Male Reproductive Organ Weights and Measurements (page 1 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
0	102	455.8	0	0.2288	3.3651	0.5418	0.4646	1.2055	0.5335	0.4319	0.9654	1.1012	0.1355
	103	427.5	0	0.1948	3.2223	0.4954	0.4941	1.2875	0.7342	0.4680	1.2022	0.9900	0.1493
	111	453.1	0	0.1802	3.5165	0.4873	0.5018	1.0564	0.4912	0.3666	0.8578	1.0468	0.0967
	112	457.1	0	0.1911	3.4637	0.5088	0.4729	1.1224	0.4663	0.8060	1.2723	1.0197	0.1166
	120	458.1	0	0.1527	2.9999	0.5360	0.5464	1.4961	0.5582	0.4656	1.0238	1.0178	0.0773
	121	482.5	0	0.1174	3.4564	0.5143	0.5710	2.0331	0.2180	0.4956	0.7136	1.2999	0.1030
	193	443.2	0	0.2268	.[b]	0.3537	0.3650	1.0989	0.5018	0.3306	0.8324	0.9429	0.1004
	194	466.8	0	0.1213	.[b]	0.3285	0.3398	0.9669	0.6689	0.3502	1.0191	1.0089	0.0743
	202	529.5	0	0.1230	3.7694	0.5694	0.5799	1.4064	0.6689	0.4137	1.0826	1.2163	0.1379
	203	567.5	0	0.2602	3.7906	0.3143	0.5187	1.3571	0.6371	0.5012	1.1383	1.0980	0.0978
	211	556.9	0	0.1990	3.3972	0.5485	0.5286	1.3513	0.7530	0.5780	1.3310	1.0696	0.1647
	212	497.7	0	0.1161	3.3585	0.5007	0.4997	1.3203	0.4456	0.3969	0.8425	1.2174	0.1354
	229	431.9	0	0.2176	3.2329	0.5540	0.4845	1.1239	0.3398	0.3148	0.6546	0.8236	0.0820
	230	440.0	0	0.1259	3.7023	0.5461	0.5698	1.0162	0.5022	0.3181	0.8203	0.9886	0.0988
	353	551.2	0	0.1157	3.5539	0.6126	0.6130	1.2675	0.7944	0.3126	1.1070	1.3235	0.1564
	354	530.7	0	0.1224	3.5053	0.5690	0.5710	1.0194	0.6105	0.5355	1.1460	1.2054	0.0928
	362	490.4	0	0.1098	3.3155	0.5537	0.5131	1.1285	0.4379	0.4025	0.8404	1.0722	0.0877
	363	570.2	0	0.2403	3.8937	0.6452	0.5853	1.4552	0.6532	0.3618	1.0150	1.0250	0.1368
	371	496.9	0	0.1399	3.2047	0.4816	0.4970	0.9500	0.4262	0.2016	0.6278	1.1324	0.1319
	372	484.8	0	0.1277	3.3201	0.5328	0.4591	1.1461	0.3799	0.2960	0.6759	1.1248	0.1423
	380	533.6	0	0.1700	3.4531	0.5670	0.5523	1.0682	0.5285	0.4278	0.9563	1.0722	0.1246
	381	518.0	0	0.1104	3.5659	0.5574	0.5238	1.2051	0.4789	0.4690	0.9479	1.1532	0.0925
	490	491.2	0	0.1205	3.1965	0.4903	0.4927	1.2379	0.4345	0.3332	0.7677	1.1828	0.0955

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Table A-45. Individual F_1 Undosed Pubertal Male Reproductive Organ Weights and Measurements (page 2 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
25	128	525.8	0	0.1143	3.7499	0.5576	0.5966	1.5074	0.5938	0.7705	1.3643	1.2308	0.1746
	135	451.4	0	0.1332	3.0331	0.5777	0.5879	1.5195	0.5777	0.4563	1.0340	1.3908	0.1001
	136	516.0	0	0.2146	3.3030	0.5294	0.4620	1.3724	0.4075	0.4662	0.8737	1.1986	0.1300
	238	588.7	0	0.3657	4.0685	0.6186	0.5945	1.3706	0.6905	0.4975	1.1880	1.4441	0.1321
	239	545.1	0	0.1066	3.5705	0.5905	0.5191	1.5134	0.5545	0.4964	1.0509	1.1735	0.1187
	247	491.9	0	0.1074	3.5871	0.5479	0.4956	1.4700	0.6527	0.4692	1.1219	1.3530	0.1622
	248	448.1	0	0.1218	3.3746	0.5252	0.5183	1.2072	0.6008	0.3379	0.9387	1.1745	0.1517
	255	437.9	0	0.1123	3.1341	0.4819	0.4259	1.1337	0.3844	0.4056	0.7900	1.3250	0.1420
	256	451.3	0	0.2259	3.3678	0.5460	0.4779	1.4249	0.5361	0.3254	0.8615	1.0805	0.1199
	264	458.0	0	0.1242	3.4602	0.5323	0.5336	1.0476	0.5557	0.4403	0.9960	1.1745	0.1175
	265	420.7	0	0.2454	3.0022	0.5227	0.4716	1.2645	0.4131	0.3045	0.7176	1.1064	0.0800
	393	486.1	0	0.1223	3.3410	0.5420	0.5427	1.0045	0.5687	0.3430	0.9117	1.2937	0.1090
	394	444.9	0	0.2820	3.1779	0.5406	0.5114	0.9570	0.6145	0.6219	1.2364	1.0600	.[c]
	402	484.4	0	0.1322	3.5203	0.5625	0.5748	1.0095	.[b]	0.3603	.[d]	1.0685	0.1241
	403	444.9	0	0.1648	3.0376	0.5733	0.5318	0.8212	0.5094	0.3185	0.8279	0.9120	0.1222
	411	502.1	0	0.2780	3.3600	0.5424	0.5372	1.1596	0.4675	0.3319	0.7994	0.9319	0.0975
	412	444.8	0	0.1103	3.0323	0.4789	0.5047	0.9144	0.5071	0.5160	1.0231	1.0979	0.1021

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US EPA ARCHIVE DOCUMENT

Table A-45. Individual F_1 Undosed Pubertal Male Reproductive Organ Weights and Measurements (page 3 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
50	152	475.0	0	0.2344	2.8718	0.4609	0.4738	1.3262	0.5878	0.3579	0.9457	0.9071	0.1370
	153	509.5	0	0.0917	2.8766	0.4733	0.4653	1.1951	0.4231	0.3769	0.8000	1.2630	0.1062
	161	496.6	0	0.0637	3.3107	0.4483	0.5089	1.5590	0.3376	.[b]	.[d]	1.0198	0.1483
	162	436.6	0	0.2243	3.6983	0.5188	0.4809	1.2291	0.4425	0.4201	0.8626	1.1810	0.1633
	169	441.3	0	0.1567	3.5169	0.5450	0.5370	1.5094	0.1316	0.3974	0.5290	1.2196	0.0815
	170	443.3	0	0.2373	3.2899	0.5517	0.4690	0.9890	0.4098	0.3710	0.7808	0.9303	0.0660
	177	583.4	0	0.1135	3.6978	0.5284	0.5303	1.2001	0.3886	0.4166	0.8052	1.1296	0.0849
	178	539.4	0	0.2760	3.5771	.[e]	0.4838	1.0209	0.3635	0.3518	0.7153	1.1637	0.0622
	184	460.5	0	0.2839	3.3020	0.5232	0.5331	1.3483	0.5548	0.3597	0.9145	1.3335	0.0853
	185	456.5	0	0.2949	2.9572	0.5273	0.4900	1.3207	0.6883	0.3854	1.0737	1.2973	0.1051
	318	453.2	0	0.2765	3.1272	0.5610	0.5329	1.0353	0.3768	0.4204	0.7972	1.1992	.[c]
	319	418.8	0	0.1257	2.8168	0.4994	0.4390	1.5458	0.4725	0.1959	0.6684	1.1721	0.1132
	327	450.2	0	0.1150	3.4679	0.4751	0.4859	1.3485	0.3626	0.3830	0.7456	1.1914	0.0880
	328	481.3	0	0.1101	3.6899	0.6185	0.6025	1.3913	0.5382	0.5127	1.0509	1.8085	0.1357
	336	445.1	0	0.2482	3.4580	0.5154	0.4792	1.1393	0.7730	0.4280	1.2010	1.0493	0.1674
	337	391.4	0	0.1155	3.5261	0.4956	0.4652	1.0645	0.5399	0.4240	0.9639	1.1481	0.2033
	344	462.7	0	0.1137	3.1441	0.5228	0.5168	0.9105	0.5168	0.4768	0.9936	1.0488	0.1013
	345	463.3	0	0.2045	3.1676	0.5165	0.5390	1.0185	0.4915	0.3728	0.8643	1.0118	0.1008
	465	516.7	0	0.1225	3.6135	0.6465	0.5751	1.3802	0.6845	0.5732	1.2577	1.3638	0.1066
	466	507.1	0	0.2228	3.6386	0.5835	0.5919	1.4296	0.5073	0.5314	1.0387	1.3732	0.0904
	474	470.5	0	0.1301	3.0407	0.5295	0.5018	1.1136	0.5431	0.4097	0.9528	1.3554	0.0904
	475	534.0	0	0.1339	3.0941	0.5354	0.5615	1.0342	0.4622	0.5808	1.0430	1.3806	0.0974
	483	483.4	0	0.1630	3.4096	0.5742	0.5592	1.1451	0.5478	0.3701	0.9179	0.9417	0.1129
	484	520.3	0	0.1167	3.4229	0.5626	0.5949	1.0096	0.6332	0.4727	1.1059	1.0403	0.1124

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Table A-45. Individual F_1 Undosed Pubertal Male Reproductive Organ Weights and Measurements (page 4 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
100	273	451.4	0	0.2215	3.2782	0.5352	0.5489	1.3072	0.5371	0.5276	1.0647	1.1598	0.0769
	274	439.6	0	0.0888	3.4442	0.5250	0.5130	1.3494	0.5284	0.4432	0.9716	1.1090	0.0863
	282	431.5	0	0.2673	3.1249	0.5227	0.4905	1.2552	0.7041	0.3673	1.0714	1.1807	0.0981
	283	448.4	0	0.1441	3.0718	0.5592	0.5311	1.2849	0.7738	0.5256	1.2994	1.2501	0.1480
	291	450.5	0	0.1226	3.2142	0.5550	0.4968	1.5505	0.4750	0.2952	0.7702	1.3397	0.1326
	292	550.7	0	0.1050	3.3397	0.5840	0.5240	1.1984	0.6140	0.4138	1.0278	1.4228	0.1397
	300	433.2	0	0.1119	3.3868	0.5378	0.5093	1.2159	0.5782	0.4712	1.0494	1.3693	0.0868
	301	430.8	0	0.2919	3.1146	0.4825	0.4550	1.1306	0.5776	0.4151	0.9927	1.0541	0.1186
	309	487.1	0	0.1081	3.3412	0.5592	0.5848	1.2499	0.4332	0.4103	0.8435	1.1337	0.1292
	310	472.0	0	0.1023	2.9940	0.4440	0.4487	1.4170	0.4185	0.3297	0.7482	1.1123	0.0725
	429	487.4	0	0.0926	3.3110	0.5179	0.4978	1.3559	0.4884	0.4703	0.9587	1.2650	0.1220
	430	471.8	0	0.2478	3.3304	0.5450	0.5396	1.1621	0.4490	0.7580	1.2070	1.0039	0.1079
	438	413.0	0	0.1028	2.8112	0.4727	0.4890	0.9805	0.4399	0.4057	0.8456	0.8805	0.1134
	439	419.8	0	0.2504	3.2651	0.5420	0.5704	0.9209	0.4346	0.3818	0.8164	0.9827	0.1622
	456	499.1	0	0.1172	3.0219	0.4866	0.4845	1.0306	0.4944	0.4872	0.9816	1.1999	0.0856
	457	477.9	0	0.1709	3.3021	0.5283	0.5296	0.8843	0.3720	0.3210	0.6930	1.0373	0.0805
	496	480.9	0	0.1333	3.0220	0.4832	0.5013	1.4515	0.4653	0.5289	0.9942	1.2825	0.0966
	497	452.7	0	0.1278	3.0872	0.5121	0.4988	1.2057	0.7266	0.5814	1.3080	1.3237	0.1276

[a]Mg/kg/day of Methoxychlor.
[b]Weight was a statistical outlier and therefore excluded.
[c]Right cowper's gland was missing.
[d]Whole prostate weight could not be calculated since the ventral or dorsolateral prostate weight was a statistical outlier and therefore was excluded.
[e]Weight was inadvertently not recorded.

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Table A-46. Individual F_1 Undosed Pubertal Male Necropsy Weights and Hormone Data (page 1 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
0	102	455.8	0.0102	0.0258	17.3740	0.0615	3.6412	5.76	51.26	13.51
	103	427.5	0.0075	0.0317	18.0013	0.0520	3.7066	5.30	73.07	15.08
	111	453.1	0.0113	0.0353	19.5246	0.0585	3.2124	5.29	41.80	14.23
	112	457.1	0.0097	0.0250	19.2624	0.0571	3.4094	5.52	65.41	8.43
	120	458.1	0.0107	0.0384	18.0002	.[b]	3.5916	6.30	93.28	11.75
	121	482.5	0.0136	0.0332	20.5409	0.0909	3.7978	4.85	60.68	11.28
	193	443.2	0.0125	0.0314	19.2811	0.0632	3.5586	6.25	83.50	9.30
	194	466.8	0.0138	0.0296	19.7410	0.0723	3.3902	6.29	63.63	6.75
	202	529.5	0.0142	0.0350	24.5303	0.0623	4.3883	5.50	69.73	17.33
	203	567.5	0.0122	0.0413	27.2819	0.0684	4.0046	6.45	82.47	14.02
	211	556.9	0.0124	0.0403	25.9640	0.0634	3.4725	5.81	79.88	10.11
	212	497.7	0.0133	0.0278	20.9472	0.0483	3.1616	5.31	75.22	7.85
	229	431.9	0.0131	0.0262	17.0942	0.0656	3.2043	6.41	70.89	8.44
	230	440.0	0.0119	0.0305	17.8310	0.0585	3.5718	5.94	72.31	11.47
	353	551.2	0.0154	0.0339	28.1650	0.0900	4.3285	7.88	94.69	8.74
	354	530.7	0.0170	.[c]	24.0154	0.0725	4.3050	5.21	72.08	9.40
	362	490.4	0.0152	0.0332	24.2748	0.0541	3.5672	6.25	79.35	8.11
	363	570.2	0.0158	0.0358	26.2265	0.0777	3.7133	5.75	64.83	13.91
	371	496.9	0.0131	0.0367	20.5352	0.0734	4.0618	6.80	76.34	12.03
	372	484.8	0.0139	0.0296	21.0057	0.0588	3.8730	6.47	43.58	19.42
	380	533.6	0.0114	0.0456	23.6092	0.0730	4.2766	5.29	72.06	8.21
	381	518.0	0.0150	0.0397	25.7823	0.0718	4.2451	6.04	81.88	8.27
	490	491.2	0.0133	0.0308	20.2215	0.0633	3.7929	5.04	62.28	18.34

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Table A-46. Individual F_1 Undosed Pubertal Male Necropsy Weights and Hormone Data (page 2 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
25	128	525.8	0.0150	0.0397	24.0352	0.0584	3.8545	6.30	80.34	12.10
	135	451.4	0.0155	0.0300	20.0693	0.1070	3.8164	6.41	61.26	10.33
	136	516.0	0.0126	0.0460	25.1794	0.0823	4.0605	6.42	58.66	10.84
	238	588.7	0.0120	0.0371	27.9005	0.0888	4.6423	5.41	64.52	14.91
	239	545.1	0.0137	0.0439	28.7184	0.0625	3.5707	4.90	69.86	29.72
	247	491.9	0.0152	0.0380	21.4653	0.0710	3.9545	6.85	54.98	11.05
	248	448.1	0.0106	0.0348	19.5704	0.0652	3.6617	6.33	61.49	10.15
	255	437.9	0.0140	0.0283	17.6268	0.0549	3.3361	4.96	71.24	12.95
	256	451.3	0.0128	0.0370	19.7834	0.0764	3.5570	5.67	65.61	10.06
	264	458.0	0.0151	0.0359	18.2701	0.0649	3.3399	7.78	66.58	12.19
	265	420.7	0.0128	0.0312	17.1725	0.0546	3.2391	7.21	80.95	8.23
	393	486.1	0.0148	0.0364	21.3331	0.0370	3.7350	5.14	62.18	16.23
	394	444.9	0.0120	0.0337	19.5454	0.0522	3.3623	5.62	98.87	21.13
	402	484.4	0.0126	0.0322	22.3750	0.0849	3.8329	5.16	85.66	7.57
	403	444.9	0.0105	0.0346	21.9173	0.0549	3.7140	6.09	94.13	12.12
	411	502.1	0.0121	0.0445	22.4424	0.0568	3.8041	6.23	66.86	9.51
	412	444.8	0.0134	0.0352	17.1265	0.0534	3.4805	6.90	63.35	10.33

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US EPA ARCHIVE DOCUMENT

Table A-46. Individual F_1 Undosed Pubertal Male Necropsy Weights and Hormone Data (page 3 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
50	152	475.0	0.0140	0.0414	21.2762	0.0736	3.9768	7.27	85.34	10.21
	153	509.5	0.0130	0.0360	22.1951	0.0512	3.9267	4.71	57.51	12.06
	161	496.6	0.0155	0.0386	27.0400	0.0749	4.1282	8.38	125.11	8.00
	162	436.6	0.0095	0.0326	18.7933	0.0657	3.7160	5.35	62.76	12.43
	169	441.3	0.0151	0.0290	18.2086	0.0822	3.7652	6.20	57.56	16.16
	170	443.3	0.0154	0.0287	17.9865	0.0640	3.6463	5.95	68.59	8.82
	177	583.4	0.0163	0.0359	25.0843	0.0699	4.1852	6.75	85.91	8.77
	178	539.4	.[d]	.[c]	23.9913	0.0836	4.5850	5.43	68.24	13.04
	184	460.5	0.0115	0.0298	20.8544	0.0628	3.4608	7.65	83.99	8.10
	185	456.5	0.0122	0.0395	19.7730	0.0513	3.4948	4.99	70.38	5.59
	318	453.2	0.0122	0.0445	19.0507	0.0646	3.4258	5.68	39.62	20.43
	319	418.8	0.0136	0.0314	16.8557	0.0568	2.4658	6.51	57.03	12.88
	327	450.2	0.0142	0.0337	16.1804	0.0578	3.1868	5.08	50.83	8.35
	328	481.3	0.0121	0.0381	18.5000	0.0483	3.6640	5.89	55.57	10.83
	336	445.1	0.0170	0.0318	19.9676	0.0633	3.2076	8.57	88.54	10.10
	337	391.4	0.0147	0.0311	16.2980	0.0548	3.0126	7.28	53.50	7.21
	344	462.7	0.0126	0.0376	18.8639	0.0671	3.8117	5.44	48.90	8.97
	345	463.3	0.0114	0.0379	20.4513	0.0671	3.9126	6.41	68.09	11.09
	465	516.7	0.0131	0.0399	20.0370	0.0617	4.2970	6.34	89.42	8.64
	466	507.1	0.0146	0.0486	21.2226	0.0673	4.1101	6.83	97.02	6.70
	474	470.5	0.0138	0.0318	19.5147	0.0574	3.6097	4.88	66.75	11.24
	475	534.0	0.0140	0.0296	25.2790	0.0641	4.0543	4.30	41.44	13.02
	483	483.4	0.0138	0.0422	22.9394	0.0460	3.8614	5.67	77.28	7.38
	484	520.3	0.0115	0.0366	27.7333	0.0608	4.7751	5.27	81.17	10.26

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US EPA ARCHIVE DOCUMENT

Table A-46. Individual F_1 Undosed Pubertal Male Necropsy Weights and Hormone Data (page 4 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
100	273	451.4	0.0085	0.0319	19.5946	0.0648	3.3694	6.08	95.07	15.15
	274	439.6	0.0123	0.0263	19.1734	0.0665	3.1107	5.75	90.80	14.03
	282	431.5	0.0124	0.0266	17.3515	0.0575	3.1822	4.57	58.28	10.28
	283	448.4	0.0120	0.0333	18.9504	0.0567	3.5363	6.59	70.36	8.15
	291	450.5	0.0136	0.0339	20.5335	0.0554	3.5341	5.35	54.83	7.95
	292	550.7	0.0169	0.0399	26.6145	0.0599	4.5553	4.63	63.12	7.82
	300	433.2	0.0147	0.0287	18.1640	0.0662	3.5483	7.06	95.20	8.87
	301	430.8	0.0109	0.0312	18.2740	0.0505	3.3773	5.93	49.78	8.70
	309	487.1	0.0148	0.0362	23.1120	0.0737	4.3041	4.79	80.77	18.95
	310	472.0	0.0137	0.0424	20.1784	0.0624	3.8856	6.59	73.01	11.53
	429	487.4	0.0149	.[e]	20.9708	0.0557	3.8278	5.36	55.45	8.72
	430	471.8	0.0117	0.0332	19.5571	0.0691	3.6504	4.62	81.98	7.50
	438	413.0	0.0115	0.0313	18.4800	0.0629	3.1510	5.27	56.76	15.36
	439	419.8	0.0140	0.0301	17.8110	0.0600	3.3430	4.37	31.09	12.51
	456	499.1	0.0138	0.0345	21.8280	0.0598	3.5756	5.97	80.23	23.30
	457	477.9	0.0148	0.0309	21.0178	0.0570	3.6709	4.97	68.20	10.49
	496	480.9	0.0154	0.0338	22.1452	0.0712	3.5872	4.81	73.52	12.89
	497	452.7	0.0134	0.0283	20.1343	0.0733	3.5262	5.80	68.95	8.41

[a]Mg/kg/day of Methoxychlor.
[b]One adrenal gland was lost prior to weighing.
[c]Thyroid was lost prior to weighing.
[d]Weight was a statistical outlier and therefore excluded.
[e]Tissue cassette containing the thyroid was mislabeled and therefore it was excluded.

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Table A-47. Individual F_1 Undosed Pubertal Male Sperm Data (page 1 of 2)

Dose[a]	Male ID	% Motile	% Progressively Motile	Epididymal Sperm Conc.[b]	Spermatid Head Conc.[c]	Daily Sperm Production[d]	Efficiency of Daily Sperm Production[e]
0	102	82	77	417.00	76.23	28.26	16.53
	103	70	67	314.02	91.20	32.23	19.78
	111	63	54	344.68	88.49	34.30	19.20
	112	61	52	331.02	55.98	21.15	12.14
	120	53	44	404.05	63.75	21.06	13.83
	121	67	52	497.52	75.22	28.70	16.32
	193	56	43	294.26	83.63	20.28	18.14
	194	22	18	213.26	57.31	12.89	12.43
	202	70	59	488.27	70.30	28.96	15.25
	203	61	51	531.79	60.79	25.10	13.19
	211	46	36	550.50	70.76	25.01	15.35
	212	68	51	551.51	48.30	17.44	10.48
	229	73	68	357.17	72.68	25.77	15.77
	230	62	54	438.81	75.43	29.57	16.36
	353	50	44	441.68	97.44	37.98	21.14
	354	61	58	455.33	66.77	25.01	14.48
	362	34	24	379.25	76.66	27.16	16.63
	363	55	41	393.02	84.37	35.49	18.30
	371	53	46	378.47	81.34	27.33	17.64
	372	68	58	519.09	126.25	44.51	27.39
	380	81	70	396.81	79.66	29.91	17.28
	381	66	49	422.57	101.42	39.35	22.00
	490	56	43	354.04	87.92	30.41	19.07
100	273	74	67	327.94	116.02	41.08	25.17
	274	65	61	369.81	98.05	36.36	21.27
	282	65	56	405.40	75.45	26.12	16.37
	283	73	60	345.16	66.47	22.26	14.42
	291	76	65	408.43	124.57	43.41	27.02
	292	86	72	464.65	76.97	27.77	16.70
	300	69	58	370.33	126.08	45.97	27.35
	301	72	58	370.88	77.31	25.86	16.77
	309	85	61	323.25	92.11	32.91	19.98
	310	61	55	353.76	95.00	30.15	20.61
	429	63	49	445.77	58.94	21.15	12.79
	430	61	56	370.39	94.13	34.62	20.42
	438	45	27	415.81	59.50	18.39	12.91
	439	65	49	343.41	101.09	35.23	21.93

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Table A-47. Individual F_1 Undosed Pubertal Male Sperm Data (page 2 of 2)

Dose[a]	Male ID	% Motile	% Progressively Motile	Epididymal Sperm Conc.[b]	Spermatid Head Conc.[c]	Daily Sperm Production[d]	Efficiency of Daily Sperm Production[e]
100	456	54	36	467.08	91.51	30.33	19.85
	457	50	32	477.54	111.98	39.70	24.29
	496	64	49	336.33	129.29	42.45	28.04
	497	74	62	366.87	88.15	28.79	19.12

[a]Mg/kg/day of Methoxychlor.
[b]Concentration in 10^6/g. Calculated as the number of sperm in the cauda epididymus (sample also used for motility analysis) plus the number of sperm used for the motility analysis divided by the weight (g) of the cauda epididymus used.
[c]Concentration in 10^6/g. Calculated as the number of spermatid heads divided by the weight (g) of the testis used.
[d]10^6/testis/day. Calculated as the total number of spermatid heads divided by 4.61 (constant for rats).
[e]10^6/g. testis/day. Calculated as the spermatid head concentration divided by 4.61 (constant for rats).

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Table A-48. Individual F_1 Undosed Pubertal Male Gross Necropsy Findings (page 1 of 1)

Dose[a]	Male ID	Finding
Scheduled Necropsy:		
0	120	Kidney: hydronephrosis, right
	193	Kidney: hydronephrosis, right
	202	Kidney: hydronephrosis, bilateral
	212	Kidney: hydronephrosis, bilateral
	354	Kidney: hydronephrosis, right
	380	Kidney: hydronephrosis, right
	381	Kidney: hydronephrosis, right
25	128	Kidney: hydronephrosis, right
	135	Kidney: hydronephrosis, right
		Large Intestines: air present
	394	Cowper's Gland: missing, right
50	318	Cowper's Gland: missing, right
	319	Caecum: gas present
	344	Kidney: hydronephrosis, right
	345	Kidney: hydronephrosis, right
	483	Kidney: hydronephrosis, right
	484	Kidney: hydronephrosis, right
100	273	Alopecia: face
		Kidney: hydronephrosis, right
	274	Kidney: hydronephrosis, right
	282	Kidney: hydronephrosis, right
	283	Kidney: hydronephrosis, right
		Large Intestines: air present
	456	Kidney: two 2 mm clear cysts on surface, right

[a]Mg/kg/day of Methoxychlor.

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Table A-49. Individual F_1 Dosed Pubertal Male Fate (page 1 of 3)

Dose[a]	Male ID	Fate
0	100[b]	Post Wean Holding Period
	101	Scheduled Sacrifice on Postnatal Day 75
	109	Scheduled Sacrifice on Postnatal Day 75
	110	Scheduled Sacrifice on Postnatal Day 75
	118	Scheduled Sacrifice on Postnatal Day 75
	119	Scheduled Sacrifice on Postnatal Day 75
	191	Scheduled Sacrifice on Postnatal Day 75
	192	Scheduled Sacrifice on Postnatal Day 75
	200	Scheduled Sacrifice on Postnatal Day 75
	201	Scheduled Sacrifice on Postnatal Day 75
	209	Scheduled Sacrifice on Postnatal Day 76
	210	Scheduled Sacrifice on Postnatal Day 76
	218	Removed from Study because Dam was Removed
	219	Removed from Study because Dam was Removed
	227	Scheduled Sacrifice on Postnatal Day 76
	228	Scheduled Sacrifice on Postnatal Day 76
	351	Scheduled Sacrifice on Postnatal Day 76
	352	Scheduled Sacrifice on Postnatal Day 76
	360	Scheduled Sacrifice on Postnatal Day 76
	361	Scheduled Sacrifice on Postnatal Day 76
	369	Scheduled Sacrifice on Postnatal Day 76
	370	Scheduled Sacrifice on Postnatal Day 76
	378	Scheduled Sacrifice on Postnatal Day 77
	379	Scheduled Sacrifice on Postnatal Day 77
	489	Scheduled Sacrifice on Postnatal Day 76
25	127	Scheduled Sacrifice on Postnatal Day 75
	133	Scheduled Sacrifice on Postnatal Day 75
	134	Scheduled Sacrifice on Postnatal Day 75
	141	Removed from Study because Dam was Removed
	142	Removed from Study because Dam was Removed
	236	Scheduled Sacrifice on Postnatal Day 75
	237	Scheduled Sacrifice on Postnatal Day 75
	245	Scheduled Sacrifice on Postnatal Day 75
	246	Scheduled Sacrifice on Postnatal Day 75
	253	Scheduled Sacrifice on Postnatal Day 76
	254	Scheduled Sacrifice on Postnatal Day 76
	262	Scheduled Sacrifice on Postnatal Day 76
	263	Scheduled Sacrifice on Postnatal Day 76
	387	Removed from Study because Dam was Removed
	391	Scheduled Sacrifice on Postnatal Day 76
	392	Scheduled Sacrifice on Postnatal Day 76

(continued)

US EPA ARCHIVE DOCUMENT

Table A-49. Individual F_1 Dosed Pubertal Male Fate (page 2 of 3)

Dose[a]	Male ID	Fate
25	400	Scheduled Sacrifice on Postnatal Day 77
	401	Scheduled Sacrifice on Postnatal Day 77
	409	Scheduled Sacrifice on Postnatal Day 77
	410	Scheduled Sacrifice on Postnatal Day 77
	418	Removed from Study because Dam was Removed
	419	Removed from Study because Dam was Removed
50	150	Scheduled Sacrifice on Postnatal Day 75
	151	Scheduled Sacrifice on Postnatal Day 75
	159	Scheduled Sacrifice on Postnatal Day 75
	160	Scheduled Sacrifice on Postnatal Day 75
	167	Scheduled Sacrifice on Postnatal Day 75
	168	Scheduled Sacrifice on Postnatal Day 75
	175	Scheduled Sacrifice on Postnatal Day 75
	176	Scheduled Sacrifice on Postnatal Day 75
	182	Scheduled Sacrifice on Postnatal Day 76
	183	Scheduled Sacrifice on Postnatal Day 76
	316	Scheduled Sacrifice on Postnatal Day 75
	317	Scheduled Sacrifice on Postnatal Day 75
	325	Scheduled Sacrifice on Postnatal Day 76
	326	Scheduled Sacrifice on Postnatal Day 76
	334	Scheduled Sacrifice on Postnatal Day 76
	335	Scheduled Sacrifice on Postnatal Day 76
	342	Scheduled Sacrifice on Postnatal Day 77
	343	Scheduled Sacrifice on Postnatal Day 77
	463	Scheduled Sacrifice on Postnatal Day 77
	464	Scheduled Sacrifice on Postnatal Day 77
	472[c]	Post Wean Holding Period
	473	Scheduled Sacrifice on Postnatal Day 76
	481	Scheduled Sacrifice on Postnatal Day 77
	482	Scheduled Sacrifice on Postnatal Day 77
100	271	Scheduled Sacrifice on Postnatal Day 75
	272	Scheduled Sacrifice on Postnatal Day 75
	280	Scheduled Sacrifice on Postnatal Day 75
	281	Scheduled Sacrifice on Postnatal Day 75
	289	Scheduled Sacrifice on Postnatal Day 75
	290	Scheduled Sacrifice on Postnatal Day 75
	298	Scheduled Sacrifice on Postnatal Day 76
	299	Scheduled Sacrifice on Postnatal Day 76
	307	Scheduled Sacrifice on Postnatal Day 76
	308	Scheduled Sacrifice on Postnatal Day 76

(continued)

US EPA ARCHIVE DOCUMENT

Table A-49. Individual F_1 Dosed Pubertal Male Fate (page 3 of 3)

Dose[a]	Male ID	Fate
100	427	Scheduled Sacrifice on Postnatal Day 76
	428	Scheduled Sacrifice on Postnatal Day 76
	436	Scheduled Sacrifice on Postnatal Day 76
	437	Scheduled Sacrifice on Postnatal Day 76
	443	Removed from Study because Dam was Removed
	454	Scheduled Sacrifice on Postnatal Day 77
	455	Scheduled Sacrifice on Postnatal Day 77
	494	Scheduled Sacrifice on Postnatal Day 76
	495	Scheduled Sacrifice on Postnatal Day 76

[a]Mg/kg/day of Methoxychlor.
[b]Female was found dead on postnatal day 24 prior to dosing.
[c]Female was found dead on postnatal day 26 prior dosing (misdirected dose).

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Table A-50. Individual F_1 Dosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 1 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
0	100	16.70	53.12	57.14	.[b]						
	101	15.07	52.09	55.47	66.04	77.45	93.35	108.91	125.36	146.30	162.57
	109	17.67	56.54	60.88	73.30	85.13	101.45	118.08	136.31	157.69	177.94
	110	16.86	61.93	65.68	77.04	88.10	102.13	115.95	130.59	149.43	166.18
	118	16.91	56.14	60.80	70.61	80.38	92.29	105.82	120.49	139.54	158.20
	119	15.51	57.93	63.86	76.20	89.01	106.77	121.25	141.00	163.10	184.77
	191	13.34	52.43	59.21	67.14	79.83	91.85	105.62	119.93	137.40	154.78
	192	12.61	54.79	60.95	73.80	87.03	98.45	114.46	133.42	150.71	172.70
	200	16.14	64.03	69.76	84.71	101.33	119.98	138.22	159.07	185.11	207.88
	201	14.06	61.08	65.47	79.77	92.31	108.53	123.64	142.83	166.44	184.76
	209	12.53	62.47	69.48	83.38	101.86	113.38	130.63	149.38	168.77	187.86
	210	15.79	63.04	69.05	80.55	93.06	108.66	124.14	142.52	163.41	183.16
	227	15.35	59.65	63.75	76.64	86.67	99.88	112.96	127.53	145.02	162.59
	228	17.84	63.92	70.19	82.50	94.87	108.88	124.53	142.73	161.49	180.21
	351	14.40	59.66	64.84	80.26	95.03	112.51	131.42	152.51	176.44	195.57
	352	15.01	56.67	61.95	75.31	87.89	103.59	120.71	141.81	163.18	180.95
	360	13.25	57.16	56.87	69.53	82.05	94.83	108.83	122.17	138.55	151.84
	361	15.58	59.11	64.70	75.49	90.33	104.73	122.83	139.34	158.73	176.72
	369	16.52	58.46	62.36	75.64	90.40	105.35	122.39	142.00	164.81	183.70
	370	12.85	57.53	58.91	71.93	85.02	99.33	115.84	135.79	156.50	178.11
	378	14.27	57.63	61.78	76.18	88.79	104.04	117.80	136.20	152.60	169.23
	379	15.62	61.37	66.32	78.86	92.63	108.37	124.69	143.10	162.09	179.55
	489	14.10	54.80	58.70	69.84	82.87	96.29	111.68	129.01	150.26	167.22

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Table A-50. Individual F_1 Dosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 2 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
25	127	14.22	58.75	62.46	74.59	89.50	105.13	122.99	142.60	163.64	181.42
	133	14.33	55.78	61.08	70.59	85.22	101.20	116.53	133.28	148.62	167.86
	134	18.11	62.08	65.87	78.57	92.04	108.20	122.29	137.55	154.72	169.80
	236	15.72	69.05	75.12	81.60	101.99	118.08	133.41	154.82	176.01	195.56
	237	14.72	63.91	69.51	82.30	94.61	111.23	127.56	145.87	168.41	187.00
	245	16.38	60.36	67.60	80.62	93.29	109.22	126.49	143.19	160.56	175.30
	246	13.88	65.48	69.75	83.57	97.20	114.12	130.35	154.20	173.02	189.25
	253	12.31	51.04	54.65	66.12	76.51	90.26	101.89	120.40	136.88	154.17
	254	14.08	52.87	58.44	71.15	83.49	99.04	112.99	130.19	148.45	165.77
	262	13.64	56.09	62.16	75.02	88.91	106.29	118.29	139.37	160.27	179.25
	263	16.12	50.32	54.17	65.66	76.17	89.85	101.80	118.45	136.63	154.80
	391	16.16	59.92	63.89	76.95	92.25	106.73	120.80	141.61	158.58	171.47
	392	16.64	61.36	65.19	79.07	93.70	109.37	124.09	144.67	161.78	177.52
	400	15.07	50.13	55.95	67.72	82.00	96.19	110.11	126.67	143.78	158.01
	401	12.29	47.19	50.17	62.09	74.88	87.59	101.54	117.54	133.85	149.54
	409	15.37	50.47	55.33	65.06	79.15	90.69	102.20	119.46	137.08	149.15
	410	15.82	48.73	52.70	63.75	74.93	87.15	99.28	112.12	129.11	144.37

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Table A-50. Individual F_1 Dosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 3 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
50	150	14.33	52.86	56.89	60.48	81.16	97.44	111.56	122.73	137.57	153.18
	151	15.58	49.26	53.93	56.72	74.41	90.83	104.39	115.89	130.64	148.13
	159	13.96	57.43	60.91	64.20	87.18	101.36	118.65	135.50	155.07	173.64
	160	14.22	57.41	61.21	66.18	87.14	100.47	113.32	122.45	140.76	152.02
	167	14.64	59.22	61.37	76.46	89.97	101.87	113.67	127.66	137.37	149.49
	168	16.87	55.90	55.05	66.24	79.49	95.17	108.17	121.91	140.47	155.22
	175	14.67	73.37	79.58	93.13	112.03	128.82	148.14	163.14	183.29	205.72
	176	14.75	65.76	72.75	85.37	102.48	117.42	135.24	149.47	167.47	184.44
	182	14.95	53.83	58.47	71.71	89.62	105.90	127.09	139.87	166.01	181.99
	183	15.77	50.33	55.16	67.23	83.55	99.81	116.95	130.09	151.52	173.73
	316	15.80	56.92	61.38	73.07	87.59	101.90	116.82	133.38	151.81	169.31
	317	15.79	55.55	59.98	72.39	84.36	100.08	110.55	124.17	136.12	148.72
	325	15.14	63.45	67.46	77.14	88.70	104.03	115.99	131.33	150.62	164.34
	326	14.06	61.64	64.29	76.81	86.87	102.01	118.40	135.60	148.34	167.28
	334	17.83	55.58	61.21	73.27	86.27	100.10	110.29	135.49	142.45	158.84
	335	18.70	54.32	58.63	70.16	85.07	100.92	116.61	129.00	155.02	174.24
	342	12.62	61.80	66.33	77.56	93.01	103.29	126.45	145.42	162.05	184.07
	343	15.09	59.94	64.51	76.05	90.07	99.37	124.49	152.11	159.57	179.08
	463	15.65	58.98	63.75	79.31	82.49	106.20	120.13	137.89	157.12	171.65
	464	13.62	68.15	72.23	86.40	102.65	118.73	134.23	153.66	173.04	191.74
	472	15.40	52.89	56.83	50.01	.[c]					
	473	15.67	56.90	58.48	68.53	81.65	94.40	108.58	124.60	144.04	158.75
	481	12.18	53.57	56.78	68.02	79.71	92.71	107.43	122.27	138.26	154.03
	482	14.63	58.12	60.45	73.60	86.26	99.49	114.52	130.72	148.31	165.13

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Table A-50. Individual F_1 Dosed Pubertal Male Anogenital Distance (mm) and Body Weights (g) on Postnatal Days 21 through 36 of the Post Wean Holding Period (page 4 of 4)

Dose[a]	Male ID	Anogenital Distance	Postnatal Day 21	22	24	26	28	30	32	34	36
100	271	16.67	55.92	59.46	69.15	81.44	92.43	102.55	114.71	132.50	142.53
	272	16.79	56.24	59.25	70.07	82.82	95.06	105.01	120.63	139.92	150.94
	280	16.71	49.20	54.36	65.21	75.51	86.92	96.13	110.83	125.86	141.21
	281	17.63	56.47	63.76	74.55	87.56	101.98	113.12	128.65	146.86	161.79
	289	18.11	68.85	74.35	84.42	95.80	110.03	123.79	138.12	153.38	168.19
	290	14.95	65.20	69.80	83.02	91.38	104.22	117.72	134.98	149.47	165.19
	298	15.14	53.04	58.87	68.81	79.55	93.56	105.53	117.05	134.56	155.15
	299	14.67	48.34	51.98	58.62	70.70	83.61	95.41	109.67	97.06	119.48
	307	16.75	50.10	55.88	68.62	80.84	96.33	106.36	125.90	141.22	158.29
	308	15.48	48.60	54.87	66.80	81.81	98.71	114.97	131.35	145.45	163.90
	427	14.17	59.47	64.13	76.80	89.44	103.31	118.58	136.92	152.43	164.26
	428	13.94	51.36	56.79	68.01	82.13	94.08	108.74	124.24	140.77	151.91
	436	18.04	62.37	66.72	77.17	87.34	99.43	109.15	123.03	137.94	150.95
	437	15.99	65.56	71.17	82.57	92.15	103.68	116.22	131.44	145.71	160.24
	454	15.80	52.77	53.25	64.83	77.34	89.70	98.42	115.92	134.14	149.61
	455	13.90	46.81	48.61	59.67	73.01	85.07	95.94	111.67	126.72	138.18
	494	13.43	57.02	63.73	75.27	86.31	94.12	108.63	123.30	137.19	151.47
	495	.[d]	62.59	70.66	82.77	93.48	105.07	121.78	136.91	153.90	168.26

[a]Mg/kg/day of Methoxychlor.
[b]Male was found dead on postnatal day 24 prior to dosing.
[c]Male was found dead on postnatal day 26 prior to dosing (misdirected dose).
[d]Measurement was inadvertently not recorded.

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Table A-51. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period
(page 1 of 4)

		Postnatal Day									
Dose[a]	Male ID	38	40	42	44	46	48	50	52	54	56
0	100[b]										
	101	178.64	197.91	215.21	231.23	251.58	268.31	286.83	301.15	318.36	330.55
	109	192.66	212.49	233.28	253.52	277.35	293.10	311.27	330.00	344.02	363.41
	110	181.23	197.95	213.05	232.20	253.75	266.32	283.25	301.20	316.43	327.69
	118	177.83	198.15	218.99	235.21	260.11	272.91	291.98	305.71	328.55	342.04
	119	206.03	231.68	247.62	267.45	294.72	309.19	329.34	347.71	371.42	385.94
	191	173.96	186.12	205.11	223.19	237.10	251.96	266.56	293.13	302.10	320.60
	192	190.55	208.47	228.16	248.50	266.01	283.22	276.31	304.05	.[c]	336.31
	200	230.03	254.86	276.45	.[d]	316.06	337.59	365.54	392.42	407.60	428.30
	201	204.47	227.55	244.42	241.90	288.55	303.54	327.19	354.86	374.14	389.12
	209	204.73	224.53	245.86	266.45	288.17	311.56	332.39	358.63	374.77	393.80
	210	198.44	220.18	238.85	259.83	276.74	292.87	314.96	340.06	375.79	366.72
	227	177.31	193.40	199.14	215.58	231.27	248.45	265.98	283.32	295.97	317.10
	228	199.81	221.18	240.08	261.33	282.81	303.65	320.81	344.49	356.14	374.90
	351	221.58	238.82	264.84	291.45	307.31	331.22	347.71	369.54	388.30	406.50
	352	203.81	219.35	246.26	270.24	289.60	309.54	331.41	346.67	366.19	387.25
	360	171.19	185.72	204.47	225.32	234.41	252.22	270.27	284.47	300.55	321.20
	361	196.35	214.49	231.05	256.34	268.36	291.13	313.50	330.31	351.03	370.14
	369	209.04	230.60	254.31	279.30	297.41	317.87	350.61	373.62	399.70	419.30
	370	204.11	224.77	245.12	271.39	291.75	317.66	349.98	370.50	395.97	418.50
	378	186.38	200.61	216.52	238.97	251.61	272.27	295.37	312.90	327.21	350.57
	379	200.15	216.88	229.03	254.80	267.75	286.15	306.01	327.67	342.27	361.46
	489	189.51	209.53	224.59	246.31	256.99	276.42	299.85	317.86	337.44	351.97

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Table A-51. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 2 of 4)

Dose[a]	Male ID	Postnatal Day 38	40	42	44	46	48	50	52	54	56
25	127	200.08	225.72	238.17	262.55	289.72	301.12	326.33	343.39	360.10	375.29
	133	178.54	198.91	207.17	226.19	236.71	248.33	260.72	277.20	285.25	299.81
	134	186.33	204.12	217.74	229.78	242.39	252.33	263.92	278.89	284.49	291.31
	236	217.60	230.24	249.54	271.91	287.47	298.52	312.84	335.12	339.39	352.05
	237	207.81	225.95	243.16	265.56	282.09	300.57	324.88	349.59	358.96	385.57
	245	197.75	210.35	226.23	243.32	253.30	262.56	272.87	295.34	300.06	307.33
	246	210.55	223.34	238.36	264.10	281.20	294.97	313.16	332.27	346.36	355.93
	253	171.71	190.52	204.05	228.82	243.24	255.75	271.18	292.36	303.03	314.05
	254	180.18	197.40	214.77	239.21	254.23	265.16	285.90	303.10	316.63	328.99
	262	197.78	214.43	231.19	247.72	265.03	275.56	294.62	314.25	316.17	330.25
	263	170.91	188.35	202.94	218.86	237.24	244.22	262.49	285.48	294.10	302.73
	391	189.15	203.28	214.64	235.10	243.03	258.75	270.63	290.19	300.33	311.42
	392	201.25	213.18	231.63	255.93	266.18	288.95	306.80	321.01	334.10	345.11
	400	176.58	193.84	207.59	228.41	240.28	255.82	275.92	289.75	299.38	316.54
	401	167.87	186.51	198.79	221.22	233.99	252.51	261.90	281.01	287.64	306.40
	409	170.72	189.58	206.53	222.96	237.97	250.39	265.17	277.68	284.27	294.70
	410	160.94	174.53	192.06	210.19	220.82	239.80	254.72	269.46	282.86	298.40

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Table A-51. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 3 of 4)

		Postnatal Day									
Dose[a]	Male ID	38	40	42	44	46	48	50	52	54	56
50	150	172.15	184.11	202.61	219.67	236.18	247.84	260.34	280.60	291.25	296.78
	151	160.48	172.73	186.28	198.75	216.02	225.65	238.75	254.99	260.06	264.04
	159	187.41	207.97	221.18	232.19	253.21	264.20	287.45	294.80	311.39	316.17
	160	169.73	183.44	193.15	204.35	223.27	230.87	254.03	261.22	277.21	281.06
	167	160.37	169.56	174.37	185.77	202.43	212.73	211.12	225.08	234.90	243.12
	168	171.17	186.18	196.54	214.01	232.19	240.12	256.00	269.33	288.13	295.36
	175	220.96	242.53	251.47	267.10	281.77	288.08	307.10	323.10	338.95	336.09
	176	199.40	219.23	231.25	245.46	255.59	274.73	289.51	306.48	311.75	315.23
	182	196.66	222.12	232.96	249.80	273.22	281.47	297.81	318.21	335.30	339.12
	183	189.37	213.08	230.56	247.89	275.77	290.54	311.27	329.69	347.02	355.49
	316	186.61	200.52	212.34	234.89	249.76	264.05	281.04	296.45	303.99	316.06
	317	163.86	171.58	183.21	196.30	207.44	219.58	234.18	249.65	259.28	267.18
	325	182.73	195.08	206.73	230.98	240.20	254.71	268.90	293.77	301.41	309.51
	326	182.08	195.41	207.34	220.40	235.00	246.16	256.91	276.01	279.44	291.74
	334	177.97	191.05	207.14	221.70	234.12	247.94	261.28	280.20	282.68	294.64
	335	193.99	211.67	230.60	250.18	264.72	280.94	295.45	314.56	312.29	320.66
	342	199.84	219.05	231.65	247.02	265.12	279.05	298.46	314.82	328.62	341.30
	343	196.44	211.75	216.12	232.63	240.22	250.36	267.90	281.17	289.86	297.02
	463	193.40	209.40	221.91	238.57	246.17	263.46	279.73	295.17	304.10	318.39
	464	209.92	226.46	242.89	265.23	270.74	285.60	300.69	313.76	314.22	340.65
	472[e]										
	473	173.88	186.54	204.36	224.40	228.82	243.65	262.32	271.73	282.66	296.68
	481	174.32	191.86	203.21	217.56	227.49	241.35	255.71	267.67	277.59	288.85
	482	184.90	200.80	215.17	233.78	244.30	260.85	279.03	293.50	308.65	326.01

(continued)

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Table A-51. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 38 through 56 of the Post Wean Holding Period (page 4 of 4)

Dose[a]	Male ID	Postnatal Day 38	40	42	44	46	48	50	52	54	56
100	271	156.94	170.14	181.64	197.25	209.00	212.32	225.01	235.11	240.10	254.68
	272	166.12	178.39	187.77	199.09	212.90	215.43	233.37	244.27	258.31	265.77
	280	152.72	165.50	172.25	188.32	197.05	212.17	235.85	238.71	248.06	261.10
	281	176.23	193.58	206.17	222.91	234.60	251.10	264.37	278.90	284.38	296.95
	289	185.59	191.48	203.86	217.50	228.55	233.05	248.16	267.46	277.09	276.75
	290	180.40	193.07	205.45	217.08	227.37	237.43	250.40	265.86	276.10	281.05
	298	169.89	189.30	200.65	220.09	234.78	245.38	257.70	274.67	283.67	289.14
	299	134.31	153.87	164.84	186.82	194.20	203.77	220.61	232.52	242.05	253.95
	307	180.56	190.37	204.12	223.82	236.83	248.10	264.11	277.63	287.53	296.27
	308	182.07	197.09	214.11	238.32	247.53	261.12	279.90	298.04	310.10	324.90
	427	186.70	199.76	218.80	236.77	244.20	264.25	281.18	298.14	299.35	315.77
	428	169.88	183.01	200.11	215.59	222.60	236.48	248.73	262.10	271.32	281.75
	436	163.03	172.51	184.96	199.68	204.72	217.17	230.29	239.93	250.31	262.51
	437	173.15	184.40	195.20	210.34	224.84	233.42	246.50	262.90	273.99	286.76
	454	169.47	173.31	197.13	215.90	225.07	238.91	249.16	272.37	282.32	294.50
	455	157.77	169.27	181.38	196.47	207.67	214.66	226.99	236.09	244.21	255.70
	494	167.85	180.51	199.51	211.85	216.91	230.96	245.08	257.29	261.60	271.50
	495	185.25	201.25	221.30	230.21	240.12	253.48	271.29	280.62	293.12	297.50

[a]Mg/kg/day of Methoxychlor.
[b]Male was found dead on postnatal day 24 prior to dosing.
[c]Weight was inadvertently not recorded.
[d]Weight was excluded because male did not have a water bottle overnight.
[e]Male was found dead on postnatal day 26 prior to dosing (misdirected dose).

US EPA ARCHIVE DOCUMENT

Table A-52. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period
(page 1 of 4)

Dose[a]	Male ID	Postnatal Day 58	60	62	64	66	68	70	72	74	76
0	100[b]										
	101	349.53	357.31	372.23	384.49	398.52	403.90	416.00	418.00	428.90	.[c]
	109	380.10	395.67	410.80	424.00	445.20	453.90	464.30	475.90	486.80	.[c]
	110	342.21	355.35	367.19	378.39	391.08	397.10	405.60	411.80	425.10	.[c]
	118	362.80	373.50	391.06	399.01	421.90	432.80	439.30	443.20	451.50	.[c]
	119	405.50	412.40	427.70	444.80	467.20	473.60	480.30	486.70	497.40	.[c]
	191	343.41	361.42	368.42	381.73	388.77	407.30	420.50	433.40	427.70	.[c]
	192	354.18	368.42	381.31	396.79	406.90	420.90	431.60	440.40	451.10	.[c]
	200	452.50	470.40	491.70	506.50	526.40	542.20	550.50	560.60	573.40	.[c]
	201	409.70	431.70	444.40	462.20	477.90	492.50	505.50	505.60	517.30	.[c]
	209	412.90	429.50	448.60	462.20	486.00	498.30	510.20	503.60	527.60	493.90
	210	381.31	398.30	413.50	428.10	444.20	451.70	465.60	469.00	482.20	544.00
	227	331.75	348.28	359.11	376.36	387.40	393.90	408.40	417.70	430.80	432.20
	228	393.41	410.20	422.20	438.10	451.30	465.00	478.10	491.30	497.30	504.10
	351	422.00	435.00	451.50	469.60	472.90	488.20	507.00	517.60	522.60	534.90
	352	403.50	423.10	443.10	456.69	466.60	477.90	497.70	511.70	511.50	532.30
	360	338.66	351.78	368.85	381.69	395.06	401.90	418.30	433.60	434.70	443.10
	361	384.28	401.70	410.70	434.70	445.30	452.20	464.40	484.30	486.60	498.70
	369	441.70	459.20	477.90	501.50	514.10	527.50	541.90	561.30	571.20	587.20
	370	440.40	470.20	487.60	510.07	523.30	544.10	544.30	561.90	567.20	585.30
	378	364.15	384.51	401.70	415.90	433.00	437.50	449.00	462.60	466.50	484.10
	379	372.64	394.44	406.50	418.30	435.90	449.20	460.30	472.80	483.10	490.90
	489	363.37	380.41	398.10	405.70	416.00	431.30	439.90	453.10	458.00	462.50

(continued)

US EPA ARCHIVE DOCUMENT

Table A-52. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period
(page 2 of 4)

		Postnatal Day									
Dose[a]	Male ID	58	60	62	64	66	68	70	72	74	76
25	127	391.10	406.10	420.20	434.30	447.70	455.00	459.70	465.30	476.10	.[c]
	133	308.13	316.99	326.04	334.95	344.93	350.10	353.34	352.96	368.78	.[c]
	134	300.85	305.09	312.92	321.79	325.53	330.74	329.08	333.38	344.38	.[c]
	236	369.18	376.58	383.53	400.70	417.10	413.20	422.90	441.50	448.50	.[c]
	237	400.40	410.60	426.20	442.80	460.00	470.10	479.90	496.90	500.10	.[c]
	245	315.48	323.80	330.64	335.84	344.81	345.90	354.43	362.26	367.67	.[c]
	246	369.87	374.74	388.00	388.83	396.47	401.50	401.30	413.20	411.90	.[c]
	253	324.62	332.78	342.92	348.35	357.96	366.59	376.00	379.84	387.83	388.21
	254	338.90	347.39	353.33	363.11	372.43	381.38	388.65	392.28	401.70	411.60
	262	342.89	342.94	360.40	360.15	374.01	382.38	382.50	402.70	404.70	405.70
	263	321.58	332.27	341.14	353.73	365.23	369.41	374.90	389.68	400.40	401.60
	391	320.68	332.23	339.32	347.65	355.12	358.61	371.11	375.04	377.88	382.08
	392	355.04	363.05	374.04	385.13	391.95	399.00	406.60	410.80	425.70	428.20
	400	325.35	336.30	352.00	363.24	378.64	384.49	391.98	400.10	402.50	401.70
	401	312.57	323.95	329.75	335.66	351.86	357.80	365.51	376.32	379.01	389.61
	409	297.04	297.80	310.85	315.39	328.65	328.36	342.39	353.56	362.64	371.80
	410	308.26	326.51	339.62	354.89	359.44	364.47	372.98	382.24	388.25	399.30

(continued)

US EPA ARCHIVE DOCUMENT

Table A-52. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period
(page 3 of 4)

		Postnatal Day									
Dose[a]	Male ID	58	60	62	64	66	68	70	72	74	76
50	150	307.36	317.10	329.13	337.92	349.74	349.54	361.68	362.82	372.06	.[c]
	151	273.34	287.94	288.35	298.58	310.92	308.53	315.96	310.62	316.45	.[c]
	159	339.59	337.67	356.09	358.66	367.29	379.63	376.61	386.29	392.97	.[c]
	160	300.48	307.46	319.74	324.35	340.15	343.77	342.50	346.68	350.97	.[c]
	167	250.18	254.83	258.43	259.57	277.13	282.51	286.73	286.71	292.91	.[c]
	168	309.56	316.20	325.17	332.28	344.51	353.13	361.29	366.48	375.55	.[c]
	175	352.62	354.57	370.77	379.09	389.83	403.60	403.70	409.10	408.30	.[c]
	176	324.07	332.07	342.30	344.88	350.98	357.73	375.30	370.85	371.92	.[c]
	182	352.82	358.33	363.82	369.65	384.50	382.53	386.94	386.52	397.40	401.20
	183	370.33	376.15	390.19	401.40	415.70	416.30	422.40	428.00	437.20	436.70
	316	320.34	337.06	346.01	351.54	366.63	368.89	369.19	379.16	390.60	.[c]
	317	280.90	289.78	299.50	311.06	368.86	323.00	326.60	336.02	341.56	.[c]
	325	315.41	324.81	336.95	344.05	347.84	358.52	359.42	365.21	375.93	376.12
	326	299.86	311.74	317.86	324.01	324.94	322.44	335.40	337.79	340.49	340.74
	334	300.93	309.50	315.15	322.46	337.86	334.06	341.50	344.46	347.01	350.80
	335	321.64	335.71	330.08	337.33	353.91	357.72	365.00	372.07	370.98	377.27
	342	352.18	363.90	370.40	378.05	390.51	399.60	412.20	420.00	425.20	431.50
	343	303.61	316.59	323.42	331.20	334.14	346.76	353.30	361.70	369.43	370.02
	463	326.13	336.35	336.13	348.51	354.02	358.44	366.30	367.72	375.72	379.26
	464	342.15	354.07	362.68	378.02	382.45	384.66	396.19	412.50	409.40	411.50
	472[d]										
	473	302.26	312.65	318.16	333.62	342.61	345.09	350.06	363.55	364.27	377.20
	481	296.44	301.77	315.08	325.72	341.57	339.12	345.83	355.67	360.10	365.19
	482	331.14	339.60	348.22	359.64	372.67	380.13	388.96	399.51	403.60	416.60

(continued)

US EPA ARCHIVE DOCUMENT

Table A-52. Individual F_1 Dosed Pubertal Male Body Weights (g) on Postnatal Days 58 through 76 of the Post Wean Holding Period (page 4 of 4)

Dose[a]	Male ID	Postnatal Day 58	60	62	64	66	68	70	72	74	76
100	271	263.35	272.01	279.75	286.39	293.92	294.46	301.01	310.01	311.70	.[c]
	272	268.60	279.13	288.15	282.43	296.55	292.16	300.71	299.71	310.05	.[c]
	280	264.56	275.94	285.36	293.28	301.01	304.01	313.74	316.66	328.05	.[c]
	281	300.95	317.13	322.45	327.76	337.48	341.03	350.02	355.89	363.20	.[c]
	289	286.46	295.72	301.08	306.73	313.53	315.86	318.10	324.09	325.88	.[c]
	290	289.15	300.45	309.14	311.04	322.02	324.73	331.33	341.78	336.10	.[c]
	298	297.51	303.19	316.11	324.38	337.30	342.32	356.60	366.00	370.00	380.67
	299	260.37	266.16	281.67	285.13	288.72	290.36	297.20	302.90	309.97	311.33
	307	301.55	311.20	315.36	326.35	333.11	334.86	342.91	351.36	352.77	360.88
	308	326.01	350.13	356.00	366.84	379.78	385.17	390.02	402.10	399.60	413.40
	427	321.50	337.07	345.50	353.20	358.11	360.01	362.62	368.65	375.63	381.79
	428	289.55	298.00	303.72	316.35	319.70	325.66	329.88	338.86	342.70	351.92
	436	267.18	276.16	284.33	293.91	303.46	305.65	305.19	320.71	317.70	325.54
	437	291.49	302.07	308.14	319.30	326.89	328.25	332.72	338.56	340.66	355.36
	454	298.29	313.13	318.67	327.06	331.63	333.64	346.33	347.46	343.31	353.50
	455	263.88	273.84	278.95	289.38	296.99	298.16	309.73	312.90	313.78	322.46
	494	279.69	287.52	293.61	299.25	307.34	313.59	320.76	323.18	325.74	331.60
	495	311.85	316.92	325.85	332.70	334.68	343.12	345.07	348.11	344.77	359.03

[a]Mg/kg/day of Methoxychlor.
[b]Male was found dead on postnatal day 24 prior to dosing.
[c]Male was necropsied prior to postnatal day 76.
[d]Male was found dead on postnatal day 26 prior to dosing (misdirected dose).

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 1 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
0	100	24	Ataxia
			Chromodacryorrhea: nose
			Found dead
			Urine: blood present
	109	32	Efflux of the dosing solution, with food
	118	57	Rooting: post dosing
	119	53	Salivation: prior to dosing
		60	Salivation: prior to dosing
	200	43	Chromodacryorrhea: nose
		44	No water bottle overnight
	201	61	Efflux of the dosing solution, through nose and mouth
	209	30	Efflux of the dosing solution
	227	33	Rooting: post dosing
	228	38	Salivation: prior to dosing
	351	30	Salivation: prior to dosing
		33	Rooting: post dosing
		37	Rooting: post dosing
		46	Rooting: post dosing
	352	33	Rooting: post dosing
		37	Rooting: post dosing
		38	Salivation: prior to dosing
		39	Salivation: prior to dosing
		41	Salivation: prior to dosing
	369	64	Salivation: prior to dosing
	370	32	Rooting: post dosing
		68	Mouth: bled after dosing
25	127	36	Chromodacryorrhea: nose
		37	Chromodacryorrhea: nose
		55	Salivation: prior to dosing
	134	37	Salivation: prior to dosing
		38	Salivation: prior to dosing
		39	Salivation: prior to dosing
		41	Salivation: prior to dosing
		42	Salivation: prior to dosing
		43	Salivation: prior to dosing
		44	Salivation: prior to dosing
		45	Salivation: prior to dosing
		46	Salivation: prior to dosing
		47	Salivation: prior to dosing
		48	Salivation: prior to dosing
		49	Salivation: prior to dosing

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US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 2 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
25	134	50	Salivation: prior to dosing
		51	Salivation: prior to dosing
		53	Salivation: prior to dosing
		54	Salivation: prior to dosing
		55	Salivation: prior to dosing
		56	Salivation: prior to dosing
		57	Salivation: prior to dosing
		58	Salivation: prior to dosing
		59	Salivation: prior to dosing
		60	Rooting: post dosing
			Salivation: prior to dosing
		61	Salivation: prior to dosing
		62	Salivation: prior to dosing
		63	Salivation: prior to dosing
		64	Salivation: prior to dosing
		65	Salivation: prior to dosing
		66	Salivation: prior to dosing
		67	Salivation: prior to dosing
		68	Salivation: prior to dosing
		69	Salivation: prior to dosing
		70	Salivation: prior to dosing
		71	Salivation: prior to dosing
		72	Salivation: prior to dosing
		73	Salivation: prior to dosing
	236	54	Salivation: prior to dosing
		59	Rooting: post dosing
		60	Salivation: prior to dosing
		65	Salivation: prior to dosing
		68	Salivation: prior to dosing
	245	57	Alopecia: limb(s)
		58	Alopecia: limb(s)
		59	Alopecia: limb(s)
		60	Alopecia: limb(s)
		61	Alopecia: limb(s)
		62	Alopecia: limb(s)
		63	Alopecia: limb(s)
		64	Alopecia: limb(s)
		65	Alopecia: limb(s)
		66	Alopecia: limb(s)
		67	Alopecia: limb(s)
		68	Alopecia: limb(s)
		69	Alopecia: limb(s)
		70	Alopecia: limb(s)
		71	Alopecia: limb(s)
		75	Alopecia: limb(s)

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 3 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
25	246	59	Rooting: post dosing
	253	47	Rooting: post dosing
	262	68	Rooting: post dosing
	263	67	Scab(s): face
		68	Scab(s): face
		69	Scab(s): face
		70	Scab(s): face
		71	Scab(s): face
		72	Scab(s): face
		73	Scab(s): face
		74	Scab(s): face
		75	Scab(s): face
	392	40	Salivation: prior to dosing
		42	Salivation: prior to dosing
		44	Salivation: prior to dosing
		46	Salivation: prior to dosing
		48	Salivation: prior to dosing
		49	Salivation: prior to dosing
		51	Salivation: prior to dosing
		52	Salivation: prior to dosing
		53	Salivation: prior to dosing
		54	Salivation: prior to dosing
		55	Salivation: prior to dosing
		56	Salivation: prior to dosing
		57	Salivation: prior to dosing
		58	Salivation: prior to dosing
		60	Salivation: prior to dosing
		61	Salivation: prior to dosing
		62	Salivation: prior to dosing
		63	Salivation: prior to dosing
		66	Salivation: prior to dosing
		67	Efflux of the dosing solution
			Salivation: prior to dosing
		68	Salivation: prior to dosing
		69	Salivation: prior to dosing
		70	Salivation: prior to dosing
		71	Salivation: prior to dosing
		72	Salivation: prior to dosing
		73	Salivation: prior to dosing
		74	Salivation: prior to dosing
		75	Salivation: prior to dosing

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US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 4 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
25	400	53	Rooting: post dosing
		56	Rooting: post dosing
			Salivation: prior to dosing
		58	Rooting: post dosing
			Salivation: prior to dosing
		59	Salivation: prior to dosing
		60	Salivation: prior to dosing
		61	Salivation: prior to dosing
		62	Salivation: prior to dosing
		63	Rooting: post dosing
		65	Salivation: prior to dosing
		66	Salivation: prior to dosing
		67	Salivation: prior to dosing
		68	Salivation: prior to dosing
		72	Salivation: prior to dosing
		73	Rooting: post dosing
			Salivation: prior to dosing
		74	Salivation: prior to dosing
		75	Salivation: prior to dosing
	401	41	Rooting: post dosing
		50	Rooting: post dosing
		51	Rooting: post dosing
		53	Rooting: post dosing
		57	Rooting: post dosing
		58	Rooting: post dosing
		63	Salivation: prior to dosing
		65	Salivation: prior to dosing
		73	Rooting: post dosing
	409	30	Chromodacryorrhea: eye, left, slight
		35	Chromodacryorrhea: eye, left
		46	Chromodacryorrhea: eye, left
		49	Chromodacryorrhea: eye, left
		50	Chromodacryorrhea: eye, left
		51	Chromodacryorrhea: eye, left
		52	Chromodacryorrhea: eye, left
		53	Teeth: upper incisors missing[c]
		56	Teeth: trimmed lower incisors
		61	Teeth: trimmed lower incisors
		63	Teeth: trimmed lower incisors
		68	Teeth: trimmed lower incisors
	410	65	Salivation: prior to dosing
		66	Rooting: post dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 5 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
50	150	32	Efflux of the dosing solution
			Rooting: post dosing
		35	Rooting: post dosing
		36	Rooting: post dosing
		47	Rooting: post dosing
	151	37	Rooting: post dosing
		56	Rooting: post dosing
	159	37	Efflux of the dosing solution
	160	40	Salivation: prior to dosing
		41	Salivation: prior to dosing
		42	Salivation: prior to dosing
		46	Salivation: prior to dosing
		47	Salivation: prior to dosing
		51	Rooting: post dosing
			Salivation: prior to dosing
		52	Salivation: prior to dosing
		53	Salivation: prior to dosing
		54	Salivation: prior to dosing
		55	Salivation: prior to dosing
		59	Rooting: post dosing
		60	Rooting: post dosing
			Salivation: prior to dosing
		61	Rooting: post dosing
		62	Salivation: prior to dosing
		63	Rooting: post dosing
			Salivation: prior to dosing
		64	Rooting: post dosing
			Salivation: prior to dosing
		65	Salivation: prior to dosing
		66	Salivation: prior to dosing
		67	Salivation: prior to dosing
		68	Salivation: prior to dosing
		69	Salivation: prior to dosing
		70	Salivation: prior to dosing
		71	Rooting: post dosing
			Salivation: prior to dosing
		74	Salivation: prior to dosing
	175	26	Piloerection
		37	Salivation: prior to dosing
		38	Rooting: post dosing
		52	Rooting: post dosing
		54	Salivation: prior to dosing
		55	Salivation: prior to dosing
		56	Rooting: post dosing
		58	Salivation: prior to dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 6 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
50	175	60	Rooting: post dosing
			Salivation: prior to dosing
		62	Salivation: prior to dosing
		68	Salivation: prior to dosing
		70	Salivation: prior to dosing
		72	Salivation: prior to dosing
		73	Salivation: prior to dosing
		74	Efflux of the dosing solution
	176	26	Piloerection
		42	Salivation: prior to dosing
		69	Salivation: prior to dosing
	182	37	Salivation: prior to dosing
		41	Salivation: prior to dosing
		44	Salivation: prior to dosing
		56	Salivation: prior to dosing
		58	Salivation: prior to dosing
		64	Salivation: prior to dosing
		65	Salivation: prior to dosing
	183	57	Efflux of the dosing solution
			Rooting: post dosing
		68	Rooting: post dosing
		72	Rooting: post dosing
	316	37	Rooting: post dosing
		55	Chromodacryorrhea: nose
	317	47	Salivation: prior to dosing
		54	Salivation: prior to dosing
		65	Salivation: prior to dosing
		66	Salivation: prior to dosing
	325	34	Rooting: post dosing
		58	Rooting: post dosing
		64	Rooting: post dosing
			Salivation: prior to dosing
	326	37	Rooting: post dosing
		43	Rooting: post dosing
		46	Rooting: post dosing
		53	Rooting: post dosing
		57	Efflux of the dosing solution
			Rooting: post dosing
		58	Rooting: post dosing
		60	Rooting: post dosing
		61	Efflux of the dosing solution
			Rooting: post dosing
		63	Rooting: post dosing
			Salivation: prior to dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 7 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
50	326	64	Rooting: post dosing
			Salivation: prior to dosing
		68	Salivation: prior to dosing
		71	Rooting: post dosing
			Salivation: prior to dosing
	334	37	Rooting: post dosing
		42	Rooting: post dosing
		47	Efflux of the dosing solution
	335	42	Rooting: post dosing
			Salivation: prior to dosing
		50	Salivation: prior to dosing
		52	Salivation: prior to dosing
		54	Salivation: prior to dosing
		58	Rooting: post dosing
			Salivation: prior to dosing
		62	Salivation: prior to dosing
		63	Rooting: post dosing
			Salivation: prior to dosing
		64	Salivation: prior to dosing
		65	Salivation: prior to dosing
		66	Salivation: prior to dosing
		67	Salivation: prior to dosing
		68	Salivation: prior to dosing
		70	Salivation: prior to dosing
		71	Salivation: prior to dosing
		74	Salivation: prior to dosing
		75	Salivation: prior to dosing
	342	38	Rooting: post dosing
		55	Rooting: post dosing
		56	Rooting: post dosing
		57	Rooting: post dosing
		58	Rooting: post dosing
		59	Rooting: post dosing
		64	Rooting: post dosing
		70	Efflux of the dosing solution
	463	36	Rooting: post dosing
		48	Rooting: post dosing
		54	Rooting: post dosing
		56	Rooting: post dosing
		57	Rooting: post dosing
		58	Rooting: post dosing
		59	Rooting: post dosing
		61	Rooting: post dosing
		63	Rooting: post dosing
		67	Rooting: post dosing
		71	Chromodacryorrhea: eye, right

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 8 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
50	472	23	Piloerection
		24	Lethargic
			Piloerection
		25	Piloerection
			Respiration: audible
		26	Found dead
	482	37	Rooting: post dosing
		39	Efflux of the dosing solution
100	271	33	Rooting: post dosing
		34	Rooting: post dosing
		35	Rooting: post dosing
		36	Rooting: post dosing
		37	Rooting: post dosing
		38	Rooting: post dosing
		50	Rooting: post dosing
		56	Rooting: post dosing
	272	23	Piloerection
		29	Efflux of the dosing solution
		33	Salivation: prior to dosing
		38	Rooting: post dosing
			Salivation: prior to dosing
		42	Rooting: post dosing
		61	Salivation: prior to dosing
		64	Rooting: post dosing
			Salivation: prior to dosing
	280	32	Rooting: post dosing
		40	Rooting: post dosing
		41	Salivation: prior to dosing
		47	Rooting: post dosing
			Salivation: prior to dosing
		54	Rooting: post dosing
		68	Rooting: post dosing
	281	32	Rooting: post dosing
		39	Efflux of the dosing solution
		50	Rooting: post dosing
		52	Rooting: post dosing
			Salivation: prior to dosing
		54	Salivation: prior to dosing
		55	Efflux of the dosing solution
		56	Salivation: prior to dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 9 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
100	281	58	Rooting: post dosing
			Salivation: prior to dosing
		62	Salivation: prior to dosing
		68	Rooting: post dosing
			Salivation: prior to dosing
		70	Rooting: post dosing
			Salivation: prior to dosing
	289	33	Rooting: post dosing
		34	Salivation: prior to dosing
		42	Salivation: prior to dosing
		43	Salivation: prior to dosing
		44	Salivation: prior to dosing
		46	Salivation: prior to dosing
		49	Salivation: prior to dosing
		56	Salivation: prior to dosing
		58	Rooting: post dosing
		60	Rooting: post dosing
			Salivation: prior to dosing
		62	Rooting: post dosing
		64	Salivation: prior to dosing
		68	Salivation: prior to dosing
		70	Salivation: prior to dosing
	290	30	Efflux of the dosing solution
		31	Rooting: post dosing
		33	Rooting: post dosing
		34	Rooting: post dosing
			Salivation: prior to dosing
		40	Salivation: prior to dosing
		41	Salivation: prior to dosing
		42	Salivation: prior to dosing
		44	Salivation: prior to dosing
		45	Salivation: prior to dosing
		46	Salivation: prior to dosing
		52	Salivation: prior to dosing
		54	Salivation: prior to dosing
		57	Salivation: prior to dosing
		60	Salivation: prior to dosing
		64	Rooting: post dosing
			Salivation: prior to dosing
	298	38	Rooting: post dosing
		50	Rooting: post dosing
		54	Rooting: post dosing
		56	Rooting: post dosing
		58	Rooting: post dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 10 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
100	298	59	Rooting: post dosing
		60	Rooting: post dosing
		63	Rooting: post dosing
		71	Rooting: post dosing
	299	32	Efflux of the dosing solution
		34	Paw: right front 4th metatarsal swollen
			Rooting: post dosing
		35	Paw: right front 4th metatarsal swollen, healing
		54	Rooting: post dosing
		59	Rooting: post dosing
	307	33	Rooting: post dosing
		39	Salivation: prior to dosing
	308	34	Salivation: prior to dosing
	427	24	Efflux of the dosing solution
		31	Rooting: post dosing
		33	Salivation: prior to dosing
		36	Rooting: post dosing
		39	Salivation: prior to dosing
		41	Rooting: post dosing
		45	Rooting: post dosing
		47	Rooting: post dosing
		48	Rooting: post dosing
		49	Rooting: post dosing
		50	Rooting: post dosing
		51	Rooting: post dosing
			Salivation: prior to dosing
		54	Salivation: prior to dosing
		58	Rooting: post dosing
		59	Rooting: post dosing
		61	Rooting: post dosing
		63	Rooting: post dosing
	428	32	Rooting: post dosing
		33	Salivation: prior to dosing
		36	Rooting: post dosing
		41	Rooting: post dosing
		49	Rooting: post dosing
		62	Salivation: prior to dosing
	436	32	Efflux of the dosing solution
		36	Rooting: post dosing
		39	Salivation: prior to dosing
		40	Salivation: prior to dosing
		44	Salivation: prior to dosing
		45	Salivation: prior to dosing
		46	Salivation: prior to dosing

(continued)

US EPA ARCHIVE DOCUMENT

Table A-53. Individual F_1 Dosed Pubertal Male Clinical Observations During the Post Wean Holding Period (page 11 of 11)

Dose[a]	Male ID	Day[b]	Clinical Observations
100	436	47	Salivation: prior to dosing
		49	Salivation: prior to dosing
		51	Salivation: prior to dosing
		55	Salivation: prior to dosing
		56	Salivation: prior to dosing
		70	Salivation: prior to dosing
	437	33	Salivation: prior to dosing
		36	Rooting: post dosing
		41	Salivation: prior to dosing
		49	Salivation: prior to dosing
	454	36	Rooting: post dosing
		41	Rooting: post dosing
		67	Rooting: post dosing
	455	41	Salivation: prior to dosing
		53	Efflux of the dosing solution
		57	Salivation: prior to dosing
		58	Salivation: prior to dosing
		60	Salivation: prior to dosing
		63	Salivation: prior to dosing
		64	Salivation: prior to dosing
		66	Salivation: prior to dosing
		67	Salivation: prior to dosing
		68	Salivation: prior to dosing
		69	Salivation: prior to dosing
		70	Salivation: prior to dosing
	494	28	Efflux of the dosing solution

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.
[c]No further notation was made unless a change occurred.

US EPA ARCHIVE DOCUMENT

Table A-54. Individual F_1 Dosed Pubertal Male Preputial Separation Data (page 1 of 2)

Dose[a]	Male ID	Day of Acquisition[b]	Body Weight (g)
0	100[c]		
	101	40	197.91
	109	40	212.49
	110	40	197.95
	118	40	198.15
	119	40	231.68
	191	42	205.11
	192	41	217.55
	200	40	254.86
	201	42	244.42
	209	40	224.53
	210	40	220.18
	227	44	215.58
	228	39	.[d]
	351	39	229.38
	352	39	212.97
	360	42	204.47
	361	41	221.40
	369	39	217.42
	370	40	224.77
	378	40	200.61
	379	40	216.88
	489	40	209.53
25	127	40	225.72
	133	43	212.83
	134	43	218.33
	236	40	230.24
	237	39	217.05
	245	40	210.35
	246	39	220.42
	253	40	190.52
	254	40	197.40
	262	41	223.08
	263	40	188.35
	391	40	203.28
	392	38	201.25
	400	41	201.68
	401	40	186.51
	409	43	217.00
	410	44	210.19

(continued)

US EPA ARCHIVE DOCUMENT

Table A-54. Individual F_1 Dosed Pubertal Male Preputial Separation Data (page 2 of 2)

Dose[a]	Male ID	Day of Acquisition[b]	Body Weight (g)
50	150	45	228.18
	151	45	207.80
	159	43	230.16
	160	44	204.35
	167	56	243.12
	168	44	214.01
	175	43	250.57
	176	44	245.46
	182	46	273.22
	183	42	230.56
	316	42	212.34
	317	49	226.20
	325	41	198.52
	326	40	195.41
	334	42	207.14
	335	42	230.60
	342	44	247.02
	343	44	232.63
	463	42	221.91
	464	42	242.89
	472[e]		
	473	42	204.36
	481	46	227.49
	482	45	238.18
100	271	43	190.57
	272	43	190.72
	280	44	188.32
	281	43	215.75
	289	45	228.90
	290	47	233.90
	298	43	210.52
	299	44	186.82
	307	42	204.12
	308	45	247.36
	427	43	229.13
	428	42	200.11
	436	46	204.72
	437	42	195.20
	454	46	225.07
	455	45	201.02
	494	53	256.13
	495	47	248.16

[a]Mg/kg/day of Methoxychlor.
[b]Postnatal day.
[c]Male was found dead on postnatal day 24 prior to dosing.
[d]Weight was inadvertently not recorded.
[e]Male was found dead on postnatal day 26 prior to dosing (misdirected dose).

US EPA ARCHIVE DOCUMENT

Table A-55. Individual F_1 Dosed Pubertal Male Reproductive Organ Weights and Measurements (page 1 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
0	100	.[b]											
	101	427.1	0	0.1670	3.2190	0.5718	0.5351	1.0381	0.4698	0.2934	0.7632	0.8555	0.0853
	109	487.1	0	0.2174	3.5903	0.4728	0.4760	0.9791	0.4740	0.3748	0.8488	1.2067	0.0930
	110	423.7	0	0.2148	3.7700	0.5228	0.4738	1.0775	0.3901	0.3532	0.7433	1.1682	0.1223
	118	461.2	0	0.0903	3.3839	0.5142	0.5398	1.3053	0.4667	0.3731	0.8398	0.9744	0.0662
	119	499.5	0	0.2576	3.7012	0.5842	0.5273	1.2419	0.5029	0.6773	1.1802	1.0526	0.0771
	191	431.2	0	0.2189	2.7273	0.4440	0.4447	0.9611	0.3410	0.2838	0.6248	0.6703	0.0745
	192	454.1	0	0.1133	2.9741	0.4958	0.4916	0.9432	0.3629	0.3333	0.6962	1.0043	0.0675
	200	580.6	0	0.0100	3.6141	0.5453	0.5697	1.0707	0.4879	0.5293	1.0172	1.1461	0.1561
	201	524.7	0	0.1086	3.7935	0.5904	0.5934	1.3405	0.5329	0.4818	1.0147	1.1559	0.1387
	209	541.4	0	0.1865	3.3101	0.4791	0.5166	1.2056	0.5736	0.3699	0.9435	1.0407	0.1157
	210	493.1	0	0.0939	3.3739	0.5335	0.5136	1.6181	0.8720	0.4216	1.2936	1.1162	0.1728
	227	437.8	0	0.2064	3.4817	0.5591	0.5026	0.9804	0.4271	0.3957	0.8228	0.9083	0.0738
	228	502.8	0	0.1287	3.4863	0.5327	0.6153	1.1054	0.5029	0.5606	1.0635	1.0297	0.0967
	351	529.3	0	0.1039	3.7113	0.5925	0.6367	1.4043	0.6177	0.4821	1.0998	1.1834	0.1598
	352	524.8	0	0.2415	3.1943	0.5201	0.5444	1.2473	0.3439	0.4570	0.8009	1.0675	0.1163
	360	442.8	0	0.1006	3.3254	0.4969	0.4595	0.7194	0.3573	0.3410	0.6983	0.7517	0.0905
	361	502.9	0	0.1074	3.6116	0.5482	0.5885	1.1740	0.5309	0.3483	0.8792	0.9484	0.1177
	369	578.2	0	0.1279	3.0782	0.4728	0.4154	1.2764	0.5844	0.3259	0.9103	1.4443	0.1464
	370	586.8	0	0.2676	3.2860	0.5391	0.5149	1.0073	0.3985	0.4603	0.8588	1.0671	0.1265
	378	486.6	0	0.1201	3.4718	0.5778	0.5593	1.0589	0.4017	0.3747	0.7764	1.1186	0.0791
	379	493.1	0	0.2219	3.8561	0.6071	0.6714	0.7349	0.5238	0.2974	0.8212	1.0247	0.1140
	489	467.5	0	0.1096	3.1752	0.4658	0.4687	0.9870	0.3574	0.4437	0.8011	1.0141	0.0911

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US EPA ARCHIVE DOCUMENT

Table A-55. Individual F_1 Dosed Pubertal Male Reproductive Organ Weights and Measurements (page 2 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
25	127	474.3	0	0.1147	3.3063	0.5483	0.5260	1.4680	0.9098	0.4360	1.3458	1.0613	0.1285
	133	362.1	0	0.1071	2.7818	0.4182	0.4783	0.8268	0.3331	0.2794	0.6125	0.9041	0.0618
	134	339.3	0	0.1706	2.9918	0.4851	0.4719	0.7555	0.2882	0.2200	0.5082	0.8179	0.0679
	236	430.4	0	0.2010	3.2396	0.4718	0.4890	0.8456	0.4360	0.2566	0.6926	0.8517	0.0662
	237	495.4	0	0.1000	3.4496	0.5490	0.5248	1.3133	0.5091	0.3746	0.8837	1.1506	0.0886
	245	374.1	0	0.1779	3.4002	0.5136	0.4597	.[c]	0.4546	0.4030	0.8576	0.8745	0.1365
	246	413.9	0	0.1334	3.1993	0.5122	0.5096	1.0790	0.5004	0.3955	0.8959	1.0808	0.1039
	253	386.6	0	0.1149	3.0519	0.4665	0.4825	1.1329	0.5168	0.2675	0.7843	1.2896	0.1336
	254	408.5	0	0.2237	3.2899	0.4896	0.4933	0.7579	0.4301	0.3190	0.7491	1.0734	0.0997
	262	403.0	0	0.1837	3.4063	0.5776	0.5147	0.8797	0.2855	0.3404	0.6259	0.8528	0.0660
	263	405.0	0	0.1153	2.7795	0.4815	0.4678	0.9561	0.3440	0.3781	0.7221	1.2974	0.0908
	391	384.1	0	0.0996	3.0738	0.5350	0.5381	0.7135	0.3561	0.2950	0.6511	0.8633	0.1018
	392	430.0	0	0.2005	3.2660	0.5501	0.5157	1.0437	0.5327	0.3169	0.8496	1.0199	0.1147
	400	403.3	0	0.1113	2.8949	0.5029	0.4953	0.5739	0.4158	0.3369	0.7527	0.8774	0.0918
	401	392.1	0	0.0850	3.2560	0.5397	0.5035	0.7898	0.4374	0.2501	0.6875	0.8772	0.1153
	409	375.3	0	0.0923	2.9303	0.4248	0.4106	0.6867	0.4111	0.3513	0.7624	0.6784	0.0835
	410	397.3	0	0.1548	3.0159	0.5192	0.5170	0.7484	0.3384	0.2287	0.5671	0.6843	0.0834

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US EPA ARCHIVE DOCUMENT

Table A-55. Individual F_1 Dosed Pubertal Male Reproductive Organ Weights and Measurements (page 3 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
50	150	374.1	0	0.2008	2.4612	0.4620	0.4043	0.7292	0.3147	0.1397	0.4544	0.5888	0.0666
	151	315.8	0	0.0892	2.6430	0.4475	0.4517	0.3829	0.3412	0.2394	0.5806	0.7258	0.0485
	159	395.3	0	0.1048	3.1688	0.4586	0.4681	0.9846	0.3620	0.3056	0.6676	0.9593	0.0851
	160	359.2	0	0.1613	3.2692	0.4258	0.4271	0.5079	0.2412	0.2604	0.5016	0.6754	0.0702
	167	300.8	0	0.1263	2.8515	0.4000	0.3713	0.2757	0.1526	0.1482	0.3008	0.4009	0.0288
	168	380.0	0	0.2167	3.2701	0.4367	0.4516	0.6021	0.3313	0.2291	0.5604	0.6972	0.0503
	175	410.3	0	0.1174	3.2051	0.4843	0.5332	0.8743	0.3014	0.2933	0.5947	0.8733	0.0816
	176	381.4	0	0.2168	3.3411	0.4684	0.4969	0.3334	0.1606	0.1205	0.2811	0.4555	0.0368
	182	396.3	0	0.2195	3.2541	0.4870	0.4704	0.7544	0.4054	0.3275	0.7329	0.7825	0.0390
	183	434.5	0	0.1230	3.1402	0.5041	0.4715	0.9523	0.3918	0.3882	0.7800	1.0564	0.0697
	316	393.5	0	0.1086	2.9885	0.5250	0.4796	0.9153	0.3837	0.3143	0.6980	1.0491	0.1161
	317	345.4	0	0.2088	2.7841	0.4811	0.4220	0.6234	0.2385	0.2876	0.5261	0.7666	0.0623
	325	368.4	0	0.2528	3.1009	0.4515	0.4306	0.7762	0.3624	0.1493	0.5117	0.8116	0.0670
	326	340.4	0	0.1931	3.3050	0.5385	0.4906	0.8156	0.3401	0.2723	0.6124	0.7164	0.0582
	334	348.6	0	0.0876	2.8904	0.4210	0.4178	0.5297	0.2203	0.1884	0.4087	0.6231	0.0785
	335	371.6	0	0.0965	3.1408	0.4278	0.4275	0.4740	0.2990	0.3207	0.6197	0.6414	0.0389
	342	433.9	0	0.1007	2.7957	0.4828	0.4687	0.6334	0.2833	0.2003	0.4836	0.9062	0.0728
	343	373.1	0	0.2833	2.9628	0.4538	0.4569	0.5537	0.2223	0.2451	0.4674	0.6165	0.0603
	463	388.2	0	0.1536	3.7485	0.6439	0.6038	1.1266	0.4916	0.3793	0.8709	0.9305	0.0910
	464	412.3	0	0.1297	3.4070	0.6063	0.5763	0.7991	0.3241	0.3674	0.6915	1.2515	0.1140
	472	.[d]											
	473	373.2	0	0.1851	2.7292	0.4383	0.4794	0.8414	0.2796	0.2286	0.5082	0.8590	0.0625
	481	377.1	0	0.1604	3.0353	0.4466	0.4564	0.6907	0.3001	0.1412	0.4413	0.6674	0.0585
	482	418.8	0	0.1056	3.3964	0.5101	0.4923	0.5413	0.3379	0.3634	0.7013	0.7386	0.0541

(continued)

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Table A-55. Individual F_1 Dosed Pubertal Male Reproductive Organ Weights and Measurements (page 4 of 4)

Dose[a]	Male ID	Sacrifice Weight	No. of Nipples	Glans Penis Weight	Paired Testis Weight	Right Epididymis Weight	Left Epididymis Weight	Seminal Vesicles with Coagulating Glands Weight	Ventral Prostate Weight	Dorso-lateral Prostate Weight	Prostate Weight	Levator Ani plus Bulbcav-ernosus Weight	Cowper's Gland Weight
100	271	307.8	.[e]	0.1631	2.8682	0.4610	0.4385	0.6575	0.2561	0.2750	0.5311	0.7225	0.0433
	272	308.1	0	0.0806	3.2534	0.4782	0.5190	0.7406	0.3385	0.2222	0.5607	0.6278	0.0645
	280	332.6	0	0.1872	2.6698	0.3838	0.3607	0.4636	0.1645	0.2168	0.3813	0.5261	0.0506
	281	367.1	0	0.0820	2.9729	0.4322	0.3973	0.8997	0.4816	0.2276	0.7092	0.9178	0.0931
	289	338.5	0	0.0928	2.7888	0.4345	0.4650	0.5696	0.2077	0.1765	0.3842	0.5048	0.0676
	290	339.9	0	0.1060	2.9356	0.4638	0.4589	0.5040	0.3233	0.2086	0.5319	0.5737	0.0636
	298	374.6	0	0.1821	2.8900	0.4439	0.4217	0.7588	0.2436	0.3428	0.5864	0.7413	0.0662
	299	307.6	0	0.1025	2.6875	0.3826	0.4008	0.6994	0.2349	0.3614	0.5963	0.7721	0.0806
	307	361.7	0	0.0976	3.0866	0.4243	0.4463	1.1025	0.3500	0.2723	0.6223	0.7648	0.0884
	308	410.4	0	0.1975	3.0438	0.5169	0.4479	0.6638	0.2759	0.2070	0.4829	0.6566	0.0525
	427	377.0	0	0.1821	3.3130	0.4943	0.4906	0.7129	0.3948	0.2853	0.6801	0.8342	0.0919
	428	350.6	0	0.0945	3.0008	0.4822	0.4585	1.0088	0.3606	0.2756	0.6362	0.8987	0.1078
	436	329.0	0	0.2336	2.6902	0.4980	0.4055	0.3701	0.2465	0.1335	0.3800	0.3597	0.0491
	437	353.4	0	0.1039	2.9425	0.4903	0.5119	0.6483	0.2725	0.2659	0.5384	0.6741	0.0914
	454	352.5	0	0.1305	2.9768	0.4123	0.3762	0.5147	0.1686	0.2793	0.4479	0.5175	0.0599
	455	323.1	0	0.0904	2.2866	0.3678	0.4090	0.3224	0.2028	0.2206	0.4234	0.5572	0.0735
	494	333.4	0	0.1173	2.4411	0.3650	0.3424	0.1557	0.1066	0.1168	0.2234	0.3109	0.0297
	495	361.1	0	0.0957	2.8922	0.4710	0.4431	0.5844	0.2824	0.2638	0.5462	0.7040	0.0725

[a]Mg/kg/day of Methoxychlor.
[b]Male was found dead on postnatal day 24 prior to dosing.
[c]Weight was a statistical outlier and therefore excluded.
[d]Male was found dead on postnatal day 26 prior to dosing (misdirected dose).
[e]Nipple count was inadvertently not recorded.

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Table A-56. Individual F_1 Dosed Pubertal Male Necropsy Weights and Hormone Data (page 1 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
0	100	.[b]								
	101	427.1	0.0123	0.0346	18.1910	0.0628	3.5231	4.86	56.78	11.79
	109	487.1	0.0100	0.0381	23.3152	0.0543	3.5372	5.83	57.04	6.35
	110	423.7	0.0091	0.0384	17.3601	0.0522	2.6016	5.87	45.74	5.91
	118	461.2	0.0113	0.0248	19.9820	0.0717	3.2753	6.46	80.12	22.85
	119	499.5	0.0105	0.0304	22.6954	0.0653	4.1098	6.29	75.58	12.76
	191	431.2	0.0111	0.0268	18.7325	0.0433	3.1053	6.05	54.52	13.68
	192	454.1	0.0123	0.0262	21.7335	0.0690	3.2987	4.42	49.73	10.05
	200	580.6	0.0169	0.0348	28.3235	0.0792	4.6789	6.17	89.52	14.21
	201	524.7	0.0149	0.0361	23.8785	0.0752	4.1902	5.37	93.08	13.17
	209	541.4	0.0083	0.0379	23.9906	0.0479	3.7870	3.97	45.24	11.92
	210	493.1	0.0151	0.0278	20.9706	0.0638	3.6910	4.77	61.87	11.00
	227	437.8	0.0146	0.0379	21.0098	0.0585	3.2438	5.78	58.58	9.69
	228	502.8	0.0130	0.0335	22.0130	0.0745	3.8221	6.48	77.12	9.52
	351	529.3	0.0167	0.0325	25.4986	0.0872	4.2555	4.70	67.10	11.10
	352	524.8	0.0115	0.0339	26.1242	0.0639	3.8803	5.47	81.17	9.24
	360	442.8	0.0139	0.0293	19.6984	0.0531	3.1373	5.78	57.84	10.13
	361	502.9	0.0149	0.0313	23.8697	0.0709	4.1610	5.91	68.76	6.15
	369	578.2	0.0158	0.0332	29.7441	0.0708	4.1673	6.55	89.12	12.95
	370	586.8	0.0134	0.0407	29.1974	0.0520	4.6046	7.42	101.72	8.06
	378	486.6	0.0143	0.0436	23.0949	0.0720	3.9463	5.38	76.54	12.76
	379	493.1	0.0151	0.0321	22.5212	0.0640	4.1018	6.44	82.43	7.56
	489	467.5	0.0124	0.0270	20.1755	0.0569	3.0270	4.93	63.03	13.50

(continued)

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Table A-56. Individual F_1 Dosed Pubertal Male Necropsy Weights and Hormone Data (page 2 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
25	127	474.3	0.0126	0.0417	23.2544	0.0671	3.7662	7.08	53.42	14.55
	133	362.1	0.0124	0.0363	15.3254	0.0808	3.0409	7.21	43.26	8.30
	134	339.3	0.0087	0.0268	13.9198	0.0509	2.7585	6.17	61.28	6.72
	236	430.4	0.0136	0.0401	19.7501	0.0695	3.5525	5.46	74.60	25.86
	237	495.4	0.0139	0.0237	25.6941	0.0719	3.7972	4.95	62.74	20.28
	245	374.1	0.0096	0.0287	15.9709	0.0747	2.9863	5.58	45.01	8.56
	246	413.9	0.0136	0.0288	17.4187	0.0749	3.4472	7.01	74.71	19.45
	253	386.6	0.0138	0.0388	16.4346	0.0527	2.7501	4.80	39.89	12.13
	254	408.5	0.0164	0.0342	18.3494	0.0487	3.3170	4.92	67.19	21.07
	262	403.0	0.0144	0.0412	16.4090	0.0697	3.0726	7.50	72.10	12.79
	263	405.0	0.0131	0.0298	17.8670	0.0551	3.145[c]	6.20	72.55	11.34
	391	384.1	0.0127	0.0245	16.5289	0.0502	2.9503	4.68	49.87	7.69
	392	430.0	0.0110	0.0363	18.8907	0.0424	3.6238	6.13	68.05	11.54
	400	403.3	0.0133	0.0325	19.0360	0.0681	3.4791	4.60	31.74	9.13
	401	392.1	0.0119	0.0282	17.7750	0.0745	3.1416	5.57	43.97	16.65
	409	375.3	0.0128	0.0328	15.9910	0.0682	2.8463	7.01	72.87	23.11
	410	397.3	0.0110	0.0236	16.3328	0.0648	3.0714	6.87	75.82	15.49

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US EPA ARCHIVE DOCUMENT

Table A-56. Individual F_1 Dosed Pubertal Male Necropsy Weights and Hormone Data (page 3 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
50	150	374.1	0.0091	0.0318	19.7483	0.0631	3.6215	6.02	80.88	16.62
	151	315.8	0.0090	0.0373	16.2480	0.0638	2.4829	6.84	74.10	8.23
	159	395.3	0.0133	0.0372	17.6295	0.0661	2.8219	5.71	63.00	11.27
	160	359.2	0.0096	0.0262	16.6874	0.0900	2.6811	6.25	71.77	9.69
	167	300.8	0.0097	0.0241	13.6263	0.0357	2.1997	5.91	68.32	8.17
	168	380.0	0.0124	0.0284	17.0853	0.0573	2.7363	6.91	39.21	14.60
	175	410.3	0.0135	0.0352	18.8605	0.0658	3.5730	6.70	62.60	10.20
	176	381.4	0.0118	0.0345	16.0590	0.0604	2.8042	7.25	60.07	9.39
	182	396.3	0.0105	0.0398	17.8934	0.0840	3.4397	7.54	75.70	11.00
	183	434.5	0.0143	0.0374	20.8716	0.0906	3.8621	8.26	84.09	11.90
	316	393.5	0.0108	0.0354	17.5201	0.0647	2.9288	7.15	53.13	14.19
	317	345.4	0.0123	0.0276	15.0278	0.0561	2.6545	5.84	43.22	14.08
	325	368.4	0.0133	0.0383	15.1952	0.0663	2.8448	5.64	57.13	8.02
	326	340.4	0.0101	0.0329	12.9719	0.0539	2.8941	5.75	53.79	5.91
	334	348.6	0.0127	0.0268	15.3440	0.0844	2.4899	6.67	67.20	11.44
	335	371.6	0.0165	0.0363	15.5117	0.0708	2.6302	6.38	57.31	10.26
	342	433.9	0.0156	0.0270	20.5394	0.0772	3.5286	6.57	65.31	10.44
	343	373.1	0.0151	0.0323	16.8578	0.0631	3.0024	5.79	55.25	7.01
	463	388.2	0.0115	0.0383	17.2925	0.0537	3.0497	7.08	73.67	8.83
	464	412.3	0.0112	0.0318	17.4624	0.0749	3.6916	5.37	44.50	8.94
	472	.[d]								
	473	373.2	0.0114	0.0329	15.7447	0.0520	2.7190	6.67	56.46	12.27
	481	377.1	0.0105	0.0402	19.7500	0.0675	2.8548	6.23	65.96	13.13
	482	418.8	0.0133	0.0418	19.6438	0.0577	3.7180	8.06	105.25	13.13

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US EPA ARCHIVE DOCUMENT

Table A-56. Individual F_1 Dosed Pubertal Male Necropsy Weights and Hormone Data (page 4 of 4)

Dose[a]	Male ID	Sacrifice Weight	Pituitary Weight	Thyroid Weight	Liver Weight	Paired Adrenal Gland Weight	Paired Kidney Weight	Thyroxine Hormone (ug/dL)	Triiodo-thyronine Hormone (ng/dL)	Thyroid Stimulating Hormone (ng/ml)
100	271	307.8	0.0061	0.0285	12.3149	0.0525	2.1784	6.19	69.71	13.53
	272	308.1	0.0097	0.0274	13.5184	0.0701	2.1256	7.23	94.17	10.14
	280	332.6	0.0076	0.0257	14.4075	0.0499	1.9297	4.65	76.93	8.46
	281	367.1	0.0116	0.0385	16.4691	0.0569	2.6955	7.13	61.01	10.31
	289	338.5	0.0089	0.0368	16.9774	0.0675	2.5005	5.74	45.42	8.11
	290	339.9	0.0094	0.0341	16.5415	0.0710	2.7105	5.33	45.33	5.53
	298	374.6	0.0109	0.0347	17.4420	0.0769	2.7614	4.66	50.22	9.76
	299	307.6	0.0118	0.0301	13.1596	0.0550	2.2916	5.19	53.95	6.95
	307	361.7	0.0133	0.0355	16.7365	0.0801	3.2258	6.99	77.34	10.85
	308	410.4	.[e]	0.0336	19.2025	0.0934	3.4961	5.47	63.98	15.72
	427	377.0	0.0124	0.0364	16.5726	0.0847	2.9054	7.52	92.96	11.40
	428	350.6	0.0123	0.0275	14.4942	0.0775	2.9338	4.06	41.76	9.48
	436	329.0	0.0112	0.0366	15.4941	0.0753	2.3444	6.28	53.90	14.78
	437	353.4	0.0113	0.0336	17.4660	0.0732	3.1032	6.30	77.69	9.55
	454	352.5	0.0133	0.0312	16.5960	0.0900	2.7056	4.81	59.33	18.92
	455	323.1	0.0097	0.0252	14.0731	0.0757	2.4382	4.24	62.65	18.98
	494	333.4	0.0094	0.0330	14.3283	0.0863	2.1888	7.72	78.44	11.53
	495	361.1	0.0122	0.0294	17.4027	0.0820	2.5392	7.23	86.43	11.25

[a]Mg/kg/day of Methoxychlor.
[b]Male was found dead on postnatal day 24 prior to dosing.
[c]Weight inadvertently recorded to only 3 decimal places.
[d]Male was found dead on postnatal day 26 prior to dosing (misdirected dose).
[e]Weight was a statistical outlier and therefore excluded.

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Table A-57. Individual F_1 Dosed Pubertal Male Sperm Data (page 1 of 2)

Dose[a]	Male ID	% Motile	% Progressively Motile	Epididymal Sperm Conc.[b]	Spermatid Head Conc.[c]	Daily Sperm Production[d]	Efficiency of Daily Sperm Production[e]
0	101	45	40	434.98	57.14	19.85	12.40
	109	76	66	374.57	70.42	27.25	15.28
	110	75	62	396.28	70.27	28.96	15.24
	118	85	72	445.13	77.52	28.61	16.82
	119	81	71	416.92	81.23	32.91	17.62
	191	52	49	374.34	146.46	43.41	31.77
	192	76	72	418.26	123.45	39.96	26.78
	200	67	59	414.53	90.56	35.92	19.64
	201	59	52	478.53	68.09	27.51	14.77
	209	55	47	469.89	73.05	26.81	15.84
	210	48	34	491.56	100.46	36.85	21.79
	227	84	74	388.98	95.64	36.44	20.75
	228	67	60	428.49	96.70	36.36	20.98
	351	49	33	345.90	87.67	34.62	19.02
	352	71	65	491.33	83.30	29.48	18.07
	360	50	35	327.29	101.68	36.85	22.06
	361	35	32	302.62	93.40	37.11	20.26
	369	61	53	431.19	95.69	32.47	20.76
	370	46	42	382.33	59.25	21.56	12.85
	378	56	45	421.42	69.76	26.46	15.13
	379	62	54	365.04	59.83	24.84	12.98
	489	59	51	377.40	128.68	44.60	27.91
100	271	65	62	372.30	64.48	19.50	13.99
	272	85	69	398.98	64.71	22.95	14.04
	280	72	64	302.81	107.88	31.02	23.40
	281	51	47	316.24	54.07	17.35	11.73
	289	73	62	352.53	83.13	25.27	18.03
	290	59	56	312.36	74.02	23.62	16.06
	298	57	51	299.40	111.19	34.30	24.12
	299	48	38	371.18	74.71	21.48	16.21
	307	35	29	283.61	84.40	27.85	18.31
	308	51	44	327.07	91.88	30.09	19.93
	427	67	62	392.10	84.50	30.59	18.33
	428	66	54	428.38	88.65	28.96	19.23
	436	47	40	361.45	78.28	23.62	16.98
	437	35	29	314.02	86.45	28.26	18.75

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Table A-57. Individual F_1 Dosed Pubertal Male Sperm Data (page 2 of 2)

Dose[a]	Male ID	% Motile	% Progressively Motile	Epididymal Sperm Conc.[b]	Spermatid Head Conc.[c]	Daily Sperm Production[d]	Efficiency of Daily Sperm Production[e]
100	454	60	51	458.32	75.88	24.49	16.46
	455	78	74	428.29	80.16	20.20	17.39
	494	69	55	317.48	110.54	29.74	23.98
	495	53	37	380.97	85.59	26.46	18.57

[a]Mg/kg/day of Methoxychlor.
[b]Concentration in 10^6/g. Calculated as the number of sperm in the cauda epididymus (sample also used for motility analysis) plus the number of sperm used for the motility analysis divided by the weight (g) of the cauda epididymus used.
[c]Concentration in 10^6/g. Calculated as the number of spermatid heads divided by the weight (g) of the testis used.
[d]10^6/testis/day. Calculated as the total number of spermatid heads divided by 4.61 (constant for rats).
[e]10^6/g. testis/day. Calculated as the spermatid head concentration divided by 4.61 (constant for rats).

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Table A-58. Individual F_1 Dosed Pubertal Male Gross Necropsy Findings (page 1 of 2)

Dose[a]	Male ID	Finding
Scheduled Necropsy:		
0	119	Kidney: hydronephrosis, right
	209	Kidney: hydronephrosis, right
	489	Testis: undescended, bilateral
25	236	Kidney: hydronephrosis, right
	245	Alopecia: limb(s)
	262	Kidney: hydronephrosis, right
	263	Alopecia: face
50	150	Kidney: hydronephrosis, right
	151	Intestines, Large: air present
		Kidney: hydronephrosis, right
		Prostate: reduced in size
		Seminal Vesicles: reduced in size
	167	Kidney: hydronephrosis, right
	317	Kidney: hydronephrosis, right
	335	Kidney: hydronephrosis, left
	464	Kidney: hydronephrosis, right
100	289	Levator Ani plus Bulbcavernosus Muscle Complex: reduced in size
		Prostate: reduced in size
		Seminal Vesicles: reduced in size
	290	Levator Ani plus Bulbcavernosus Muscle Complex: reduced in size
		Prostate: reduced in size
		Seminal Vesicles: reduced in size
	299	Intestines, Large: air present
		Prostate: reduced in size
		Seminal Vesicles: reduced in size
	428	Testis: undescended, left
	494	Prostate, Dorsolateral: reduced in size
		Prostate, Ventral: reduced in size
		Seminal Vesicles: reduced in size

(continued)

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Table A-58. Individual F_1 Dosed Pubertal Male Gross Necropsy Findings (page 2 of 2)

Dose[a]	Male ID	Finding
Unscheduled Necropsy:		
0	100	Intestines, Small and Large: no ingesta or feces present Stomach: no food present Urinary Bladder: blood present
50	472	Esophagus: hole; Dosing solution present in the thoracic cavity, misdirected dose

[a]Mg/kg/day of Methoxychlor.

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APPENDIX II

PROTOCOL

EPA Contract No.: 68-W-01-023 (Battelle Prime Contractor)
RTI Contract No.: 65U-08055.001.017
RTI Study Code: Rt02-ED04 **6/06/02**
RTI Master Protocol No.: RTI-839

TITLE: Validation of the *In Utero*/Lactational Exposure Screening Protocol With Methoxychlor

SPONSOR: Battelle Memorial Institute
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1			
2			
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TABLE OF CONTENTS

1.0 Objective and Background 5
2.0 Materials and Methods 6
2.1 Test Substance 6
2.2 Chemical Safety and Handling 7
2.3 Dose Formulation and Analysis 7
2.4 Animals 8
2.4.1 Species and Supplier 8
2.4.2 Live Animals and Species Justification 8
2.4.3 Total Number, Age, and Weight 8
2.4.4 Quality Control 9
2.4.5 Sentinels 9
2.4.6 Quarantine 9
2.5 Animal Husbandry 9
2.5.1 Housing, Feed, and Water 9
2.5.2 Environmental Conditions 10
2.5.3 Animal Identification 10
2.5.4 Limitation of Discomfort 10
2.5.5 Breeding 11
3.0 Experimental Design 11
3.1 Study Design 11
Table 1. Study Design and Target Doses 13
Figure 1. Study Design for In Utero/Lactational Exposure Assay 14
3.2 Chemical and Dosage Selection 15
3.2.1 Chemical Selection 15
3.2.2 Dose Selection 15
3.3 Allocation and Treatment of F0 Maternal Animals 22
3.4 F0 Dams and F1 Litters Prior to Weaning 22
3.4.1 F0 Maternal Gestation, Parturition, and Lactation 22
3.4.2 Terminal Blood Collection and Disposition of F0 Females 23
3.4.3 F1 Progeny 24
3.4.3.1 Birth and Perinatal Observations 24
3.4.3.2 Standardization of Litter Sizes 24
3.5 Treatment and Evaluation of F1 Weanlings 24
3.5.1 Uterotrophic Cohort 25

TABLE OF CONTENTS (continued)

3.5.2 F1 Weanling Female Pubertal Cohort 26
3.5.3 F1 Weanling Male Pubertal Cohort 26
3.6 Necropsy of F1 Offspring 27
3.6.1 Terminal Blood Collection 27
3.6.2 Gross Necropsy and Organ Weights 27
3.6.3 Histology and Pathology 28
4.0 Statistical Analyses 29
5.0 Retention of Specimens and Records 30
6.0 Quality Control/Quality Assurance Procedures 30
7.0 Reporting 31
8.0 Personnel 31
9.0 Study Records to be Maintained 33
10.0 References 34

Attachment: Material Safety Data Sheet (MSDS): Methoxychlor

1.0 OBJECTIVE AND BACKGROUND

Concern has been expressed that the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) Tier 1 screening battery does not include an assay which exposes animals during perinatal life, during which the fetus/neonate is exquisitely sensitive to endocrine disruption. The objective of this assay is to detect reproductive and developmental effects in male and female rat offspring mediated by alterations in the estrogen, androgen, and thyroid (EAT) signaling pathways, resulting from exposure to the dam during gestation and lactation or from direct exposure to the offspring from weaning through puberty. It may be used to: (1) replace a number of protocols recommended by EDSTAC for the Tier 1 screening battery, (2) serve as a follow-up test for certain chemicals for which a full multigeneration test had been run prior to the upgrading of the protocol in 1998, and/or (3) augment the current developmental toxicity testing protocol. The endpoints were selected for their potential to respond to EAT-induced alterations of development and include those that are both sensitive to disruption and can be easily detected in the offspring.

The Food Quality Protection Act of 1996 and the Safe Drinking Water Act of 1996 required the EPA to develop and implement a screening program for determining the potential in humans for estrogenic (and anti-estrogenic) effects from pesticides. This program has been expanded on the advice of the EDSTAC to include androgenic (and anti-androgenic) effects and effects from thyroid-hormone (TH)-like (or anti-TH) substances.

The EDSTAC, assembled by the EPA in 1996, believed, to the best of its knowledge, that the recommended Tier 1 screening battery, if validated, would have the necessary breadth and depth to detect any currently known disruptors of EAT hormones. There was concern, however, that chemical substances or mixtures could produce effects from prenatal/prehatch exposure that would not be detected from pubertal or adult exposure (EDSTAC, 1998, Vol. 1, Chapter 5). Furthermore, there were differing views with the EDSTAC about whether there is scientific evidence of known endocrine disruptors or reproductive toxicants that can affect the prenatal stage of development without affecting the adult or prematuration stages, and whether effective doses and affected endpoints may differ among the three life stages.

The EDSTAC therefore recommended that EPA take affirmative steps, in collaboration with industry and other interested parties, to attempt to develop a protocol for a full life cycle (i.e., with embryonic exposure and evaluation of the adult offspring) developmental exposure screening assay that can be subjected to validation and standardization. The EDSTAC believed such an assay must involve prenatal or prehatch exposure and retention of offspring through puberty to adulthood and provide structural, functional, and reproductive assessment.

The EDSTAC recognized the difficulty in developing a developmental exposure screening assay that meets both the criteria specified above and the more general criteria for selecting T1S assays set forth in Chapter 3 of the EDSTAC report. However, the EDSTAC believed it is worth

the effort. Furthermore, the EDSTAC provided brief protocols for *in utero* and *in ovo* developmental screening assays that could be further evaluated for this purpose (an expanded discussion of an *in utero* protocol, similar to this EDSP assay, was included in EDSTAC report, 1998, Volume II, Appendix O).

Finally, the EDSTAC recommended that if such an assay were identified, validated, and standardized, the decision on whether it should be included in the T1S battery should include an evaluation of its potential to replace one or more of the recommended T1S assays and its overall impact to the cost effectiveness of the T1S battery (EDSTAC, 1998, Vol. 1, Chapter 5). The proposed protocol has been identified by the EPA as the "*In Utero*/Lactational Exposure Testing Protocol" and has been assigned for development under the EDSP. The objective of this bioassay is to detect effects mediated by alterations in the estrogen, androgen, and thyroid-signaling pathways as a consequence of exposure during pre- and postnatal development in the laboratory rat. The treatment paradigm allows for an evaluation of effects on organogenesis, sexual differentiation, and puberty. In using a developing system as the basis for the test, it is understood that modes of action, other than those of the estrogen, androgen, and thyroid-signaling pathways, may be involved in the induction of toxicity. As such, any observed effects will have to be interpreted in light of the overall weight of the evidence that they are endocrine dependent. RTI, as the lead laboratory for this assay for the EDSP, is suggesting that if this protocol is implemented, it should be used in place of a number of protocols recommended by EDSTAC in the Tier 1 screening battery, such as the *in vitro* steroidogenesis and placental aromatase assays and the *in vivo* male Hershberger assay, the uterotrophic female assay, and either or both pubertal assays, as a "Tier 1.5" assay, or as a follow-up test for chemicals for which a full multigeneration test had been completed prior to the upgrading of the protocol in the OPPTS 1998 testing guidelines.

2.0 MATERIALS AND METHODS

2.1 Test Substance

Common Name:	Methoxychlor
Chemical Name:	Benzene, 1,1'-(2,2,2-trichloroethylidene)bis(4-methoxy-9C1)
Synonyms:	1,1,1-Trichloro-2,2-bis(4-methoxyphenyl)ethane; 1,1,1-Trichloro-2,2-bis(*p*-anisyl)ethane
CAS No.:	72-43-5
Molecular Formula:	C16H15Cl302
Molecular Weight:	345.65
Appearance:	Colorless crystals (technical, gray flaky powder)

Odor:	Slightly fruity
Melting Point:	87°C
Density/Specific Gravity:	1.41 @ 25°C
Solubility:	Readily soluble in aromatic, chlorinated, and ketonic solvents and vegetable oils
Vehicle:	stripped (α-tocopherol [Vitamin E] removed) Mazola® corn oil
Supplier:[a]	
Batch/Lot Number:[a]	
Purity:[a]	
Storage Conditions:[a]	

[a] All additional information on the test chemical (e.g., supplier, batch/lot number, purity, storage conditions of bulk chemical and of dosing suspensions, etc.) will be added to the protocol by amendment.

2.2 Chemical Safety and Handling

See methoxychlor MSDS in Attachment.

2.3 Dose Formulation and Analysis

The dosing suspensions will be prepared at a frequency determined by stability tests performed prior to the start of the study. Suspensions will be prepared at Battelle Chemical Repository, Sequim, WA, and stored in wide-mouth, amber bottles. They will be shipped via 24-hour express delivery and logged into the RTI Materials Handling Facility prior to transfer to the Reproductive and Developmental Toxicology Laboratory for dosing. The test materials will be suspended in Mazola® stripped (α-tocopherol [Vitamin E] removed) corn oil (CAS No. 8001-30-7), with the concentration determined by the following formula:

$$\text{Concentration (mg / ml)} = \frac{\text{Dose (mg / kg / day)}}{\text{Dosage volume (5 ml / kg / day)}}$$

An aliquot of each dose level per formulation will be analyzed by Battelle. The dosing bottles will be identified at RTI by a five-digit, random number Rx code and a color code. Personnel, other than the Laboratory Supervisor, Project Toxicologist, and Study Director, will not be informed of the test chemicals or formulation concentrations until all laboratory work is completed (i.e., the study technicians will be "blind" for chemical and dose). Aliquots from the

dosing bottles will be collected on the first day of dosing (gestation day [gd] 6) and on the first postnatal day [pnd] 0, and pnd 7, 14, and 21 and will be shipped to Battelle Chemical Repository, Sequim, WA, for analysis.

2.4 Animals

2.4.1 Species and Supplier

The proposed test animals will be the Sprague Dawley Derived Outbred Albino Rat Crl:CD®(SD) IGS BR supplied by Charles River Laboratories, Inc., Raleigh, NC.

2.4.2 Live Animals and Species Justification

The use of live animals has been requested by the Sponsor. Alternative test systems are not available for the assessment of effects of chemicals on reproduction and development in intact mammals for determining the potential risk for humans from endocrine-mediated effects of pesticides and other chemicals. The Charles River CD® rat has been the subject of choice on reproductive and developmental toxicology contracts at RTI since 1976, and has been used for other reproductive toxicology studies with this test material. Large historical data bases for reproductive performance and prevalence of spontaneous malformations in control rats are available from studies conducted at RTI (currently based on over 600 control litters) as well as from the supplier (Charles River, 1988). This strain of rat has been proven to have robust fertility and fecundity, and does not present any unusual endocrinological patterns. This study does not unnecessarily duplicate any previous study.

2.4.3 Total Number, Age, and Weight

Number of Females:	100 (nulliparous females procured specifically for this study)	
Number of Males:	110 (breeding stock used for multiple studies on this contract)	
Age on Receipt:	Females: ~8-10 weeks	Males: ~10-12 weeks
Female Weight Range:	200-300 g on gd 0	

The number of animals assigned to each dose group is based on the breeding efficiency of the colony and the Sponsor's requirement for at least ten confirmed-pregnant animals per dose group. Minimum sample size requirements for statistical comparison of data among treatment groups were also considered in determining the number of animals assigned to each dose group. It is anticipated that 60 timed-mated, sperm-positive females (15 per group), to generate at least ten pregnant females per group, will be used in this study.

2.4.4 Quality Control

The shipment of nulliparous, virgin females will be quarantined on arrival, and quality control evaluation will be initiated within one day after receipt. Within one day after receipt, five female rats will be chosen from the shipment, sacrificed, and blood collected for assessment of viral antibody status. Heat-inactivated serum will be sent to BioReliance (Rockville, MD) for their Level 1 rat antibody screen. The viral screen will consist of evaluation for the presence of antibodies against the following: Toolan H-1 virus (H-1), Sendai virus, Pneumonia virus of mice (PVM), rat coronavirus/sialodacryoadenitis (RCV/SDA), Parvo virus, Kilham rat virus (KRV), CAR Bacillus, and Mycoplasma pulmonis (*M. Pul.*). In addition, fecal samples from representative animals will be externally examined for intestinal parasites.

2.4.5 Sentinels

After the assignment of F0 dams to treatment groups, four sperm-negative female rats will be arbitrarily selected, eartagged, and designated as sentinels (see Section 2.5.5, Breeding). They will be singly housed in the study room(s), with feed and water available *ad libitum* (as described below). They will be examined once daily by cageside observation for morbidity or mortality at the same time as the clinical observations or morbidity/mortality checks for the study animals. The clinical condition of sentinel animals will be recorded only in the event that an animal is moribund or found dead. If a sentinel animal is terminated moribund, blood will be collected at termination and serum samples frozen. During the final disposition of the F0 females and the last necropsy of the F1 offspring, the surviving sentinel females (two/time) will be terminated, blood samples collected, and serum samples prepared. All sentinel serum samples will be submitted to BioReliance (Rockville, MD) for serological evaluation (see above section on Quality Control).

2.4.6 Quarantine

Upon receipt, animals will be quarantined for seven days, with the prior concurrence of the RTI Animal Research Facility (ARF) veterinarian. They will be observed daily for general health status and ability to adapt to ARF husbandry conditions. They will be released from quarantine, if suitable for use (based on QC results), by the attending ARF veterinarian or his designate.

2.5 Animal Husbandry

2.5.1 Housing, Feed, and Water

During the quarantine period, animals will be randomly assigned to cages. Sperm-positive F0 females will be singly housed, and F1 male and female postweanlings will be multiply housed, then singly housed, if necessary, in solid-bottom polycarbonate cages (8"x19"x10.5") fitted with stainless steel wire lids (Laboratory Products, Rochelle Park, NJ). Sani-Chip® cage bedding (P.J. Murphy, Forest Products, Inc., Montville, NJ) will be used in all solid-bottom cages.

Breeder males will be housed in suspended cages. Pelleted feed will be available *ad libitum* for the male breeder rats, the F0 females during quarantine, the F0 females during the rest of gestation and lactation, and for the retained F1 males and females. Deionized water, produced at RTI from tap water from the Durham, NC water system, will be filtered and available *ad libitum* to breeder males and females during cohabitation via an automatic water delivery system (Edstrom Industries Inc., Waterford, WI). Deionized water will be available in plastic bottles with stainless-steel sipper tubes *ad libitum* to the F0 females during quarantine, the F0 females during gestation and lactation, and for the retained F1 males and females. The chow will be pelleted Purina Certified Rodent Chow® No. 5002 (PMI, Inc., St. Louis, MO). The analysis of the rodent chow for chemical composition and possible chemical contamination and analysis of Durham City water will be provided by the suppliers and maintained in the study records. In addition, each lot number of Purina 5002 feed used will be analyzed by the supplier for concentrations of the phytoestrogens genistein, daidzein, and glycitein. An aliquot of each lot number will be retained frozen for possible future analytical chemistry. The "metabolizable energy content" of the feed (label value) will also be recorded and reported. It is anticipated that contaminant levels will be below certified levels for both feed and water and will not affect the design, conduct, or conclusions of this study. Rat chow will be stored at approximately 60-70°F, and the period of use will not exceed six months from the milling date. At all times, animals will be housed, handled, and used according to the NRC Guide (NRC, 1996).

2.5.2 Environmental Conditions

Environmental conditions in the ARF will be continuously monitored, recorded, and controlled during the course of the study by an automated system (Siebe/Barber-Colman Network 8000 System with Version 4.4.1 Signal® software (Siebe Environmental Controls (SEC)/ Barber-Colman Company, Loves Park, IL). Animal rooms used for this study will be maintained on a 14:10 hour light:dark cycle. Target conditions for temperature and relative humidity ranges in the animal rooms will be between 64-79°F (18-26°C) and 30-70%, respectively, with 10-15 air changes per hour (NRC, 1996). Temperature and/or relative humidity excursions outside the mandated range(s) will be documented in the study records and the final report.

2.5.3 Animal Identification

During quarantine, male breeders and females will be individually identified by a unique eartag (National Band and Tag Co., Newport, KY). Confirmed-mated females will also be given a dam number on gd 0, which will be used as an identifier for cage cards and all study records. All selected study weanling F1 males and females will also be uniquely identified by eartag at weaning. All data generated during the course of this study will be tracked by these numbers.

2.5.4 Limitation of Discomfort

Some adult toxicity may be caused by exposure at the high doses of the test material. Discomfort or injury to animals will be limited, in that if any animal becomes severely debilitated

or moribund, it will be humanely terminated by CO_2 inhalation. All necropsies will be performed after terminal CO_2 asphyxiation. F1 pnd 4 culled pups will be euthanized by decapitation.

2.5.5 Breeding

For breeding, individual females will be placed in the home cage of singly-housed males (i.e., one male and one female). On the following morning and each morning thereafter, the females will be examined for the presence of vaginal sperm or a vaginal copulation plug (Hafez, 1970). The day on which vaginal sperm or plugs are found will be designated as gd 0. These females are presumed pregnant. The initial sperm-positive females (dams), designated the F0 generation, will be housed individually or with their litters until final disposition. Sperm-negative females will be retained in the same male's cage and checked for sperm or vaginal plug on successive mornings until insemination occurs or the treatment groups are filled, whichever comes first. When all treatment groups are filled, four sperm-negative females will be arbitrarily designated as sentinels (see Section 2.4.5, Sentinels) and remaining sperm-negative females will be sacrificed by asphyxiation with CO_2. Selected male and female offspring, designated the F1 generation, will be housed as described above. The fate of all animals will be fully documented.

3.0 EXPERIMENTAL DESIGN

3.1 Study Design

The study will consist of three dose groups and one vehicle control group, each group comprised of 15 mated F0 females distributed by a randomization scheme, stratified by body weight so that the mean body weights per group are equivalent across all groups on gd 0. The F0 study females will be dosed by gavage once daily for 36 consecutive days (gd 6 through pnd 21). Table 1 presents the study design and target doses of the test chemical. A graphical representation of the study design is presented in Figure 1 below.

Tentative Study Dates[a] (to be added to the protocol by amendment)

Nulliparous females arrive at RTI:

Cohabitation of breeding pairs:

F0 gd 0:

F0 dosing begins (gd 6):

F0 dosing ends (pnd 21):

Parturition of F1 offspring (pnd 0):

Weaning of F1 offspring (pnd 21):

Final Disposition of F0 dams:

Assignment of F1 offspring to cohorts (pnd 21):

Uterotrophic cohort dosing period (pnd 21-24):

Sacrifice of uterotrophic cohort (pnd 24):

Female pubertal cohort dosing period (pnd 21-42):

Sacrifice of female pubertal cohort (pnd 42):

Male pubertal cohort dosing period (pnd 21-70):

Sacrifice of male pubertal cohort (on pnd 70):

Submission of nonaudited draft final report:

Submission of audited draft final report:

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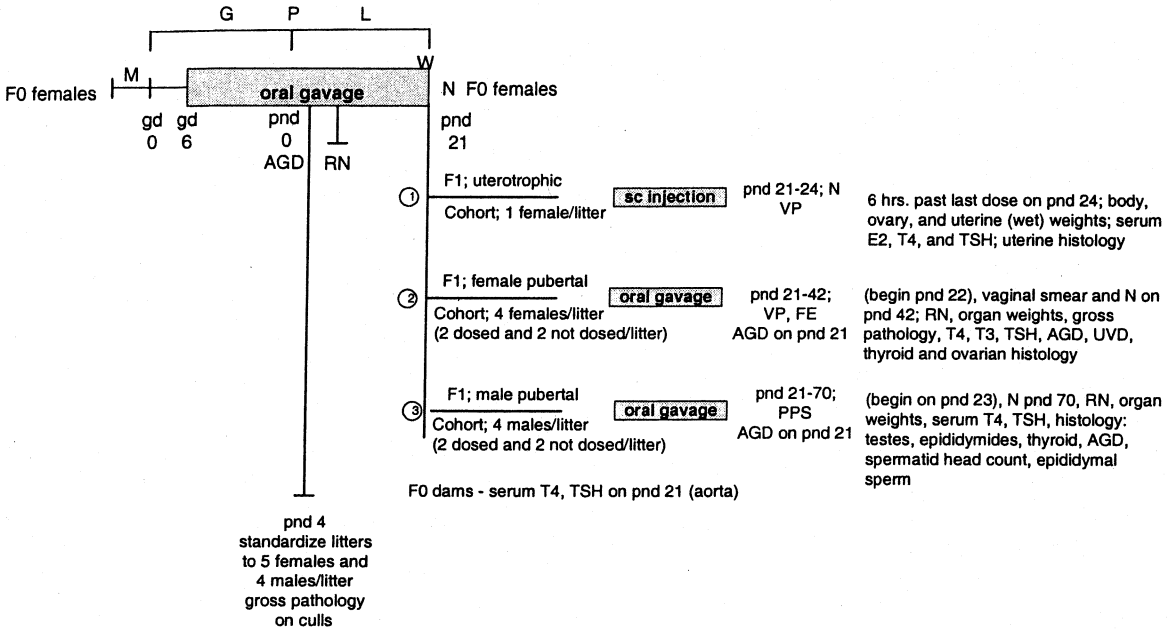
[a] The end dates are tentative and will depend on the dates of insemination and the duration of gestation and lactation of the F0 dams with F1 offspring.

Table 1. Study Design and Target Doses

	Group Number			
	1[a]	2	3	4
F0 Females				
No.	15	15	15	15
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	gavage	gavage	gavage	gavage
F1 Pubertal Females				
No.	≥10	≥10	≥10	≥10
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	gavage	gavage	gavage	gavage
F1 Pubertal Males				
No.	≥10	≥10	≥10	≥10
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)[b]	5	5	5	5
Route	gavage	gavage	gavage	gavage
F1 Uterotrophic Females				
No.	≥10	≥10	≥10	≥10
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	sc injection	sc injection	sc injection	sc injection

Figure 1. Study Design for In Utero/Lactational Exposure Assay



Key:

M = mating	RN = examination for retained nipples in F1 males and females on pnd 11-13
G = gestation	W = wean (pnd 21)
gd = gestational day	N = necropsy
P = parturition	VP = acquisition of vaginal patency (females)
pnd = postnatal day	PPS = acquisition of preputial separation (males)
AGD = anogenital distance	FE = first estrus
L = lactation	UVD = urethral vaginal distance

[ ] direct exposure to F0 dams and postweanling F1 offspring

3.2 Chemical and Dosage Selection

3.2.1 Chemical Selection

The chemical selected for this first validation study of the *in utero*/lactational exposure screening protocol is methoxychlor (MXC). MXC is an organochlorine pesticide in use as a DDT substitute to control insects. It has known endocrine effects (Gray et al., 1988). The *in vivo* metabolite of MXC, 2,2-bis(*p*-hydroxyphenol)-1,1,1-trichloroethane (HPTE), has selective agonist activity through the estrogen receptor (ER) alpha and antagonist activity through ER beta and the androgen receptor (AR) (Waters et al., 2000). MXC has been shown to inhibit androgen receptor-dependent transcriptional activity *in vitro* (Maness et al., 1998), so it also acts as an antiandrogen. In female mice and rats, MXC is positive in the uterotrophic assay with ovariectomized adults or weanlings, causing increased uterine weights. It stimulates ER expression in the uteri of neonatal (days 1-4) and immature (days 10-14) mice after ip injection for four days of MXC (Eroschenko et al., 1996). It also reduced the number of implants and newborns in a multigeneration study of dietary MXC (Aoyama et al., 2000). The day of vaginal opening was accelerated and body weight at acquisition was reduced by MXC administered by ip injection to female rats on pnd 10-14 (Respess et al., 1999). In male mice and rats with *in utero* exposure, MXC disrupted the morphology and growth of the developing testis (Cupp and Skinner, 2000). Perinatal and juvenile exposure to MXC reduced testicular size and Sertoli cell numbers in adult rats (Johnson et al., 2000). Perinatal exposure to dams on gd 18 to parturition and directly to pups on pnd 1-5 resulted in increased lateral prostate lobe (but not ventral lobe) weight in adult male offspring (Stoker et al., 1999). Since MXC (and its metabolite HPTE) has estrogenic, anti-estrogenic, and anti-androgenic properties, mediated through interactions with the ERα and β and the AR, because MXC and HPTE can compete for binding to the ER (Cupp and Skinner, 2000) and because it also affects circulating TSH and T4 levels (Gray et al., 1989), it was chosen as the first chemical for validation of this assay.

3.2.2 Dose Selection

MXC will be dosed by oral gavage to F0 maternal animals from gd 6 through pnd 21 and by oral gavage to the F1 male and female pubertal cohorts (pnd 21-42 for females, pnd 42-70 for males). It will also be administered by subcutaneous (sc) injection on pnd 21-24 to the F1 female uterotrophic cohort.

Based on a literature search and input from Dr. L. Earl Gray, Jr. (EPA NHEERL), the doses for the oral gavage dosing will be 0, 25, 50, and 100 mg/kg/day with MXC in corn oil at 5 ml/kg. The doses for the sc injection administration are set to the same levels (0, 25, 50, and 100 mg/kg/day, as a place holder) at the same dosing volume (5 ml/kg). For the uterotrophic cohort, with administration only on pnd 21-24, the F1 female pups will be approximately 40-60 g body weight. Therefore, the volume administered by sc injection will be approximately 0.2-0.3 ml/female. The justification for the doses and routes is as follows.

The doses selected represent the mid range of gavage doses identified in the literature. Doses used and effects observed are discussed by sex, males first.

Males

White et al. (2001) exposed Sprague-Dawley rats in a one-generation study design to MXC in the diet at 10, 100, and 1000 ppm (with MXC intakes calculated for this protocol of 0.7, 6.7, and 66.7 mg/kg/day), from gd 7 for F0 animals to pnd 77 for F1 offspring. The authors reported only increased splenic basal and stimulated lymphocyte proliferation response in F1 males (but not F1 females), especially following developmental exposure. Cupp and Skinner (2000, 2001) dosed pregnant rodents with MXC at 50 mg/kg/day from gd 7 through gd 15. Embryonic gonads were collected on gd 16, pnd 4, and pnd 17 during testis development. Effects on the testis were observed only on pnd 17, with gross reduction in the testicular interstitium. They confirmed the MXC effects with *in vitro* testis organ cultures, which exhibited inhibited/disrupted testicular cord formation and increased cell growth. Johnson et al. (2000) gavaged rat dams with MXC at 0, 50, 50, or 150 mg/kg/day for the last week of gestation and the first week of lactation. Male pups were dosed directly from pnd 7 to 42. The offspring males in the two highest dose groups exhibited fewer testicular spermatids and reduced numbers of Sertoli cells as adults. Stoker et al. (1999) dosed rat dams by gavage to MXC from gd 18 through pnd 5 at 50 mg/kg/day. Male offspring were examined on pnd 90. They exhibited increased prostate lateral lobe (but not ventral lobe) weight, with an increased incidence in the number and severity of inflammation in the lateral prostate. Chapin et al. (1996, 1997; Harris et al., 1996) exposed pregnant rats to MXC at 0, 5, 50, and 150 mg/kg/day for the week before and after parturition (see above), with offspring pups dosed directly from pnd 7 to pnd 21 or pnd 42. In the male offspring, anogenital distance was unaffected, but male preputial separation was delayed at 50 and 150 mg/kg/day by eight and 34 days, respectively. Epididymal sperm counts were reduced at 150 mg/kg/day, and testes and epididymal weights were reduced at 50 and 150 mg/kg/day; seminal vesicle weights were reduced at all doses. The F1 animals (15/dose group) at adulthood were mated to untreated animals twice. Males at 150 mg/kg/day impregnated 3/30 untreated females versus 21/30 in controls; litter size was unaffected.

Anderson et al. (1994, 1995) evaluated MXC in Long-Evans hooded rats under an alternative reproduction test (ART) protocol. It was administered by gavage at 0, 50, or 200 mg/kg/day to F0 males and females, starting at three weeks of age and continuing for 14 weeks in males or 18 weeks in females through gestation and lactation. For the F0 males as adults, ejaculated sperm counts, caudal epididymal sperm counts, and epididymal, ventral prostate, and seminal vesicle weights were all reduced at both doses. MXC suppressed both GnRH and hCG-stimulated testosterone levels; LH levels were significantly higher after GnRH challenge.

Gray et al. (1989) dosed rats at weaning through puberty, mating, and gestation to pnd 15 of lactation by gavage with MXC at 0, 25, 50, 100, and 200 mg/kg/day. In the males, MXC markedly reduced growth; seminal vesicle, cauda epididymis and pituitary weights; and cauda epididymal sperm content. Puberty was delayed at 100 and 200 mg/kg/day. Testicular spermatid

measures were much less affected than cauda sperm measures. Testis weight and histology were slightly affected, and testicular sperm production and sperm morphology and motility were unaffected. Endocrine function of the testes and pituitary was altered by MXC. Leydig cell testosterone production from hCG challenge was reduced, and pituitary levels of prolactin, TSH, and FSH were altered (serum levels of prolactin, FSH, and LH were unaffected). Serum TSH was reduced by 50% at 100 and 200 mg/kg/day, while pituitary levels were increased. In spite of these effects on males, the fertility of the treated males, mated with untreated females, was unaffected.

Gray et al. (1999) dosed weanling male Long-Evans hooded rats by gavage with MXC at 0, 200, 300, or 400 mg/kg/day for ten months. The treated males were then mated to untreated females. MXC delayed puberty by as much as ten weeks at the top dose, and reduced fertility and copulatory plug formation in a dose-related manner at the initial mating. During mating, treated males exhibited shorter latencies to mount and ejaculate versus control males (with the number of intromissions prior to ejaculation unaffected), indicating that MXC enhanced male arousal. Most MXC-treated males mated, but time to pregnancy was lengthened. Very low sperm counts were associated with infertility, while prolonged delays in puberty were associated with reduced fecundity. MXC at 200-400 mg/kg/day did not mimic chronic effects of exposure to 17β-estradiol on testicular or pituitary hormone levels. MXC affected the CNS, epididymal sperm numbers, and accessory sex organs without affecting the secretion of LH, prolactin, or testosterone. Therefore, MXC did not alter pituitary endocrine function in either an estrogenic or anti-androgenic manner.

Goldman et al. (1986) investigated the effects of MXC on the pituitary and hypothalamic components of the male rat reproductive system at dose levels that did not affect the testis. Male Long-Evans rats were gavaged daily with MXC at 0, 25, or 50 mg/kg/day, starting at 21 days of age for eight weeks. There were no effects on serum LH, FSH, or prolactin levels, and no effects on pituitary concentrations of LH or FSH. Pituitary prolactin was elevated at both doses (and pituitary fragments *in vitro* released more prolactin than control fragments). The authors concluded that the reproductive effects of MXC may be mediated, at least in part, through early increased prolactin concentration and release, which in turn affects hypothalamic levels of GnRH and subsequent pituitary and gonadal adverse responses.

When MXC was administered by oral gavage to male rats at 70 days and to female rats at 14 days at 0, 100, or 200 mg/kg/day, MXC inhibited spermatogenesis, with degenerative fatty changes in the Sertoli cells. Degeneration changes in spermatogonia and spermatocytes were also observed, with some seminiferous tubules devoid of all cellular elements except spermatogonia. The epithelium of the ductus epididymis also exhibited cytoplasmic vacuolation and distention of the lumen (Bal, 1984).

Sar et al. (2001) exposed pregnant SD rats to MXC in the diet at 800 ppm (approximately 53 mg/kg/day). Inguinal mammary glands from F1 male offspring exhibited greater total glandular area and increased numbers of branch points, lateral buds, and terminal end buds than controls (F1 female offspring mammary glands were unaffected).

Welshons et al. (1999) have reported that fetal exposure (gd 11-17) of very low doses of MXC (20 and 2000 μg/kg) result in increased prostate weight in adult male offspring.

Therefore, the doses selected should result in effects on the male testis and accessory sex organs, in delay in preputial separation, effects on testicular spermatid and epididymal sperm counts, and serum hormone levels, including effects on TSH from the pituitary and T4 from the thyroid.

Females

The effects of MXC on female reproduction have been more extensively researched and reported. Exposure of MXC at 0, 10, 100, or 1000 ppm in the diet (0, 0.7, 6.7, or 66.7 mg/kg/day, respectively) to F0 SD rats did not produce increased splenic lymphocyte proliferation under either basal or stimulated conditions in F1 females (F1 males did respond with increased proliferation) (White et al., 2001). When Sar et al. (2001) exposed pregnant SD rats to 800 ppm MXC in the diet (approximately 53 mg/kg/day), there was no effect on F1 female offspring inguinal mammary glands when evaluated for total glandular area and number of branch points, lateral buds, and terminal end buds (inguinal mammary glands for F1 male offspring were affected).

Both rats and mice (either ovariectomized adult or intact immature females) respond to short-term daily dosing of MXC by increased uterine weights (Aoyama et al., 2000 and Respess et al., 1999 in rats; Eroschenko, 1997 and Eroschenko et al., 2000 in mice). Female SD pups were administered MXC on pnd 10-14 by ip injection of 0, 0.3, 3, or 300 mg/kg/day. Pups were sacrificed on pnd 15, 23, 31, and 70. Day of vaginal opening was accelerated by four days, and body weight at acquisition was reduced (by 25 g) at 300 mg/kg/day. Ovarian and uterine weights were increased at 300 mg/kg/day on pnd 15 (Respess et al., 1999).

One-day-old female mice (five to eight/group) were administered MXC by ip injection for 14 days at 0.1, 0.5, or 1.0 mg MXC (corresponding to 14-71, 68-357, or 135-714 mg/kg/day, respectively). Three months later, the females were paired with proven breeder, untreated males and checked daily for vaginal copulation plugs. Maternal females were necropsied 18 days after insemination. All mice from the three MXC groups mated, with dose-related, decreased numbers of pregnant animals on gd 18. The mean number of live fetuses/litter was reduced at 0.5 and 1.0 mg MXC. Ovarian corpora lutea were reduced only at 1.0 mg MXC. No effects were observed at 0.1 mg MXC. The authors concluded that MXC did not affect mating but did affect initiation and/or maintenance of pregnancy. Therefore, the neonatal exposure to MXC may affect the hypothalamic-pituitary-ovarian axis as well as the uterine environment (Swartz and Eroschenko, 1998).

MXC was administered to pregnant mice on day 1, 2, 3, or 4 of pregnancy at 400 or 800 μg/g body weight (400 or 800 mg/kg). At 400 mg/kg on day 1 or 2, MXC induced delays in implantation. At 800 mg/kg/day on day 1 or 2, only 50% of the females exhibited implanted

conceptuses, and the number of embryos/female was significantly reduced. Administration of lower doses of MXC or at later times did not affect implantation. However, embryonic development and transport were delayed at 400 and 800 mg/kg/day, administered on days 3 or 4. Reciprocal embryo transfers with embryos from MXC-treated dams (800 mg/kg on day 1), transferred into untreated females, resulted in no implantations (control donor embryos exhibited a 79% implantation rate). The authors concluded that MXC acts as an estrogen agonist in the uterus and oviduct but acts as an antiestrogen in the ovary. MXC also affects normal preimplantation embryonic development (Hall et al., 1997). Swartz and Vial (1996) have also reported that exposure to MXC early in pregnancy disrupts implantation.

Cummings and Perreault (1990) also reported that MXC administered by gavage to rats on days 1-3 of pregnancy (sperm positive = day 0) at 0, 100, 200, or 500 mg/kg/day resulted in accelerated embryo transport from the oviducts into the uterus on days 2 and 3 at 200 and 500 mg/kg/day. The top dose also reduced the total number of embryos recovered on the third day, 100 mg/kg/day also accelerated embryo transport, and 200 mg/kg/day reduced the number of total embryos recovered. This acceleration of embryonic transport appears to be the primary cause of MXC-induced preimplantation embryonic loss when exposure to MXC occurs after fertilization.

Gavage dosing of dams from gd 14 to pnd 7 (Chapin et al., 1996, 1997; Harris et al., 1996) to MXC at 0, 5, 50, and 150 mg/kg/day resulted in dose-dependent amounts of MXC and metabolites in milk and plasma of both dams and pups. Lactating mice were administered MXC by ip injection for 14 days (pnd 1-14) at 0, 1.0, 2.0, or 5.0 mg of technical grade MXC. At pnd 15, suckling female pups were necropsied. Stimulatory changes in the vagina and uterine horns indicated that MXC was excreted in milk and remained biologically active in the suckling mice. Higher MXC doses also caused "cellular atypia" in the uterine horns (Appel and Eroschenko, 1992).

Sexually mature CD-1 virgin female mice were administered technical grade MXC by oral gavage at 0, 1.25, 2.5, or 5.0 mg for five days/week for two or four weeks (Martinez and Swartz, 1991) or to just 50 mg for five days/week for four weeks (Martinez and Swartz, 1992). Twenty-four hours after the last dose, the females were necropsied. MXC caused dose-dependent, persistent vaginal estrus and reduced ovarian weights. Ovaries from females at 2.5 and 5.0 mg exhibited an increased number of atretic large follicles (Martinez and Swartz, 1991) and increased lipid accumulation in interstitial and thecal cells at 5.0 mg MXC (Martinez and Swartz, 1992). The authors concluded that MXC appeared to mimic estrogen-induced effects on the female reproductive system, and that the exposed ovarian cells appeared to be unable to synthesize and secrete steroids.

Mouse neonates were administered 14 daily ip injections of 0, 0.05, 0.1, 0.5, or 1.0 mg MXC. Exposure to 0.5 or 1.0 mg MXC increased reproductive tract weights three-fold due to excessive fluid accumulation, induced vaginal cornification, and accelerated vaginal opening by ten days (similar to 10 μg 17β-estradiol). The surface alterations in the vagina and uterus induced by MXC (cornified cells without complex surface microridges, uterine cells with dense microvilli

growth, atypical morphology and separation) were different than those induced by estradiol (Eroschenko, 1991).

Cummings and Laskey (1992, 1993) administered MXC to female rats at a range of doses during days 1-8 of pregnancy; the females were terminated on day 9. Ovaries were removed and incubated. Incubation medium and serum from the rats were analyzed for progesterone, estradiol, and testosterone *ex vivo*. *In vivo* MXC treatment reduced serum progesterone but had no effect on ovarian secretion of progesterone *in vitro*. Conversely, MXC had no effect on serum estradiol levels (testosterone was undetectable in serum) but induced a reduction in the rates of ovarian estradiol and testosterone secretion. Cummings and Gray (1989) have also shown that MXC blocks pregnancy in female rats in a dose- and time-dependent pattern. Exposure on gd 1-3 (preimplantation) resulted in decreased implantations and uterine weight, while exposures on gd 4-8 (peri-implantation) increased resorptions to 100%, decreased uterine weight, and reduced serum progesterone without altering the number of implantations, ovarian weight, or corpora lutea (effect levels for both dosing regimens were >200-500 mg/kg/day). However, Cummings and Gray (1987) reported that MXC affects the decidual cell response of the uterus but not other progestational parameters in the female rat.

Immature female rats were administered MXC (or other compounds) by oral gavage at 250 mg/kg 24 hours prior to evaluation of uterine peroxidase activity. MXC alone increased uterine peroxide activity by increasing RNA and protein synthesis, as did estradiol alone. Co-administration of progesterone or tamoxifen blocked this stimulation induced by both MXC and estradiol (Cummings and Metcalf, 1995a). The same authors exposed immature female rats to MXC (500 mg/kg) or estradiol (E2; 10 μg/rat), and uteri were evaluated for the presence of estrogen-induced protein (IP), also known as creatine kinase. Both MXC and E2 stimulated IP. The induction of IP by MXC was time- and dose-dependent. This induction by MXC or E2 was blocked by actinomycin D (which blocks DNA-dependent RNA synthesis) or cycloheximide (which inhibits pattern synthesis), indicating the induction requires RNA and protein synthesis. Progesterone did not block the induction of IP by either E2 or MXC. In fact, Cummings (1997) has proposed MXC as a model for environmental estrogens. Interestingly, MXC and E2 do not exhibit additivity or synergism in the reproductive tract of ovariectomized mice (Eroschenko et al., 2000).

Neonatal female mice received 14 days ip injections of 0, 0.05, 0.1, 0.5, or 1.0 mg (approximately 0, 7-35, 14-71, 68-357, or 135-714 mg/kg/day) of technical MXC. At three, six, and 12 months, vaginal smears were collected and ovaries were examined (E2 at 10.0 μg, ip, was used as the positive control). All MXC doses (and E2) increased the duration of vaginal cornification. MXC at 0.5 and 1.0 mg and E2 induced ovarian atrophy, relative ovarian weight depression, and depletion of corpora lutea. However, MXC doses of 0.05 or 0.1 mg produced opposite effects: ovaries remained heavy, large, and filled with corpora lutea. At all MXC doses, except 1.0 mg, follicular cysts were present. The authors concluded that the stimulatory effects of MXC at low doses and the inhibiting effects of MXC at high doses mimicked the effects of E2 at low and high doses and were probably due to alterations of the hypothalamic-hypophyseal

(anterior pituitary) function (Eroschenko et al., 1995). Prenatal exposure (gd 11-17) to low doses (0.01 or 10 mg/kg) of MXC in mice alters the uterine response to estrogen as adults (Howdeshell et al., 1999).

MXC also affects endometriosis in rats. Endometriosis was surgically induced in sixty female rats on pnd 0. On pnd 21, all rats were ovariectomized and the size of fully-developed endometriotic implants measured. Also starting on pnd 21, these rats were treated daily for three weeks with MXC, 250 mg/kg ± 2 mg/rat of progesterone (E2 at 1.0 μg/rat was also used). On day 42, the rats were terminated and the size of the endometriotic implants remeasured. Ovariectomy plus treatment altered the growth of endometrosis. Progesterone or vehicle produced full regression. Both E2 and MXC increased the size of the endometriotic implants; exposure to MXC or E2 + progesterone did not alter the growth (Cummings and Metcalf, 1995b).

Chapin et al. (1996, 1997; Harris et al., 1996; Johnson et al., 2000) dosed F0 maternal rats with MXC by gavage from gd 14 to pnd 7 (starting one week before and ending one week after parturition) at 0, 5, 50, or 150 mg/kg/day. F1 offspring were directly dosed at the same dose levels as their dams from pnd 7 to pnd 21 (weaning) or to pnd 42. In the female offspring, anogenital distance was unaffected, but vaginal opening was accelerated in all groups. Adult F1 female estrous cyclicity was disrupted at 50 and 150 mg/kg/day. Females in these groups also exhibited reduced rates of pregnancy and delivery. Uterine weights, corrected for pregnancy, were reduced in all treated pregnant females. All groups of treated females exhibited uterine dysplasia and less mammary gland alveolar development. Estrous levels of FSH were lower in all groups, and estrous progesterone levels were lower at 50 and 150 mg/kg/day, attributed to fewer corpora lutea secondary to ovulation defects. The author concluded that 5 mg/kg/day is not a NOEL or a NOAEL, and that effects on female puberty, ovarian weights, uterine weights, and female hormone data imply that the sites of MXC action are both central and peripheral.

Shimizu et al. (2000) evaluated MXC in teratogenicity studies in rats (Jcl:SD) and rabbits (Kbl:JW). Rats were dosed by gavage on gd 6 through 19 at 0, 1, 50, or 150 mg/kg/day, and rabbits were dosed by gavage on gd 6 through 27 at 0, 1, 15, or 45 mg/kg/day. At the two highest dose groups in both species, there was decreased maternal body weight gains and feed consumption during the dosing period. At 150 mg/kg/day in rats, gravid uterine weight was reduced, and resorptions and fetal deaths were increased, resulting in decreased number of live fetuses. Fetal body weights were reduced, but anogenital distance was unaffected at 150 mg/kg/day; there were no treatment-related fetal rat abnormalities at any dose. In rabbit fetuses, fetal body weights were reduced at 45 mg/kg/day. Rabbit fetuses in the mid and high dose groups exhibited increased incidences of 13th rib pairs and of 27 presacral vertebrae (both designated as fetal skeletal variations in the presence of maternal toxicity). Therefore, MXC was not teratogenic in either species but did result in *in utero* deaths at 150 mg/kg/day in rats.

It is clear that 150 mg/kg/day is too high, resulting in *in utero* deaths when administered to the dams starting on gd 6 (Shimizu et al., 2000) and as planned in this protocol, although it is well tolerated in dams and perinatal offspring when administered starting on pnd 14 (Chapin et al.,

1996, 1997; Harris et al., 1996; Johnson et al., 2000). Therefore, the top dose for this study will be 100 mg/kg/day, an effective dose (Gray et al., 1989). The low dose chosen for this study will be 25 mg/kg/day, which resulted in demonstrable effects by Gray et al. (1989). The mid dose chosen, 50 mg/kg/day, has also been shown to produce adverse effects in the offspring (Gray et al., 1989; Goldman et al., 1986; Anderson et al., 1994, 1995; Johnson et al., 2000).

3.3 Allocation and Treatment of F0 Maternal Animals

All sperm-positive F0 female rats (dams) will be assigned to treatment groups by a stratified randomization method designed to provide uniform mean body weights across dosage groups at the initiation of gestation (gd 0). Methoxychlor in vehicle (three dose levels) or the vehicle alone will be administered by gavage daily, once in the morning, from gd 6 through pnd 21 (day of birth designated pnd 0), at a 5 ml/kg dosing volume per time. If dams are in the process of delivery (usually on pnd 22±1) at the time of scheduled dosing, they will not be dosed at that time but on the next scheduled morning dosing time (with documentation in the study records). The volume of dosing formulation given to presumed pregnant and lactating females will be adjusted, based on each animal's most recent body weight or the current weight on a scheduled weighing day. The dosing formulations will be administered using a 16-gauge, two-inch curved dosing needle (Perfektum®, Popper and Sons, New Hyde Park, NY), fitted to a syringe of appropriate volume. The route of administration (gavage) was specified by the Sponsor.

3.4 F0 Dams and F1 Litters Prior to Weaning

3.4.1 F0 Maternal Gestation, Parturition, and Lactation

Clinical observations of F0 maternal animals will be documented at least once daily on gd 0-5 (prior to dosing period) and at least twice daily during the dosing period, at dosing, and one to two hours postdosing throughout the dosing period (gd 6 through pnd 21) until weaning of the F1 litters. The examining technicians will be unaware of the dosage levels (i.e., "blind for dose") of the test material. Observations will be made for (but not limited to):

a. Any response with respect to body position, activity, coordination, or gait
b. Any unusual behavior such as head flicking, compulsive biting or licking, circling, etc.
c. The presence of:
    1. Convulsions, tremors, or fasciculations
    2. Increased salivation
    3. Increased lacrimation or red-colored tears (chromodacryorrhea)
    4. Increased or decreased urination or defecation (including diarrhea)
    5. Piloerection
    6. Mydriasis or miosis (enlarged or constricted pupils)

7. Unusual respirations (fast, slow, labored, audible, gasping, or retching)
8. Vocalization

All F0 dams will be weighed in the morning on gd 0 and daily in the morning during the dosing period, gd 6 through pnd 21, for calculation of dosing volume. Daily maternal body weights will be reported. F0 maternal weight gains will be calculated for gd 0-6 (pretreatment), 6-9, 9-12, 12-15, 15-18, 18-20, pnd 0-4, 4-7, 7-14, 14-21, gd 0-20 (gestation period), gd 6-20, and pnd 0-21 (treatment period). If dams are in the process of delivery (usually on pnd 22±1), they will not be weighed at that time but weighed when delivery is complete (with documentation in the study records).

F0 maternal feed consumption will be evaluated in the morning for gd 0-6 (pretreatment), gd 6-9, 9-12, 12-15, 15-18, 18-20, pnd 0-4, 4-7, 7-14, 14-21, gd 0-20 (gestation period), gd 6-20, and pnd 0-21 (treatment period). Maternal feed consumption will be reported as g/animal/day and as g/kg body weight/day.

Beginning on gd 20, each female will be examined twice daily (a.m. and p.m.) for evidence of littering. Dosing will continue through parturition through pnd 21. If the dam is in the process of littering at the usual time of dosing, she will not be dosed at that time but will be dosed at the next scheduled morning dosing time. Signs of dystocia or other signs of difficulty at parturition will be recorded. Dams that have not produced a litter by calculated gd 26 will be necropsied. Nonpregnant uteri will be stained in 10% ammonium sulfide (Salewski, 1964) to determine pregnancy status. Any dams whose whole litters are born dead or die prior to pnd 21 will be sacrificed, the number of uterine implantation scars will be recorded, and a sample of mammary tissue (one abdominal mammary gland with nipple, surrounding skin, and underlying mammary tissue) and both ovaries and pituitary will be retained in buffered neutral 10% formalin for possible future examination.

3.4.2 Terminal Blood Collection and Final Disposition of F0 Females

F0 females which are moribund, abort, or deliver early (with offspring not viable outside the uterus) will be sacrificed by CO_2 asphyxiation, necropsied, and discarded. Intact fetuses (in utero, aborted, or delivered early) will be examined externally and viscerally (with focus on the reproductive system) and discarded. Any F0 dams whose litters are born dead or die prior to pnd 21 will be sacrificed and examined as described above.

On pnd 21 of each F1 litter, each F0 dam will be euthanized by CO_2 asphyxiation. Blood will be collected from the abdominal aorta for T4 and TSH determinations. F0 maternal carcasses will then be discarded.

3.4.3 F1 Progeny

3.4.3.1 Birth and Perinatal Observations

All pups will be counted, sexed, and examined externally as soon as possible on the day of birth (pnd 0) to determine the number of total, viable, and stillborn members of each litter. Each live pup will be weighed individually and anogenital distance measured at birth (pnd 0) by vernier calipers or microscopically with an eyepiece grid and platform micrometer. Grossly malformed pups will be sacrificed and examined externally and viscerally. Pups that are stillborn or die before pnd 4 will be examined externally and viscerally by Staples' technique (Staples, 1974), and any abnormal tissues or specimens will be retained in buffered neutral 10% formalin until the study report is finalized.

Pups will be examined daily and will be counted, weighed, sexed, and examined externally on pnd 0, 2, 4, 7, 10, 14, 17, and 21. Pups which die or are sacrificed moribund on pnd 5-21 will be necropsied; any abnormal tissues or specimens will be retained in buffered neutral 10% formalin until the study report is finalized. Survival indices will be calculated on pnd 0, 4, 7, and 14 and at weaning on pnd 21. The body weights and sexes of the F1 pups will be recorded on an individual basis, but the pups will not be uniquely identified at this stage (except if F1 males exhibit retained nipples; see below). All pups will be examined for physical abnormalities at birth and throughout the lactation and postwean period.

The presence (and number) or absence of retained nipples and areolae on the ventrum will be recorded for all F1 male and female offspring on pnd 11-13. Any males with one or more nipples or areolae will be uniquely marked within the litter (dye on tail) until weaning.

3.4.3.2 Standardization of Litter Sizes

On pnd 4, the size of each litter will be adjusted to nine pups (five females and four males), if possible. There will be a minimum of ten litters per dose group. Natural litters with ten or fewer pups will not be standardized. Natural litters which cannot be standardized to five females and four males will be discarded, if possible. Pups from larger litters will not be fostered to smaller litters, since the unit for statistical comparison is the litter; fostering will prevent litter-based analyses. A gross necropsy will be performed on all culled pups. The F0 dams will be allowed to rear their remaining F1 young to pnd 21.

3.5 Treatment and Evaluation of F1 Weanlings

All litters will be weaned on pnd 21.

3.5.1 Uterotrophic Cohort

On pnd 21, one female from each litter will be chosen for the uterotrophic cohort. Females will be dosed sc from pnd 22-24 and evaluated on pnd 24. Clinical observations of F1 females assigned to the uterotrophic cohort will be documented at least twice daily (at dosing and one to two hours postdosing) throughout the dosing period (pnd 22 through pnd 24). The examining technicians will be unaware of the test materials or dosage levels. Observations will be made for (but not limited to):

a. Any response with respect to body position, activity, coordination, or gait
b. Any unusual behavior such as head flicking, compulsive biting or licking, circling, etc.
c. The presence of:
    1. Convulsions, tremors, or fasciculations
    2. Increased salivation
    3. Increased lacrimation or red-colored tears (chromodacryorrhea)
    4. Increased or decreased urination or defecation (including diarrhea)
    5. Piloerection
    6. Mydriasis or miosis (enlarged or constricted pupils)
    7. Unusual respirations (fast, slow, labored, audible, gasping, or retching)
    8. Vocalization

Beginning on pnd 22, each F1 female will be dosed with the same dose level as her mother but via subcutaneous injection on pnd 22 through 24. Each animal will be weighed every other day prior to treatment and the body weight recorded. Each female will be examined daily for vaginal patency on pnd 21 through 24 (see Section 3.5.2). Treatments are administered sc daily using an 22-gauge needle and a 1 cc glass (disposable) tuberculin syringe for each treatment, from pnd 22 and continuing through pnd 24. The treatments will be administered on a mg/kg body weight basis, adjusted based on the most recent body weight, and the volume of the dose administered will be recorded each day. Dosing solutions/suspensions will be well mixed to keep the chemical in suspension prior to and throughout dosing.

Females will be necropsied six hours after the last dose on pnd 24. Body weight and paired ovary and uterus weight (wet) will be determined. Blood will collected from the abdominal aorta for determination of serum estradiol, T4, and TSH. The uterus will be evaluated histopathologically.

3.5.2 F1 Weanling Female Pubertal Cohort

The four remaining females from each litter will be divided into dosed (n=2) and nondosed (n=2) groups per litter on pnd 21. At this time, anogenital distance (AGD) will be measured and recorded with the individual pup weight using a Vernier calipers (precision to 0.1 mm). The test compound or vehicle will be administered via gavage from pnd 21-42, based on daily body weights. Clinical observations (see Section 3.5.6.1 above) of F1 females assigned to the pubertal cohort will be documented at least twice daily (at dosing and one to two hours postdosing) throughout the dosing period (pnd 21 through pnd 42). All F1 females will be weighed in the morning on pnd 21 and every other day in the morning during the dosing period on pnd 22 through pnd 42 for adjustment of dosing volume, based on the most recent body weight. F1 female weight gains will be calculated for pnd 21-22, 22-24, 24-26, 26-28, 28-30, 30-32, 32-34, 34-36, 36-38, 38-40, 40-42, and 21-42 (treatment period). F1 female body weights will also be recorded on the day of acquisition of vaginal patency.

Beginning on pnd 22, each F1 study female will be examined daily for vaginal patency. The appearance of a small "pin hole," a vaginal thread, as well as complete vaginal opening should all be recorded on the days they are observed. The day of complete vaginal patency is the endpoint used in the analysis for the age of vaginal opening. However, if a sufficient number of animals within any treatment group show persistent threads for greater than three days, a separate analysis should be conducted using the age at which the thread was first observed. Body weight at acquisition of complete vaginal patency will be recorded.

Beginning on the day of vaginal opening and continuing until pnd 42, daily vaginal smears will be obtained from each F1 female, stained with Toluidine Blue, and evaluated under low- and high-power light microscopy for the presence of leukocytes, nucleated epithelial cells, or cornified epithelial cells to determine the age at the first complete vaginal cycle and/or any effects on estrous cyclicity. This provides a means to determine the age of first estrus and/or the first vaginal cycle, and distinguishes pseudoprecocious puberty from true precocious puberty. The vaginal smears will be classified as diestrus (presence of leukocytes), proestrus (presence of nucleated epithelial cells), estrus (presence of cornified epithelial cells), or metestrus (presence of approximately equal numbers of leukocytes and large folded epithelial cells with translucent nuclei). Prolonged estrus shall be defined as exhibiting cornified cells with no leukocytes for three or more days; and prolonged diestrus as the presence of leukocytes for four or more days. On pnd 42, all F1 females will be shaved on the ventrum and examined for nipples/areolae at necropsy.

3.5.3 F1 Weanling Male Pubertal Cohort

The four males from each litter will be divided into dosed (n=2) and nondosed (n=2) groups per litter on pnd 21. At this time, AGD will be measured. AGD will be recorded with the individual pup weight using a Vernier calipers (precision to 0.1 mm). The test compound or vehicle will be administered via gavage from pnd 21 to pnd 70, based on daily body weights.

Clinical observations (see Section 3.5.1 above) of F1 males assigned to the pubertal cohort will be documented at least twice daily (at dosing and one to two hours postdosing) throughout the dosing period (pnd 21 through pnd 70). All F1 males will be weighed in the morning on pnd 21 and every day in the morning during the dosing period on pnd 22 through pnd 70 for adjustment of dosing volume, based on the most recent body weight. F1 male weight gains will be calculated for pnd 21-22, 22-24, 24-26, 26-28, 28-30, 30-32, 32-34, 34-36, 36-38, 38-40, 40-42, 42-44, 44-46, 46-48, 48-50, 50-52, 52-54, 54-56, 56-58, 58-60, 60-62, 62-64, 64-66, 66-68, 68-70, and 21-70 (treatment period). F1 male body weights will also be recorded on the day of acquisition of preputial separation (see below).

Beginning on pnd 23, each F1 study male will be examined daily for preputial separation. The appearance of partial and complete preputial separation or a persistent thread of tissue between the glans and prepuce should all be recorded if and when they occur. In addition, the body weight at complete preputial separation should be recorded. However, if a sufficient number of animals within any treatment group show persistent threads for greater than three days, a separate analysis should be conducted using the age at which the thread was first observed.

3.6 Necropsy of F1 Offspring

3.6.1 Terminal Blood Collection

At scheduled necropsy of the F1 females (on pnd 24 or 42) and males (on pnd 70), after terminal anesthesia (CO_2 asphyxiation), the animals will be weighed and the maximum amount of blood will be taken by external cardiac puncture and placed in a labeled tube. The blood will be allowed to clot and centrifuged under refrigeration at approximately 1400 x g for approximately ten minutes. The resulting serum will be frozen at approximately -20°C for subsequent analysis of E2 (uterotrophic cohort), thyroxine (T4), triiodothyronine (T3), and thyroid stimulating hormone (TSH) at RTI.

3.6.2 Gross Necropsy and Organ Weights

Once each F1 animal is bled (see Section 3.7.1), it will be necropsied and internal thoracic and abdominal organs and cavities examined. Any abnormalities will be documented.

At necropsy, F1 females assigned to the female pubertal cohort will be examined externally for the number of nipples, AGD, and urethral-vaginal distance (UVD). The following organs will be dissected out and weighed: liver, kidneys (paired), adrenal glands (paired), ovaries (paired), uterus (see below), pituitary, and fixed thyroid (with attached portion of trachea removed). For the uterine dissection, care must be taken to remove mesenteric fat from the uterine horns and not damage the uterus so that the uterine fluid is retained. The uterus and cervix will be separated from the vagina and the weight of the uterus with fluid recorded. The uterus will then be placed on a paper towel, slit to allow the fluid contents to leak out, gently blotted dry, and reweighed. All organs will be weighed to the nearest 0.1 mg. Adrenal glands will be

weighed immediately (to minimize drying out of tissues). The thyroid and ovaries will be processed for microscopic evaluation. The adrenals will be weighed immediately to prevent drying out prior to weighing.

At scheduled necropsy, on approximately pnd 70, F1 males will be shaved on the ventrum and examined externally for retained nipples. The thoracic and abdominal organs and cavities will be examined and any abnormalities documented. The following organs will be dissected out and weighed: paired testes, epididymides (whole left and right separately), prostate (intact and separated into ventral and dorsolateral lobes), seminal vesicles with coagulating glands (and fluid), Cowper's glands, glans penis, levator ani plus bulbcavernosus muscle complex, liver, adrenal glands (paired), kidneys (paired), pituitary, and fixed thyroid (with attached portion of trachea removed). All organs will be weighed to the nearest 0.1 mg. During necropsy, care must be taken to remove mesenteric fat with small surgical iris scissors from these tissues such that the fluid in the sex accessory glands is retained. Small tissues such as the adrenals, as well as tissues that contain fluid, will be weighed immediately to prevent partial drying prior to weighing.

At the time of sacrifice, one testis from each F1 male will be frozen at approximately -20°C for subsequent enumeration of testicular homogenization-resistant spermatid heads from high dose and control males. In addition, one cauda epididymis from each F1 male will be immediately removed, weighed, and seminal fluid from the cauda will be assessed for sperm number. Sperm number will be assessed using an HTM-IVOS (Version 10.8 S) automated sperm analysis system (Hamilton-Thorne Research, Beverly, MA).

3.6.3 Histology and Pathology

For F1 females, the pituitary, ovaries, uterus, and thyroid with attached portion of trachea will be dissected out, the ovaries, uterus, and pituitary weighed, and the tissues placed in Bouin's fixative for 24 hours, after which they will be rinsed and stored in 70% alcohol. Once the tissues are fixed, the trachea will be carefully removed from the fixed thyroid (to retain glandular integrity) and weighed. The tissues will then be embedded in paraffin, sectioned at 3-5 microns, and stained with hematoxylin and eosin (H and E) for subsequent histological evaluations. Optional tissues for histopathology include the vagina, liver, paired kidneys, and paired adrenal glands (if warranted), which will be processed as above. Stained sections will be evaluated by a Board Certified veterinary pathologist for pathologic abnormalities and potential treatment-related effects. Thyroids should be evaluated for morphologic changes, such as altered follicular epithelial height, the relative number and staining characteristics of colloid, the extent of thyroid vascular supply, and the density, size, and shape of the thyroid follicles. Ovarian histology should include an evaluation of corpus luteum development and the presence of atretic follicles.

For F1 males, one testis, one epididymis, the pituitary, and the thyroid with attached portion of trachea will be dissected out, the testis, epididymis, and pituitary weighed, and the tissues placed in Bouin's fixative for 24 hours, after which they will be rinsed and stored in 70% alcohol (with the trachea removed from the thyroid, and the thyroid weighed; see above) until

embedded in paraffin. They will then be sectioned at 3-5 microns and stained with hematoxylin and eosin (H and E) for subsequent histological evaluations. The other testis will be weighed and frozen for subsequent analysis (see below). The other epididymis will also be weighed and used for sperm counts (see below). Optional tissues for histopathology include the liver, paired kidneys, and adrenal glands (paired), as indicated by altered organ weight (change of "significant magnitude"), which will be processed as above. Stained sections will be evaluated by a Board Certified veterinary pathologist for pathologic abnormalities and potential treatment-related effects. Thyroids should be evaluated for morphologic changes, such as altered follicular epithelial height, the relative number and staining characteristics of colloid, the extent of thyroid vascular supply, and the density, size, and shape of the thyroid follicles. The other testis per male will be frozen for subsequent evaluation. The one testis and epididymis per male (fixed) will be evaluated for spermatogenesis, spermiogenesis, status of seminiferous tubules in the testis, and sperm in the epididymis, as well as the structural integrity of these organs. The whole, unfixed epididymis per male will be used for evaluation of sperm count. The one frozen testis per male will be used to enumerate homogenization-resistant spermatid heads for calculation of daily sperm production (DSP) and efficiency of DSP (Robb et al., 1978; Sharpe et al., 1995).

4.0 STATISTICAL ANALYSES

The unit of comparison will be the pregnant female, the litter, or the retained F1 offspring, as appropriate. Treatment groups will be compared to the concurrent control group using either parametric ANOVA under the standard assumptions or robust regression method (Zeger and Liang, 1986; Royall, 1986; Huber, 1967), which does not assume homogeneity of variance or normality. The homogeneity of variance assumption will be examined via Levene's test (Levene, 1960), which is more robust to the underlying distribution of the data than the traditional Bartlett's test. If Levene's test indicates lack of homogeneity of variance ($p<0.05$), robust regression methods will be used to test all treatment effects. The robust regression methods use variance estimators that make no assumptions regarding homogeneity of variance or normality of the data. They will be used to test for overall treatment group differences, followed by individual tests for exposed vs. control group comparisons (via Wald Chi-square tests), if the overall treatment effect is significant. The presence of linear trends will be analyzed by GLM procedures in SAS® Release 8 for homogenous data or by robust regression methods for nonhomogenous data (SAS Institute Inc., 1999a, b, c, d, e, 2000). Standard ANOVA methods, as well as Levene's test, are available in the GLM procedure of SAS® Release 8, and the robust regression methods are available in the REGRESS procedure of SUDAAN® Release 8.0 (RTI, 2001).

If Levene's test does not reject the hypothesis of homogeneous variances, standard ANOVA techniques will be applied for comparing the treatment groups. The GLM procedure in SAS® 8.0 will be used to evaluate the overall effect of treatment and, when a significant treatment effect is present, to compare each exposed group to control via Dunnett's Test (Dunnett, 1955, 1964). For the litter-derived percentage data (e.g., periodic pup survival indices), the ANOVA will be weighted according to litter size. A one-tailed test (i.e., Dunnett's test) will be

used for all pairwise comparisons to the vehicle control group, except that a two-tailed test will be used for parental and pup body weight and organ weight parameters, feed consumption, percent males per litter, and anogenital distance.

Frequency data such as offspring survival indices will not be transformed. All indices will be analyzed by the chi-square test for independence for differences among treatment groups (Snedecor and Cochran, 1967) and by the Cochran-Armitage test for linear trend on proportions (Cochran, 1954; Armitage, 1955; Agresti et al., 1990). When chi-square reveals significant ($p<0.05$) differences among groups, then a Fisher's exact probability test, with appropriate adjustments for multiple comparisons, will be used for pairwise comparisons between each treatment group and the control group. Acquisition of developmental landmarks (e.g., vaginal patency and preputial separation), as well as anogenital distance, will also be analyzed by analysis of covariance (ANCOVA; in addition to ANOVA analysis) using body weight at acquisition and at a fixed postnatal age in days, or at measurement as the covariate. For correlated data (e.g., body and organ weights at necropsy, with more than one pup/sex/litter), SUDAAN® software (RTI, 2001) will be used for analysis of overall significance, presence of trend, and pairwise comparisons to the control group values. Organ weights will be analyzed by Analysis of Covariance (ANCOVA) using the initial (assignment to group) body weight and body weight at necropsy as the covariate, when there is a significant effect on body weight. When statistically significant effects are observed, treatment means will be examined further using LSMeans.

A test for statistical outliers (SAS® Release 8) will be performed on F0 maternal body weights, feed consumption (in g/day), and retained F1 male or female body and organ weights. If examination of pertinent study data do not provide a plausible biologically sound reason for inclusion of the data flagged as "outlier," the data will be excluded from summarization and analysis and will be designated as outliers. If feed consumption data for a given animal for a given observational interval (e.g., pnd 0-7 or 7-14 during the lactational exposure period) are designated outliers or unrealistic, then summarized data for this animal encompassing this period (e.g., pnd 0-21 for the lactational exposure period) also will not include this value. For all statistical tests, $p \leq 0.05$ (one- or two-tailed) will be used as the criterion for significance.

5.0 RETENTION OF SPECIMENS AND RECORDS

All specimens and records which remain the responsibility of RTI will be retained in the RTI archives for two years at the performing laboratory's expense. Beyond two years, continued retention will be at additional cost to the Sponsor.

6.0 QUALITY CONTROL/QUALITY ASSURANCE PROCEDURES

Quality control (QC) and quality assurance (QA) procedures will follow those outlined in the Quality Assurance Project Plan (QAPP) prepared for this study.

7.0 REPORTING

An executive summary will be prepared describing the number and strain of rats used in the study, the doses and chemical tested, and the effects with levels of statistical significance for all endpoints. Electronic and hard copies of spreadsheets containing the raw data from all animals will be provided for each endpoint. In addition, the spreadsheet should include treatment means, standard deviation, standard error, coefficient of variation, and sample number below each endpoint. Data presented for F1 females should include animal number and treatment, block and day of necropsy (if study conducted in blocks or if females killed on pnd 42 and 43), age and weight at vaginal opening, ovarian, uterine (with and without fluid), kidneys, adrenals, liver, pituitary, thyroid, body weights at weaning and scheduled necropsy, body weight change from pnd 22 to necropsy, and serum E2 (uterotrophic cohort), T3, T4, and TSH. Data presented for F1 males should include animal number and treatment, block and day of necropsy (if study conducted in blocks or if males killed on pnd 70 and 71), age and weight at preputial separation, liver, adrenal glands, kidneys, pituitary, thyroid, male reproductive and accessory sex organ weights (see Section 3.6.2), covaried by body weights at weaning (if appropriate) and scheduled necropsy, body weight change from weaning (pnd 21) to necropsy, and serum T3, T4, and TSH. Data summary tables containing the mean, standard deviation, standard error, coefficient of variation, and sample size for each treatment group will be provided for all endpoints. Organ weights will be presented as absolute and as relative to weaning and terminal body weight, and after covariance adjustment for weaning and necropsy body weight. Summaries of any histopathologic findings with photomicrographs of significant observations will also be provided.

8.0 PERSONNEL

Study Director:	Julia D. George, Ph.D.
Project Toxicologist:	Rochelle W. Tyl, Ph.D., DABT
ARF Veterinarian:	Donald B. Feldman, D.V.M., ACLAM
ARF Manager:	Frank N. Ali, M.B.A., RLATG, ILAM
Laboratory Supervisor:	Melissa C. Marr, B.A., RLATG
Data Analyst and Reproductive Toxicity Supervisor:	Christina B. Myers, M.S.
Statistical Advisor:	Gayle. S. Bieler, M.S.

Research Data Entry Assistant:	Timothy W. Wiley, B.S.
Research Biologist:	William R. Ross, B.A.
Biologists:	Vickie I. Wilson Lawson B. Pelletier, RVMT, LAT
Biological Laboratory Assistants:	Marian C. Rieth, RVMT Robin T. Krebs, LAT Melody P. Gower Malcolm D. Crews, LAT
Endocrinology/Andrology:	Patricia A. Fail, Ph.D. Carol S. Sloan, M.S. Kristi D. Vick, B.S. Timothy W. Wiley, B.S.
Quality Assurance:	Doris J. Smith, B.S., Manager Celia D. Keller, M.S. Patricia D. Hall Marcia D. Phillips, M.S. D. Denise Rowe, M.L.S. Tiffany M. Kennedy, B.S. Jennifer E. Jones, B.S. Erica D. Shinauld, B.S.
Histology:	Tsai-Ying Chang, B.S. HT-ASCP
Pathology:	John C. Seely, D.V.M., ACVP (EPL, Inc.)

Additional study team members to be determined.

9.0 STUDY RECORDS TO BE MAINTAINED

Protocol and any Amendments
List of any Protocol Deviations
List of Standard Operating Procedures
Animal Requisition and Receipt Records
Quarantine Records
Temperature and Humidity Records for the Animal Room(s)
Animal Research Facility Room Log(s)
Durham City Water Analysis (analyzed monthly, reported annually)
Feed Type, Source, Lot Number, Dates Used, Certification, Analytical Results
Dosage Code Records Containing Five-Digit Rx Code, Color Code, and Concentration
F0 Mating Records
F0 Maternal Gestational and Lactational Records
F0 Terminal Blood Collection and Final Disposition
Dose Formulation Receipt and Use Records
F1 Distribution into Groups
F1 Dosing Forms

F1 Postwean Dosing Period:	Body Weights Clinical Signs Acquisition of Vaginal Patency Acquisition of Preputial Separation Estrous Cyclicity
F1 Necropsy Records:	Body weight, organ weights, gross observations, required (and optional, if done) organ histopathology

Statistical Analysis Records
Histopathology Report
Serum Estradiol Analysis (E2)
Serum Thyroid Hormone Analyses (T3, T4, TSH)
Correspondence

10.0 REFERENCES

Agresti, A., C.R. Mehta, and N.R. Patel (1990). Exact inference for contingency tables with ordered categories. *J. Amer. Statist. Assoc.* **85**, 453-458.

Anderson, S.A., P.A. Fail, B.J. McTaggart, R.W. Tyl, and L.E. Gray, Jr. (1994). Reproductive toxicity of methoxychlor (M) in corn oil to male and female Long-Evans hooded rats using the alternative reproduction test protocol (ART). *Biol. Reprod.* **50 (Suppl. 1),** 101.

Anderson, S.A., S.W. Pearce, P.A. Fail, B.J. McTaggart, R.W. Tyl, and L.E. Gray, Jr. (1995). Validation of the alternative reproductive test protocol (ART) to assess toxicity of methoxychlor in rats. *The Toxicologist* **15(1),** 164.

Aoyama, H., R.E. Chapin, K. Ebino, and S. Teramoto (2000). Endocrine disrupting effects of organochlorine pesticides and their reproductive and developmental toxicity. *Teratology* **62(3),** 7A-8A (Abstract No. SIII-3).

Appel, R.J., and V.P. Eroschenko (1992). Passage of methoxychlor in mice and reproductive organs of nursing female mice. 1. Light and scanning electron microscopic observations. *Reprod. Toxicol.* **6(3),** 223-231.

Armitage, P. (1955). Test for linear trends in proportions and frequencies. *Biometrics* **11**, 375-386.

Bal, H.S. (1984). Effect of methoxychlor on reproductive systems of the rat. *Proc. Soc. Exp. Biol. Med.* **176(2),** 187-196.

Chapin, R.E., M.W. Harris, M.D. Shelby, R.J. Smialowicz, V.C. Moser, S. Padilla, R.C. MacPhail, S. Berone, A.C. Lockhart, and M.A. Mauney (1996). The effects of perinatal/juvenile pesticide exposure on adult CNS, immune, and reproductive function in rats. *The Toxicologist* **30(Part 2),** 52.

Chapin, R.E., M.W. Harris, B.J. Davis, S.M. Ward, R.E. Wilson, M.A. Mauney, A.C. Lockhart, R.J. Smialowicz, V.C. Moser, L.T. Burka, and B.J. Collins (1997). The effects of perinatal/juvenile methoxychlor exposure on adult rat nervous, immune and reproductive system function. *Fundam. Appl. Toxicol.* **40(1),** 138-157.

Charles River (1988). *Embryo and Fetal Developmental Toxicity (Teratology) Control Data in the Charles River Crl:CD® BR Rat.* Charles River Laboratories, Inc., Wilmington, MA.

Cochran, W. (1954). Some methods for strengthening the common $\chi 2$ tests. *Biometrics* **10**, 417-451.

Cummings, A.M. (1997). Methoxychlor as a model for environmental estrogens. *Crit. Rev. Toxicol.* **27(4),** 367-379.

Cummings, A.M., and Gray, L.E. Jr. (1987). Methoxychlor affects the decidual cell response of the uterus but not other progestational parameters in female rats. *Toxicol. Appl. Pharmacol.* **90(2),** 330-336.

Cummings, A.M., and Gray, L.E. Jr. (1989). Antifertility effect of methoxychlor in female rats: dose- and time-dependent blockage of pregnancy. *Toxicol. Appl. Pharmacol.* **97,** 454-462.

Cummings, A.M., and J. Laskey (1992). Methoxychlor administration during early pregnancy alters ovarian steroidogenesis. *The Toxicologist* **12(1),** 432.

Cummings, A.M., and J. Laskey (1993). Effect of methoxychlor on ovarian steroidogenesis: role in early pregnancy loss. *Reprod. Toxicol.* **7(1),** 17-23.

Cummings, A.M., and J.L. Metcalf (1995a). Methoxychlor regulates rat uterine estrogen-induced protein. *Toxicol. Appl. Pharmacol.* **130(1),** 154-160.

Cummings, A.M., and J.L. Metcalf (1995b). Effects of estrogen, progesterone, and methoxychlor on surgically induced endometriosis in rats. *Fundam. Appl. Toxicol.* **27(2),** 287-290.

Cummings, A.M., and S.D. Perreault (1990). Methoxychlor accelerates embryo transport through the rat reproductive tract. *Toxicol. Appl. Pharmacol.* **102(1),** 110-116.

Cupp, A.S., and M.K. Skinner (2000). Effect of the endocrine disruptor methoxychlor and its metabolite HPTE on morphology and growth of the developing testis. *Biol. Reprod.* **62(Suppl. 1),** 286.

Cupp, A.S., and M.K. Skinner (2001). Actions of the endocrine disruptor methoxychlor and its estrogenic metabolite on in vitro embryonic rat seminiferous cord formation and perinatal testis growth. *Reprod. Toxicol.* **15(3),** 317-326.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50,** 1096-1121.

Dunnett, C.W. (1964). New tables for multiple comparisons with a control. *Biometrics* **20**, 482-491.

Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) (1998) Final Report, Volume I.

Eroschenko, V.P. (1991). Ultrastructure of vagina and uterus in young mice after methoxychlor exposure. *Reprod. Toxicol.* **5(5),** 427-435.

Eroschenko, V.P., A.A. Abuel-Atta, and M.S. Grober (1995). Neonatal exposures to technical methoxychlor alters ovaries in adult mice. *Reprod. Toxicol.* **9(4),** 379-387.

Eroschenko, V.P., T.J. Johnson, and A.W. Rourke (2000). Estradiol and pesticide methoxychlor do not exhibit additivity or synergism in the reproductive tract of adult ovariectomized mice. *J. Toxicol. Environ. Health* **60(6),** 407-421.

Eroschenko, V.P., A.W. Rourke, and W.F. Sims (1996). Estradiol or methoxychlor stimulates estrogen receptor (ER) expression in uteri. *Reprod. Toxicol.* **10(4),** 265-271.

Eroschenko, V.P., W.J. Swartz, and L.C. Ford (1997). Decreased superovulation in adult mice following neonatal exposures to technical methoxychlor. *Reprod. Toxicol.* **11(6),** 807-814.

Goldman, J.M., R.L. Cooper, G.L. Rehnberg, J.F. Hein, W.K. McElroy, and L.E. Gray, Jr. (1986). Effects of low subchronic doses of methoxychlor on the rat hypothalamic-pituitary reproductive axis. *Toxicol. Appl. Pharmacol.* **86(3),** 474-483.

Gray, L.E. Jr., J.S. Ostby, J.M. Ferrell, E.R. Sigmon, and J.M. Goldman (1988). Methoxychlor induces estrogen-like alterations of behavior and the reproductive tract in the female rat and hamster: effects on sex behavior, running wheel activity, and uterine morphology. *Toxicol. Appl. Pharmacol.* **96(3),** 525-540.

Gray, L.E. Jr., J. Ostby, J. Ferrell, G. Rehnberg, R. Linder, R. Cooper, J. Goldman, V. Slott, and J. Laskey (1989). A dose-response analysis of methoxychlor-induced alterations of reproductive development and function in the rat. *Fundam. Appl. Toxicol.* **12,** 92-108.

Gray, L.E. Jr., J. Ostby, R.L. Cooper, and W.R. Kelce (1999). The estrogenic and antiandrogenic pesticide methoxychlor alters the reproductive tract and behavior without affecting pituitary size or LH and prolactin secretion in male rats. *Toxicol. Ind. Health* **15(1-2),** 37-47.

Hafez, E.S.E. (Ed.) (1970). *Reproduction and Breeding Techniques for Laboratory Animals.* Lea and Febiger, Philadelphia, PA.

Hall, D.L., L.A. Payne, J.M. Putnam, and Y.M. Huet-Hudson (1997). Effect of methoxychlor on implantation and embryo development in the mouse. *Reprod. Toxicol.* **11(5),** 703-708.

Harris, M.W., R.E. Chapin, E.A. Haskins, J.D. Allen, B.J. Collins, B.J. Davis, A.C. Lockhart, and M. Mauney (1996). The effects of perinatal/juvenile pesticide exposure on adult reproductive function. I. Methoxychlor. *The Toxicologist* **30(1 Part 2),** 144.

Howdeshell, K.L., L.C. Alworth, R. Ruhlen, and F.S. vom Saal (1999). Prenatal exposure to diethylstilbestrol and methoxychlor alters uterine response to estrogen in adult mice. *Amer. Zool.* **39(5),** 25A.

Huber, P.J. (1967). The behavior of maximum likelihood estimates under nonstandard conditions. In: *Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability* **1,** 221-233.

Johnson, L., R.E. Chapin, M.W. Harris, R.L. Silge, A.C. Guidry, and W.R. Lee (2000). Perinatal/juvenile exposure to methoxychlor reduces Sertoli cell numbers in adult rats. *The Toxicologist* **54(1),** 364.

Levene, H. (1960). Robust tests for the equality of variance. In: *Contributions to Probability and Statistics* (I. Olkin, S.G. Ghurye, W. Hoeffding, W.G. Madow, and H.B. Mann, Eds.), Palo Alto, CA, Stanford University Press, pp. 278-292.

Maness, S.C., D.P. McDonnell, and K.W. Gaido (1998). Inhibition of androgen receptor-dependent transcriptional activity by DDT isomers and methoxychlor in HepG2 human hepatoma cells. *Toxicol. Appl. Pharmacol.* **151(1),** 135-142.

Martinez, E.M., and W.J. Swartz (1991). Effects of methoxychlor on the reproductive system of the adult female mouse. 1. Gross and histologic observations. *Reprod. Toxicol.* **5(2),** 139-147.

Martinez, E.M., and W. J. Swartz (1992). Effects of methoxychlor on the reproductive system of the adult female mouse. 2. Ultrastructural observations. *Reprod. Toxicol.* **6(1),** 93-98.

NRC (1996). *Guide for the Care and Use of Laboratory Animals.* Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council. Revised 1996.

Respess, D.S. Jr., R.L. Carr, N.M. Cox, C.P. McCoy, A.B. Moore, and J.E. Chambers (1999). Evaluation of the reproductive parameters in rats affected by the interactions of polychlorinated biphenyls and methoxychlor resulting from exposure during development. *The Toxicologist* **48(1),** 374-375.

Robb, G.W., R.P. Amann, and G.H. Killian (1978). Daily sperm production and epididymal sperm reserves of pubertal and adult rats. *J. Reprod. Fertil.* **54,** 103-107.

Royall, R.M. (1986). Model robust confidence intervals using maximum likelihood estimators. *International Statistical Review* **54**, 221-226.

RTI (2001). **SUDAAN User's Manual, Release 8.0.** Research Triangle Park, NC: Research Triangle Institute.

Salewski, E. (1964). Farbemethode zum makroskopischen Nachweis von Implantationsstellen am Uterus der Ratte. *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.* **247,** 367.

Sar, M., R. Sriperumbudlar, B. McIntyre, E. Bartolucci, and L. You (2001). Effects of dietary exposure to genistein and methoxychlor on mammary gland development in juvenile rats. *The Toxicologist* **60(1),** 295.

SAS Institute Inc. (1999a). *SAS® Language Reference: Concepts*, Version 8, Cary, NC: SAS Institute Inc. 554 pp.

SAS Institute Inc. (1999b). *SAS/STAT® Users' Guide*, Version 8, Cary, NC: SAS Institute Inc. 3884 pp.

SAS Institute Inc. (1999c). *SAS® Language Reference: Dictionary*, Version 8, Cary, NC: SAS Institute Inc. 1244 pp.

SAS Institute Inc. (1999d). *SAS® Procedures Guide*, Version 8, Cary, NC: SAS Institute Inc. 1643 pp.

SAS Institute Inc. (1999e). *SAS® Companion for the Microsoft Windows Environment*, Version 8, Cary, NC: SAS Institute Inc. 562 pp.

SAS Institute Inc. (2000). *SAS/STAT® Software: Changes and Enhancements, Release 8.1*, Cary, NC: SAS Institute Inc. 554 pp.

Sharpe, R.M., J.S. Fisher, M.M. Millar, S. Jobling, and J.P. Sumpter (1995). Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. *Env. Health Perspect.* **103,** 1136-1143.

Shimizu, N., K. Hayashi, H. Kawa-Katsu, K. Mezawa, T. Iida, Y. Kubo, H. Kushida, M. Kikuta, K. Takahashi, H. Hojo, H. Aoyama, and S. Teramato (2000). Teratogenicity studies in rats and rabbits with methoxychlor (MXC). *Teratology* **62(3),** 45A (Abstract No. P-116).

Snedecor , G.W., and W.G. Cochran (1967). *Statistical Methods.* Sixth Edition, Iowa State University Press, Ames, IA.

Staples, R.E. (1974). Detection of visceral alterations in mammalian fetuses. *Teratology* **9,** 7.

Stoker, T.E., C.L. Robinette, and R.L. Cooper (1999). Perinatal exposure to estrogenic compounds and the subsequent effects on the prostate of the adult rat: evaluation of inflammation in the ventral and lateral lobes. *Reprod. Toxicol.* **13(6),** 463-472.

Swartz, W.J., and V.P. Eroschenko (1998). Neonatal exposure to technical methoxychlor alters pregnancy outcome in female mice. *Reprod. Toxicol.* **12(6),** 565-573.

Swartz, W.J., and L.J. Vial, Jr. (1996). Exposure to methoxychlor early in pregnancy disrupts implantation. *FASEB J.* **10(3),** A260.

Waters, K.M., S. Safe, K.S. Korach, and K.W. Gaido (2000). Investigating the mechanism of methoxychlor toxicity through estrogen receptors alpha and beta using cDNA array technology. *The Toxicologist* **54(1),** 239.

Welshons, W.V., S.C. Nagel, K.A. Thayer, B.M. Judy, and F.S. vom Saal (1999). Low-dose bioactivity of xenoestrogens in animals: fetal exposure to low doses of methoxychlor and other xenoestrogens increases adult prostate size in mice. *Toxicol. Ind. Health* **15(1-2),** 12-25.

White, K.L. Jr., J.A. McCay, D.L. Musgrove, D.R. Germolec, R.R. Newbold, K.B. Delclos, and T.L. Guo (2001). Enhanced CD3-mediated splenocyte proliferation in F0 and F1 generations of SD rats following exposure to endocrine disruptors: ethinyl estradiol, nonylphenol, genistein, vinclozolin, and methoxychlor. *The Toxicologist* **60(1),** 29.

Zeger, S. and K. Liang (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* **42,** 121-130.

ATTACHMENT

Material Safety Data Sheet (MSDS): Methoxychlor

CHEM SERVICE -- F910 METHOXYCHLOR
MATERIAL SAFETY DATA SHEET
NSN: 655000F051063
Manufacturer's CAGE: 8Y898
Part No. Indicator: A
Part Number/Trade Name: F910 METHOXYCHLOR

General Information

Company's Name: CHEM SERVICE INC
Company's Street: 660 TOWER LN
Company's P. O. Box: 3108
Company's City: WEST CHESTER
Company's State: PA
Company's Country: US
Company's Zip Code: 19381-3108
Company's Emerg Ph #: 215-386-2100/215-692-3026
Company's Info Ph #: 215-692-3026/800-452-9994
Record No. For Safety Entry: 001
Tot Safety Entries This Stk#: 001
Status: SE
Date MSDS Prepared: 25JAN95
Safety Data Review Date: 19SEP96
Preparer's Company: CHEM SERVICE INC
Preparer's St Or P. O. Box: 660 TOWER LN
Preparer's City: WEST CHESTER
Preparer's State: PA
Preparer's Zip Code: 19381-3108
MSDS Serial Number: CCDMW

Ingredients/Identity Information

Proprietary: NO
Ingredient: METHOXYCHLOR (IARC CARCINOGEN - GROUP 3) *96-3*
Ingredient Sequence Number: 01
NIOSH (RTECS) Number: KJ3675000
CAS Number: 72-43-5
OSHA PEL: 15 MG/CUM
ACGIH TLV: 10 MG/CUM

Physical/Chemical Characteristics

Appearance And Odor: COLORLESS CRYSTALLINE SOLID W/FRUITY/PLEASANT ODOR
Melting Point: 186.8-192F
Solubility In Water: INSOLUBLE

Fire and Explosion Hazard Data

Extinguishing Media: CO2, DRY CHEMICAL POWDER/SPRAY

Reactivity Data

Stability: YES
Materials To Avoid: STRONG OXIDIZING AGENTS
Hazardous Poly Occur: NO

Health Hazard Data

LD50-LC50 Mixture: ORAL LD50(RAT): 6000 MG/KG
Route Of Entry - Inhalation: YES
Route Of Entry - Skin: YES
Route Of Entry - Ingestion: YES
Health Haz Acute And Chronic: SKIN/EYES: CAN CAUSE IRRITATION. CAN BE IRRITATING TO MUCOUS MEMBRANES. MAY BE HARMFUL IF ABSORBED THROUGH THE SKIN, INHALED/IF SWALLOWED. EXPOSURE CAN CAUSE KIDNEY/LIVER DAMAGE.
Carcinogenicity - NTP: NO
Carcinogenicity - IARC: NO
Carcinogenicity - OSHA: NO
Explanation Carcinogenicity: NONE
Signs/Symptoms Of Overexp: IRRITATION
IF NO BURNS HAVE OCCURRED, CLEANSE W/SOAP & WATER. INHALATION: REMOVE TO FRESH AIR. GIVE OXYGEN/CPR IF NEEDED. IF IN SHOCK, KEEP WARM/QUIET. INGESTION: INDUCE VOMITING. DON'T GIVE LIQUIDS/INDUCE VOMITING IF UNCONSCIOUS/CONVULSING. IF VOMITING, WATCH CLOSELY TO MAKE SURE AIRWAY DOESN'T BECOME OBSTRUCTED BY VOMIT. OBTAIN MEDICAL ATTENTION IN ALL CASES.

Precautions for Safe Handling and Use

Steps If Matl Released/Spill: EVACUATE AREA. WEAR OSHA REGULATED EQUIPMENT. VENTILATE AREA. SWEEP UP & PLACE IN AN APPROPRIATE CONTAINER. HOLD FOR DISPOSAL. WASH CONTAMINATED SURFACES TO REMOVE ANY RESIDUES.
Waste Disposal Method: BURN IN A CHEMICALS INCINERATOR EQUIPPED W/AN AFTERBURNER & SCRUBBER/DISPOSE OF IN ACCORDANCE W/LOCAL, STATE & FEDERAL REGULATIONS.
Precautions-Handling/Storing: KEEP TIGHTLY CLOSED. STORE IN A COOL, DRY PLACE. STORE ONLY W/COMPATIBLE CHEMICALS. THIS PRODUCT IS FURNISHED FOR LABORATORY USE ONLY.
Other Precautions: AVOID CONTACT W/SKIN, EYES & CLOTHING. DON'T BREATHE VAPORS. PRODUCT MAY NOT BE USED AS DRUGS, COSMETICS, AGRICULTURAL/ PESTICIDAL PRODUCTS, FOOD ADDITIVES/AS HOUSEHOLD CHEMICALS.

Control Measures

Respiratory Protection: USE APPROPRIATE OSHA/MSHA APPROVED SAFETY EQUIPMENT.
Ventilation: THIS CHEMICAL SHOULD BE HANDLED ONLY IN A HOOD.

Eye Protection: EYE SHIELDS
Work Hygienic Practices: REMOVE/LAUNDER CONTAMINATED CLOTHING BEFORE REUSE. CONTACT LENSES SHOULDN'T BE WORN IN THE LABORATORY.
Suppl. Safety & Health Data: PERSONS NOT SPECIFICALLY/PROPERLY TRAINED SHOULDN'T HANDLE THIS CHEMICAL/ITS CONTAINER. ALL CHEMICALS SHOULD BE CONSIDERED HAZARDOUS-AVOID DIRECT PHYSICAL CONTACT. DATA INFORMATION IS FOR ACETONE.

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Transportation Data

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Disposal Data

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Label Data

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APPENDIX III

CHEMISTRY REPORT

Battelle
Putting Technology To Work

Chemical Repository Services for the EDSP
EPA Contract No. 68-W-01-023

Chemistry Report for WA 2-23
Methoxychlor in Mazola Corn Oil

November 17, 2005

Prepared By:

Eric A. Crecelius, Ph.D.
Chemical Repository Manager

11/17/05
Date

Approved By:

Richard M. Ecker
Director, Marine Sciences Laboratory

11/17/05
Date

Battelle Marine Sciences Laboratory
1529 West Sequim Bay Road
Sequim, WA 98382

Submitted to:

Dr. Julia George

Center for Life Sciences and Toxicology
Research Triangle Institute

PO Box 12194

Research Triangle Park, NC 27709

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Chemistry Report for WA 2-23
Methoxychlor in Mazola Corn Oil

Reviewed by: RM Baker for

Deborah Coffey, Quality Assurance Officer

Battelle Marine Sciences Laboratory

Date: 11/17/05

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Chemistry Report for WA 2-23
Methoxychlor in Mazola Corn Oil

Parameter	Chemical
Compound Name	Methoxychlor
CAS #	72-43-5
Central File No.	CF-1839
Initial Receipt Date	06/13/02
Expiration Date	6/2005
Manufacturer	Sigma, Inc.
Lot Number	049H1328
Battelle Study #	WA 2-23-02-01
Method	SW 846, 8015B Modified

Executive Summary

The chemical purity of methoxychlor determined by the manufacturer was 95.2%. The purity result from Battelle-Sequim by GC-FID was determined to be 89.7%. Three concentrations of methoxychlor, 5, 10, and 20 mg/mL, were tested for stability in corn oil. Observed concentrations for the 5, 10, and 20 mg/mL tests dropped below 90% of the target concentration within 3, 4, or 5 weeks after initiation of the stability trial, respectively. Thus, the average day 0 concentrations were tested for stability. Based on the final regression model and the lower 95% confidence limit of the slope, the day 0 concentration of methoxychlor was expected to stay greater than or equal to 90% of the target concentration for up to an estimated 25 to 40 days. Thus, stability testing of the methoxychlor stock solution in corn oil was considered stable at the 5 and 10 mg/mL concentrations for 5 weeks, and at the 20 mg/mL concentration for only 3 weeks.

Mazola corn oil was purchased from local grocery stores, to be used as a carrier for the stability testing. The peroxide concentration was measured on 6-17-02 in triplicate as an indicator of decomposition. The average peroxide number in the Mazola corn oil was consistent with the request that the oil have a peroxide number less than 3 meq/kg.

The concentrations of methoxychlor in the formulations analyzed before shipment to RTI were in the range of 87% to 108% of the nominal. The concentration in formulations after use ranged 82% to 99% of the nominal. In-life chemistry recoveries for all doses ranged from 83% to 101%.

US EPA ARCHIVE DOCUMENT

TABLE OF CONTENTS

Page

1.0 INTRODUCTION 1

2.0 GENERAL METHODS 1

2.1 CHEMICAL PROCUREMENT 1
2.2 CHEMICAL PURITY 3
2.3 PREPARATION OF STOCK MATRICES FOR STABILITY ANALYSIS 3
2.4 ANALYTICAL CHEMISTRY FOR STABILITY TESTING 4
2.5 STATISTICAL ANALYSIS OF STABILITY 4
2.6 ANALYTICAL CHEMISTRY FOR IN-LIFE TESTING 4

3.0 RESULTS 5

3.1 CHEMICAL PURITY 5
3.2 ANALYTICAL CHEMISTRY FOR STABILITY TESTING 5
3.3 STATISTICAL RESULTS OF STABILITY TRIAL 5
3.4 CHEMISTRY RESULTS FOR THE ANALYSIS OF IN-LIFE SAMPLES 7

4.0 CONCLUSIONS 8

APPENDIX A: MANUFACTURER'S CERTIFICATE OF ANALYSIS/PURITY A.1
APPENDIX B: PURITY AND STABILITY TESTING PLAN B.1
APPENDIX C: ANALYTICAL RESULTS OF STABILITY TESTING C.1
APPENDIX D: STATISTICAL REPORT D.1
APPENDIX E: CHEMISTRY RESULTS FOR THE ANALYSIS OF IN-LIFE SAMPLES . E.1
APPENDIX F: DEVIATIONS F.1

LIST OF TABLES

Page

Table 1. Chemical Procurement Information 3

Table 2. Stock Matrix Composition for Stability Testing 4

Table 3. Summary of Statistical Results for Methoxychlor 7

LIST OF FIGURES

Page

Figure 1. EDSP Requisition Form for Methoxychlor 2

Figure 2. Observed Concentration of Methoxychlor with a Target Concentration of 5,000 µg/mL (A), 10,000 µg/mL (B), and 20,000 µg/mL (C) Against Time 6

US EPA ARCHIVE DOCUMENT

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1.0 INTRODUCTION

The goal of the Battelle-Sequim, Marine Sciences Laboratory (MSL) Chemical Repository for the Endocrine Disruptor Screening Program (EDSP) is to provide the participating laboratory with requested chemicals of documented quality at required concentrations and in a matrix appropriate for different toxicological tests. The EDSP Chemical Repository supplies the manufacturer's information regarding purity and stability, the material safety data sheet (MSDS) chemical information, and independent analysis of purity and stability in a matrix specified by the Purity and Stability Testing Plan made in collaboration with the requesting Principal Investigator. Additional analysis associated with the in-life studies are also provided when requested. This report is the product of such a request.

Under Work Assignment (WA) 2-23 and Battelle-Sequim Study Number WA 2-23-02-01, Dr. Julia George from the Center for Life Sciences and Toxicology, Research Triangle Institute, requested purity and stability testing of methoxychlor (Figure 1). Electronic files submitted to the EDSP Data Coordination Center in support of this work assignment are CRF_WA-2-23_Methoxychlor-cornoil.doc, PSTP_ WA-2-23_Methoxychlor-cornoil.doc, DSUM_ WA-2-10_2-14_2-23.xls, DAF_WA-2-10_2-14_2-23.doc, and ILSUM_WA-2-23_Methoxychlor-cornoil.doc.

2.0 GENERAL METHODS

Methods of standard operation of the Chemical Repository are addressed in the procedure, EDSP.C-001-01, The EDSP Chemical Repository. This procedure addresses chemical procurement including procurement of controlled substances, when applicable, which have unique permitting, ordering, handling, inventory, and storage requirements; chemical receipt and chain of custody, chemical log-in and labeling, inventory, chemical storage; stock solution preparation, documentation and archiving; test solution preparation, documentation and shipping; chemical disposal, and repository maintenance over time. The quality assurance (QA) requirements for procurement of chemicals for use in the Chemical Repository are addressed in procedure, MSL-A-012, Procurement. Each purchase requisition receives QA review to determine what is being ordered and which specific requirements apply.

2.1 Chemical Procurement

As requested by Dr. Julia George, methoxychlor, (CAS No. 72-43-5) was purchased for purity and stability analysis and an *in utero*/lactational exposure (Figure 1). Methoxychlor was purchased from Sigma, Inc. and lot number 049H1328 was initially received on 06/13/02 with an expiration date of 4/2006 (Table 1). The chemical was left in the original container, logged in to the Chemical Management System (CMS) and given a CMS barcode and unique log in number (CF-1839) as per the QA Project Plan (QAPP) for the EDSP Chemical Repository. The chemical was stored in a cool, dry location at room temperature, away from direct sunlight.

Corn oil (expiration dates 4-03 and 9-03) was purchased on 9-04-01 and 6-17-02 from local grocery stores, Mark and Pack and Quality Foods Center respectively, to be used as a carrier for the stability testing. The oil had no visual defects and was stored frozen. The peroxide concentration was measured on 6-17-02 in triplicate as an indicator of decomposition following the procedures in the Battelle, Columbus SOP #CCB_IV-001-04. It was requested that the oil have a peroxide number less than 3 meq/kg. Any bottles that did not meet this requirement were discarded.

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EDSP Chemical Request Form

For EPA WA: 2-23-02-01

Study Director

Name: Dr. Julia George
Affiliation: Center for Life Sciences and Toxicology
Research Triangle Institute
Location: PO Box 12194
Research Triangle Park, NC 27709
Telephone number: 919-541-5862

Bioassay Information

Proposed Bioassay: *In utero*/Lactational exposure

Test Chemical: Methoxychlor (MSL CF 1839)

Carrier(s): corn oil (Mazola)

Concentrations/Dilution Series: 5 mg/mL, 10 mg/mL, and 20 mg/mL

*Consider if analysis method detection limit which may be determined in Purity analysis is above or below desired test concentrations?

In vitro or *in vivo* tests? *In vivo*

Organism to be tested: rat

Method of test solution administration: oral gavage and subcutaneous administration

Planned/proposed test duration: 8 weeks

Chemical Information

Chemical Name: Methoxychlor

CAS: 72-43-5

Any known purity information: may refer to attached documentation
Manufacturer's Purity Information: 95.2% pure
Any known stability information: may refer to attached documentation
Manufacturer's Stability Information: stable
Desired purity (%) for test? 95% or greater

Figure 1. EDSP Requisition Form for Methoxychlor

Table 1. Chemical Procurement Information

Parameter	Chemical
Compound Name	Methoxychlor
CAS #	72-43-5
Central File No.	CF-1839
Initial Receipt Date	06/13/02
Expiration Date	6/2005
Manufacturer	Sigma, Inc.
Lot Number	049H1328
Manufacturer's Purity	95.2%
Storage Conditions	Cool, dry place/room temp.
Battelle Study #	WA 2-23-02-01
Method	SW 846, 8015B Modified

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2.2 Chemical Purity

Chemical purity was verified by chromatographic analysis to determine areas under peaks other than the principal peak and then compared to the manufacturer's certificate of analysis/purity (Appendix A). No statistical analyses were performed for the verification of chemical purity. General methods are documented in the procedure, EDSP.D-012-01, Chemical Repository Summary Displays and Statistical Analyses for the EDSP Data Coordination Center (DCC).

Purity verification was conducted by making a solution in hexane of about 100 µg/mL. This matrix was then run on a gas chromatograph with a flame ionization detector (GC-FID). A hexane blank was also run on the GC-FID. The purity was determined by first identifying the peaks in the chromatogram of the methoxychlor that were the same as the peaks in the analysis of the blank hexane sample. The areas associated with these common peaks were then eliminated by inhibiting integration and the remaining peaks were reported as a percentage of the total peak area. The percentage associated with the largest peak represented the purity of methoxychlor. The GC was set up with an auto sampler and a 30 m x 0.25 mm, DB-5 capillary column. The temperature program was set to start at 50 ºC, and ramped at 20ºC/min to a final temperature of 320ºC. The injection port temperature was set at 270ºC and the detector temperature at 320ºC. The auto sampler was set to inject 1 µL of the matrix dilution. One replicate was analyzed.

2.3 Preparation of Stock Matrices for Stability Analysis

A general study plan for stability testing based on the WA 2-23 request from Dr. Julia George was developed as the stability test protocol and is presented in Appendix B. Stock solutions were prepared to arrive at the chemical concentrations requested for stability analysis (Table 2). All samples were analyzed in triplicate so that a mean concentration and relative standard deviation (RSD) could be determined. General methods are documented in EDSP.D-012-01.

Methoxychlor stock matrices were prepared on 6-18-02 for testing as described in Table 2. Briefly, for the 5 mg/mL methoxychlor, 0.2518 g was weighed into a 50 mL Class A volumetric flask and corn oil was added to the 50 mL mark. The solution was agitated by hand shaking for approximately five minutes until all of the methoxychlor was dissolved. For the 10 mg/mL methoxychlor, 0.5006 g was weighed into a 50 mL Class A volumetric flask and corn oil was added to the mark. The solution was agitated in a similar manner until all of the chemical

Table 2. Stock Matrix Composition for Stability Testing

Study and Duration	Test Chemical	Target Concentration	Sample ID	Stock Matrix
WA 2-23-02-01 10 Weeks	Methoxychlor	5 mg/mL	1839-1a-1	0.2518 g in 50 mL corn oil
		10 mg/mL	1839-1a-2	0.5006 g in 50 mL corn oil
		20 mg/mL	1839-1a-3	1.0111 g in 50 mL corn oil

was dissolved. For the 20 mg/mL methoxychlor, 1.0111 g was weighed into a 50 mL Class A volumetric flask and corn oil was added to the mark. The solution was agitated in a similar manner until all of the chemical was dissolved. All solutions were transferred to ashed, amber glass bottles. Bottles were labeled and stored at 4ºC ± 2ºC for the duration of the test.

Density of the Mazola corn oil was measured as 0.91 g/mL for these samples. Using an Excel spreadsheet, the weight of corn oil was converted to a volume (i.e., g corn oil / density). Lower and upper 95% confidence bounds on the density of corn oil from a sample of two lots were estimated as 0.89 and 0.93 g/mL respectively.

2.4 Analytical Chemistry for Stability Testing

Chemical stability was evaluated under storage conditions (4°C) and matrix specifications as requested by the participating laboratory. At initiation and at each time period throughout the duration of the test, the concentration was determined by chromatographic analysis. Triplicate aliquots were tested for each concentration. The frequency of determinations and the duration of testing were determined by the requesting principal investigator and the chemists based on *a priori* knowledge about chemical stability. General methods are documented in EDSP.D-012-01.

Methoxychlor stock solution was sampled by weighing ~1 g of sample into a 30 mL amber glass, ashed vial and adding 25 mL of hexane using a volumetric pipette. For samples 1839-1a-1, 1839-1a-2, and 1839-1a-3 analysis was then conducted by adding 0.1 mL of the hexane solution and 0.02 mL of internal standard 5a androstane and 0.88 mL of hexane to the GC auto sampler vial. A corn oil blank was prepared the same way. This solution was then run on the GC-FID for quantification. The major peak determined during the purity analysis of methoxychlor was used for this analysis. Continuing calibration verification (CCV) samples, with the corn oil diluted by a factor of 250, were analyzed to demonstrate on-going calibration accuracy.

2.5 Statistical Analysis of Stability

Log linear degradation curves were fit to the data to describe the chemical concentration vs. time trends and their dependence on storage conditions and solvent matrix. Lack of fit and residual plots were evaluated to determine the form of the regression. Power calculations based on the observed variability were used to determine the sensitivity of the test to detect degraded concentrations. General methods are documented in SOP EDSP.D-012-01.

2.6 Analytical Chemistry for In-Life Testing

Analytical methods associated with in-life testing were similar to those described in Section 2.4.

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3.0 RESULTS

3.1 Chemical Purity

Battelle-Sequim ran a GC-FID purity scan on the methoxychlor. The chromatogram, after solvent blank correction, showed one large peak that had the appropriate retention time for methoxychlor and several very small peaks. The area of the methoxychlor peak was 89.7% of the total area of all peaks in the chromatogram. Chemical purity of methoxychlor determined by the manufacturer was 95.2% (Appendix A).

3.2 Analytical Chemistry for Stability Testing

Chemical stability testing was initiated on 6-18-02. Chemical concentration was determined 11 times over a period of 12 weeks. The analytical and quality control (QC) results are presented in Appendix C. A single preparation blank was analyzed with every batch for quality control purposes. There were no detectable concentrations of methoxychlor in the blanks. CCV results ranged from 87.4% to 112%. Internal standards were analyzed with each sample and these results ranged from 97.1% to 111%. The MDL was 115 ug/mL.

Both lots of Mazola corn oil had peroxide numbers less than 3 meq/kg as required for biological testing (Appendix C). The average peroxide number in the Mazola corn oil with an expiration date of 4-03 was 2.07 meq/kg (RSD = 5.9%). The average peroxide number in the Mazola corn oil with an expiration date of 9-03 was 1.38 meq/kg (RSD = 7.8%).

3.3 Statistical Results of Stability Trial

A plot of methoxychlor with a target concentration of 5,000 μg/mL against time shows a significant decline in concentration (Figure 2). All data points were less than 90% of the target concentration after three weeks. Thus, the average day 0 concentration of 4673 μg/mL was tested for stability. Based on the final regression model and the lower 95% confidence limit of the slope, the concentration of methoxychlor was expected to stay greater than or equal to 90% of the average day 0 concentration for up to an estimated 40 days (Table 3). Thus, this stock solution was considered stable for 5 weeks. The complete statistical analysis is presented in Appendix D.

All observations of methoxychlor with a target concentration of 10,000 μg/mL were less than 90% of the target concentration after 4 weeks. Again, the average day 0 concentration of 9027 μg/mL was tested for stability (Figure 2). Based on the final regression model and the lower 95% confidence limit of the slope, the concentration of methoxychlor was expected to stay greater than or equal to 90% of the average day 0 concentration for an estimated 35 days (Table 3). Thus, this stock solution was considered stable for 5 weeks. The complete statistical analysis is presented in Appendix D.

All observations of methoxychlor with a target concentration of 20,000 μg/mL were less than 90% of the target concentration after 5 weeks. Again, the average day zero concentration of 18369 μg/mL was tested for stability (Figure 2). Based on the final regression model and the lower 95% confidence limit of the slope, the concentration of methoxychlor was expected to stay greater than or equal to 90% of the average day 0 concentration for an estimated 25 days (Table 3). Thus, this stock solution was considered stable for 3 weeks. The complete statistical analysis is presented in Appendix D.

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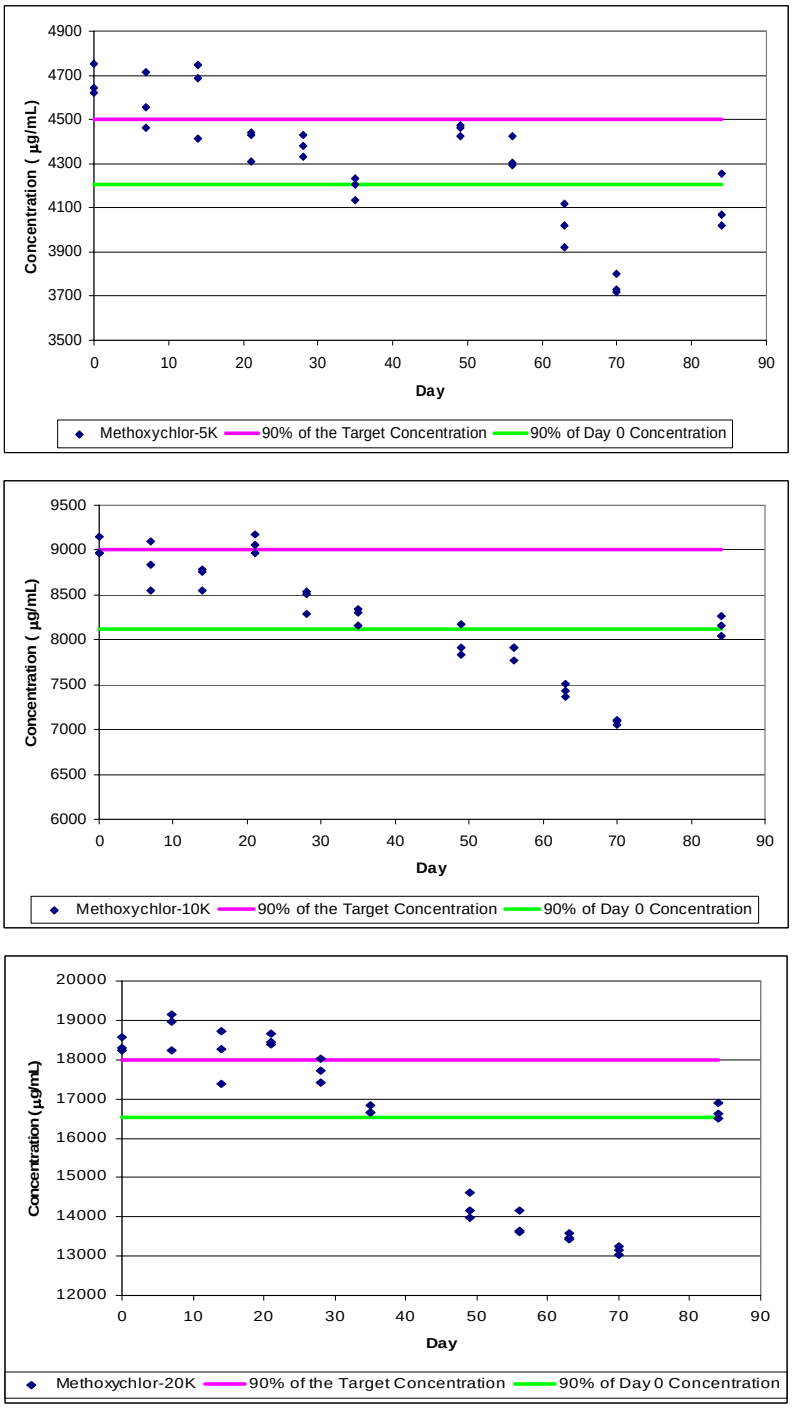

Figure 2. Observed Concentration of Methoxychlor with a Target Concentration of 5,000 µg/mL (A), 10,000 µg/mL (B), and 20,000 µg/mL (C) Against Time

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Table 3. Summary of Statistical Results for Methoxychlor

WA 2-23-02-01 Statistical Analysis conducted by Valerie Cullinan Using Minitab Version 13.32, Minitab Inc., 1999.	1839-1a-1 Methoxychlor-5K	1839-1a-2 Methoxychlor-10K	1839-1a-3 Methoxychlor-20K
Target Concentration (μg/mL)	5000	10000	20000
Number of determinations	1	1	1
Number of days tested	84	84	84
Number of replicates per day	3	3	3
Number of outliers removed	0	0	0
Number of observations removed	0	0	0
Overall Mean Concentration	4319	8259	16328
95% Upper CL	4402	8445	16966
error degrees of freedom	32	32	32
1-sample t-test of Ho: μ >= Target	S[a]	S	S
estimated intercept of ln(concentration) against time	8.4447	9.1075	9.8428
estimated slope of ln(concentration) against time	-0.0020	-0.0024	-0.0039
standard error of slope	0.0003	0.0003	0.0006
error degrees of freedom	31	31	31
Significance test of lack-of-fit for final model	S	S	S
Significance test of Ho: β = 0 vs. H1: β = 0	S	S	S
Lower 95% CL of β	-0.003	-0.003	-0.005
Upper 95% CL of β	-0.001	-0.002	-0.003
Maximum Percent Loss (using LCL)	2.0%	2.4%	4.0%
Mean Percent Loss (using bhat)	1.6%	1.9%	3.1%
LN(90% of Target)	8.4118	9.1050	9.7981
Number of days until at 90% of Target (using LCL)	13	1	9
Conclusion using Target Concentration:	**Stable for 1 wks**	**Stable for 0 wks**	**Stable for 1 wks**
Average Day 0 Concentration	4673	9027	18369
LN(90% of Day 0 Concentration)	8.3441	9.0026	9.7130
Number of days until at 90% of Day 0 Concentration (using LCL)	40	35	25
Conclusion using Day 0 Concentration:	**Stable for 5 wks**	**Stable for 5 wks**	**Stable for 3 wks**

[a] Significant at α = 0.05

3.4 Chemistry Results for the Analysis of In-Life Samples

The concentrations of methoxychlor in the formulations analyzed before shipment to RTI were in the range of 87% to 108% of the nominal. The concentration in formulations after use ranged 82% to 99% of the nominal. In-life chemistry recoveries for all doses ranged from 83% to 101%. The complete analysis is presented in Appendix E.

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4.0 CONCLUSIONS

The stated purity of methoxychlor by the manufacturer was 95.2%; Battelle-Sequim determined the compound to be 89.7% pure. Stability testing of methoxychlor in corn oil concluded that the chemical was stable at the 5 mg/mL and 10 mg/mL concentrations for a period of 5 weeks, and at the 20 mg/mL concentration for a period of 3 weeks.

The level of peroxide measured in corn oil used for the stability trial was consistent with the request that the oil have a peroxide number less than 3 meq/kg.

The concentrations of methoxychlor in the formulations analyzed before shipment to RTI were in the range of 87% to 108% of the nominal. The concentration in formulations after use ranged 82% to 99% of the nominal. In-life chemistry recoveries for all doses ranged from 83% to 101%.

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APPENDIX A

MANUFACTURER'S CERTIFICATE OF ANALYSIS/PURITY

SIGMA

CF#1839

Certificate of Analysis

TEST	LOT {049H1328} RESULTS
Product Name	Methoxychlor
Product Number	M1501
CAS Number	72435
Formula	$C_{16}H_{15}Cl_3O_2$
Formula Weight	345.7
APPEARANCE	LIGHT ORANGE POWDER WITH A LIGHT TAN CAST
SOLUBILITY	CLEAR FAINT YELLOW SOLUTION AT 200 MG PLUS 4.0 ML OF ETHANOL
IR SPECTRUM	CONSISTENT WITH STRUCTURE
PURITY BY GAS CHROMATOGRAPHY	95.2%
QC ACCEPTANCE DATE	APRIL 1999

David Feldker, Manager
Analytical Services

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APPENDIX B

PURITY AND STABILITY TESTING PLAN

EDSP Purity Analysis and Stability Testing Plan for Methoxychlor

Chemical Name: Methoxychlor (MSL CF Login 1839)

CAS Number: 72-43-5

Lot Number: 049H1328, 2 100g bottles, stored at RT in Bldg5 Rm 219

Expiration date: 6/05

Manufacturer's Purity Information: 95.2%

Manufacturer's Stability Information: stable

MSL Purity Results:
Purity (%) To be determined at MSL by GC-FID scan

MDL has not been determined.

Bioassay Information: Pesticide, see MSDS

Study Director
Name: Dr. Julia George
Affiliation: RTI
Location: RTP, NC
Telephone number: 919-541-5862

Proposed Bioassay: WA 2-23

Test Chemical: Methoxychlor

CAS: 72-43-5

Carrier(s): Mazola corn oil

Concentrations/Dilution Series: 5, 10, and 20 mg/mL

Below MDL determined in Purity Analysis?

In vitro or in *vivo tests*? *In vivo*

Organism to be tested: Rat

Method of test solution administration: Oral gavage and subcutaneous administration

Planned/Proposed test duration: 8 weeks

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Design of Stability Test: 5, 10 and 20 mg/mL in glass at 4 deg. C in the dark for 70days, analyzed weekly in triplicate by GC detector

Number of replicates: 3

Duration: 10 weeks, sampling each week

Other factors:
Temperature regime(s): 4 deg. C
Test container type: Glass
Light or dark: Dark except when container is removed for sampling or handling
Other

Statistical testing: Regression analysis of the slope for concentration versus time

Resulting records package:
Manufacturer's certificate of analysis or purity
MSDS
Records:

- date sample received;
- date(s) sample analyzed;
- sample matrix;
- electronic file identification codes (when applicable to identify instrument data files);
- data summary reports;
  - Chemical repository confirmatory test results of chemical identity and purity;
  - Chemical repository test results of lot-to-lot variation in chemical purity;
  - Chemical repository periodic assessment results of changes in purity of stock solutions and dilutions and generation of degradation products
- QC data reports;
- data qualifying flags; and
- dilution factor(s).

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APPENDIX C

ANALYTICAL RESULTS OF STABILITY TESTING

Table C1. Methoxychlor concentration in Mazola Corn Oil (µg/mL)

Target Conc.	Sample ID	Date	Methoxychlor	Average	RSD	Recovery
5000 ug/ml	1839-1a-1-1 R-1	6/18/2002	4641			
5000 ug/ml	1839-1a-1-1 R-2	6/18/2002	4754	4673	1.51%	93.5%
5000 ug/ml	1839-1a-1-1 R-3	6/18/2002	4623			
10000 ug/ml	1839-1a-2-1 R-1	6/18/2002	8966			
10000 ug/ml	1839-1a-2-1 R-2	6/18/2002	8967	9027	1.16%	90.3%
10000 ug/ml	1839-1a-2-1 R-3	6/18/2002	9147			
20000 ug/ml	1839-1a-3-1 R-1	6/18/2002	18556			
20000 ug/ml	1839-1a-3-1 R-2	6/18/2002	18305	18369	0.90%	91.8%
20000 ug/ml	1839-1a-3-1 R-3	6/18/2002	18245			
blank	Corn Oil (T=0)	6/19/2002	115 U			
5000 ug/ml	1839-1a-1-2 R-1	6/25/2002	4558			
5000 ug/ml	1839-1a-1-2 R-2	6/25/2002	4716	4579	2.80%	91.6%
5000 ug/ml	1839-1a-1-2 R-3	6/25/2002	4462			
10000 ug/ml	1839-1a-2-2 R-1	6/25/2002	8550			
10000 ug/ml	1839-1a-2-2 R-2	6/25/2002	9101	8830	3.12%	88.3%
10000 ug/ml	1839-1a-2-2 R-3	6/25/2002	8840			
20000 ug/ml	1839-1a-3-2 R-1	6/25/2002	18246			
20000 ug/ml	1839-1a-3-2 R-2	6/25/2002	19156	18786	2.55%	93.9%
20000 ug/ml	1839-1a-3-2 R-3	6/25/2002	18957			
blank	Corn Oil (week 1)	6/25/2002	115 U			
5000 ug/ml	1839-1a-1-3 R-1	7/2/2002	4414			
5000 ug/ml	1839-1a-1-3 R-2	7/2/2002	4688	4617	3.86%	92.3%
5000 ug/ml	1839-1a-1-3 R-3	7/2/2002	4748			
10000 ug/ml	1839-1a-2-3 R-1	7/2/2002	8554			
10000 ug/ml	1839-1a-2-3 R-2	7/2/2002	8788	8701	1.47%	87.0%
10000 ug/ml	1839-1a-2-3 R-3	7/2/2002	8760			
20000 ug/ml	1839-1a-3-3 R-1	7/2/2002	17396			
20000 ug/ml	1839-1a-3-3 R-2	7/2/2002	18262	18129	3.73%	90.6%
20000 ug/ml	1839-1a-3-3 R-3	7/2/2002	18729			
blank	Corn Oil (week 2)	7/2/2002	115 U			
5000 ug/ml	1839-1a-1-4 R-1	7/9/2002	4432			
5000 ug/ml	1839-1a-1-4 R-2	7/9/2002	4310	4394	1.66%	87.9%
5000 ug/ml	1839-1a-1-4 R-3	7/9/2002	4441			
10000 ug/ml	1839-1a-2-4 R-1	7/9/2002	9058			
10000 ug/ml	1839-1a-2-4 R-2	7/9/2002	9171	9063	1.16%	90.6%
10000 ug/ml	1839-1a-2-4 R-3	7/9/2002	8961			
20000 ug/ml	1839-1a-3-4 R-1	7/9/2002	18456			
20000 ug/ml	1839-1a-3-4 R-2	7/9/2002	18668	18502	0.80%	92.5%
20000 ug/ml	1839-1a-3-4 R-3	7/9/2002	18383			
blank	Corn Oil (week 3)	7/9/2002	115 U			
5000 ug/ml	1839-1a-1-5 R-1	7/16/2002	4333			
5000 ug/ml	1839-1a-1-5 R-2	7/16/2002	4428	4381	1.08%	87.6%
5000 ug/ml	1839-1a-1-5 R-3	7/16/2002	4383			
10000 ug/ml	1839-1a-2-5 R-1	7/16/2002	8506			
10000 ug/ml	1839-1a-2-5 R-2	7/16/2002	8284	8444	1.65%	84.4%
10000 ug/ml	1839-1a-2-5 R-3	7/16/2002	8541			

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Table C1. continued

Target Conc.	Sample ID	Date	Methoxychlor	Average	RSD	Recovery
20000 ug/ml	1839-1a-3-5 R-1	7/16/2002	17714			
20000 ug/ml	1839-1a-3-5 R-2	7/16/2002	18021	17719	1.69%	88.6%
20000 ug/ml	1839-1a-3-5 R-3	7/16/2002	17423			
blank	Corn Oil (week 4)	7/16/2002	115 U			
5000 ug/ml	1839-1a-1-6 R-1	7/23/2002	4132			
5000 ug/ml	1839-1a-1-6 R-2	7/23/2002	4205	4190	1.23%	83.8%
5000 ug/ml	1839-1a-1-6 R-3	7/23/2002	4232			
10000 ug/ml	1839-1a-2-6 R-1	7/23/2002	8302			
10000 ug/ml	1839-1a-2-6 R-2	7/23/2002	8156	8267	1.19%	82.7%
10000 ug/ml	1839-1a-2-6 R-3	7/23/2002	8344			
20000 ug/ml	1839-1a-3-6 R-1	7/23/2002	16667			
20000 ug/ml	1839-1a-3-6 R-2	7/23/2002	16642	16718	0.66%	83.6%
20000 ug/ml	1839-1a-3-6 R-3	7/23/2002	16845			
blank	Corn Oil (week 5)	7/23/2002	115 U			
5000 ug/ml	1839-1a-1-7 R-1	8/6/2002	4475			
5000 ug/ml	1839-1a-1-7 R-2	8/6/2002	4461	4453	0.61%	89.1%
5000 ug/ml	1839-1a-1-7 R-3	8/6/2002	4423			
10000 ug/ml	1839-1a-2-7 R-1	8/6/2002	7841			
10000 ug/ml	1839-1a-2-7 R-2	8/6/2002	7913	7975	2.18%	79.8%
10000 ug/ml	1839-1a-2-7 R-3	8/6/2002	8171			
20000 ug/ml	1839-1a-3-7 R-1	8/6/2002	13984			
20000 ug/ml	1839-1a-3-7 R-2	8/6/2002	14609	14252	2.26%	71.3%
20000 ug/ml	1839-1a-3-7 R-3	8/6/2002	14162			
blank	Corn Oil (week 7)	8/6/2002	115 U			
5000 ug/ml	1839-1a-1-8 R-1	8/13/2002	4295			
5000 ug/ml	1839-1a-1-8 R-2	8/13/2002	4302	4340	1.65%	86.8%
5000 ug/ml	1839-1a-1-8 R-3	8/13/2002	4423			
10000 ug/ml	1839-1a-2-8 R-1	8/13/2002	7775			
10000 ug/ml	1839-1a-2-8 R-2	8/13/2002	7916	7867	1.02%	78.7%
10000 ug/ml	1839-1a-2-8 R-3	8/13/2002	7910			
20000 ug/ml	1839-1a-3-8 R-1	8/13/2002	14169			
20000 ug/ml	1839-1a-3-8 R-2	8/13/2002	13655	13816	2.21%	69.1%
20000 ug/ml	1839-1a-3-8 R-3	8/13/2002	13624			
blank	Corn Oil (week 8)	8/13/2002	115 U			
5000 ug/ml	1839-1a-1-9 R-1	8/20/2002	4116			
5000 ug/ml	1839-1a-1-9 R-2	8/20/2002	3922	4018	2.41%	80.4%
5000 ug/ml	1839-1a-1-9 R-3	8/20/2002	4017			
10000 ug/ml	1839-1a-2-9 R-1	8/20/2002	7507			
10000 ug/ml	1839-1a-2-9 R-2	8/20/2002	7363	7434	0.97%	74.3%
10000 ug/ml	1839-1a-2-9 R-3	8/20/2002	7430			
20000 ug/ml	1839-1a-3-9 R-1	8/20/2002	13464			
20000 ug/ml	1839-1a-3-9 R-2	8/20/2002	13438	13494	0.56%	67.5%
20000 ug/ml	1839-1a-3-9 R-3	8/20/2002	13580			
blank	Corn Oil (week 9)	8/20/2002	115 U			
5000 ug/ml	1839-1a-1-10 R-1	8/27/2002	3731			
5000 ug/ml	1839-1a-1-10 R-2	8/27/2002	3719	3750	1.18%	75.0%
5000 ug/ml	1839-1a-1-10 R-3	8/27/2002	3801			

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Table C1. continued

Target Conc.	Sample ID	Date	Methoxychlor	Average	RSD	Recovery
10000 ug/ml	1839-1a-2-10 R-1	8/27/2002	7057			
10000 ug/ml	1839-1a-2-10 R-2	8/27/2002	7087	7085	0.39%	70.9%
10000 ug/ml	1839-1a-2-10 R-3	8/27/2002	7111			
20000 ug/ml	1839-1a-3-10 R-1	8/27/2002	13038			
20000 ug/ml	1839-1a-3-10 R-2	8/27/2002	13238	13140	0.76%	65.7%
20000 ug/ml	1839-1a-3-10 R-3	8/27/2002	13145			
blank	Corn Oil (week 10)	8/27/2002	115 U			
5000 ug/ml	1839-1a-1-12 R-1	9/10/2002	4022			
5000 ug/ml	1839-1a-1-12 R-2	9/10/2002	4067	4115	3.01%	82.3%
5000 ug/ml	1839-1a-1-12 R-3	9/10/2002	4255			
10000 ug/ml	1839-1a-2-12 R-1	9/10/2002	8263			
10000 ug/ml	1839-1a-2-12 R-2	9/10/2002	8047	8157	1.33%	81.6%
10000 ug/ml	1839-1a-2-12 R-3	9/10/2002	8160			
20000 ug/ml	1839-1a-3-12 R-1	9/10/2002	16620			
20000 ug/ml	1839-1a-3-12 R-2	9/10/2002	16515	16679	1.20%	83.4%
20000 ug/ml	1839-1a-3-12 R-3	9/10/2002	16902			
blank	Corn Oil (week 12)	9/10/2002	115 U			

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Table C.2. CCV Data for Methoxychlor Concentration in Mazola Corn Oil [1]

Time	Sample Name	Methoxychlor (ug/mL)	Recovery	PD
T=0	EDSP Mix1 5 ug/ml	4.81	96.2%	3.8%
	EDSP Mix1 5 ug/ml	5.16	103%	3.2%
	EDSP Mix1 5 ug/ml	5.12	102%	2.4%
	EDSP Mix1 5 ug/ml	5.10	102%	2.0%
Week 1	EDSP Mix1 5 ug/ml	4.94	98.8%	1.2%
	EDSP Mix1 5 ug/ml	5.06	101%	1.2%
	EDSP Mix1 5 ug/ml	5.08	102%	1.6%
	EDSP Mix1 5 ug/ml	5.07	101%	1.4%
Week 2	EDSP Mix1 5 ug/ml	4.99	100%	0.2%
	EDSP Mix1 5 ug/ml	5.02	100%	0.4%
	EDSP Mix1 5 ug/ml	4.94	98.8%	1.2%
	EDSP Mix1 5 ug/ml	4.97	99.4%	0.6%
Week 3	EDSP Mix1 5 ug/ml	5.00	100%	0.0%
	EDSP Mix1 5 ug/ml	5.13	103%	2.6%
	EDSP Mix1 5 ug/ml	5.05	101%	1.0%
	EDSP Mix1 5 ug/ml	5.07	101%	1.4%
	EDSP Mix1 5 ug/ml	4.88	97.6%	2.4%
Week 4	EDSP Mix1 5 ug/ml	4.85	97.0%	3.0%
	EDSP Mix1 5 ug/ml	5.03	101%	0.6%
	EDSP Mix1 5 ug/ml	4.95	99.0%	1.0%
	EDSP Mix1 5 ug/ml	4.97	99.4%	0.6%
Week 5	EDSP Mix1 5 ug/ml	5.00	100%	0.0%
	EDSP Mix1 5 ug/ml	4.80	96.0%	4.0%
	EDSP Mix1 5 ug/ml	4.67	93.4%	6.6%
	EDSP Mix1 5 ug/ml	4.48	89.6%	10.4%
Week 7	EDSP Mix1 5 ug/ml	4.93	98.6%	1.4%
	EDSP Mix1 5 ug/ml	5.25	105%	5.0%
	EDSP Mix1 5 ug/ml	5.62	112%	12.4%
	EDSP Mix1 5 ug/ml	5.52	110%	10.4%
Week 8	EDSP Mix1 5 ug/ml	4.86	97.2%	2.8%
	EDSP Mix1 5 ug/ml	5.31	106%	6.2%
	EDSP Mix1 5 ug/ml	5.30	106%	6.0%
	EDSP Mix1 5 ug/ml	5.47	109%	9.4%
Week 9	EDSP Mix1 5 ug/ml	4.61	92.2%	7.8%
	EDSP Mix1 5 ug/ml	4.84	96.8%	3.2%
	EDSP Mix1 5 ug/ml	4.93	98.6%	1.4%
	EDSP Mix1 5 ug/ml	5.01	100%	0.2%
Week 10	EDSP Mix1 5 ug/ml	4.37	87.4%	12.6%
	EDSP Mix1 5 ug/ml	4.50	90.0%	10.0%
	EDSP Mix1 5 ug/ml	4.53	90.6%	9.4%
	EDSP Mix1 5 ug/ml	4.54	90.8%	9.2%
Week 12	EDSP Mix1 5 ug/ml	4.75	95.0%	5.0%
	EDSP Mix1 5 ug/ml	4.95	99.0%	1.0%
	EDSP Mix1 5 ug/ml	4.97	99.4%	0.6%
	EDSP Mix1 5 ug/ml	4.96	99.2%	0.8%

[1] Corn oil was diluted by a factor of 250 for these analyses.

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Text Box C1. Calibration Standard Preparation

Calibration Standard EDSP Mix 1
Calibrations were performed using a five-point calibration curve labeled EDSP Mix 1 A thru E. This mix is used for Atrazine, Fenerimol, 4,4' DDE, Methoxychlor and Vinclosolin analyzed by GC-FID. These standards were made by serial dilutions of standards for each compound. • Atrazine standard was made by weighing 0.0499 g of the neat material into a 50 mL volumetric flask. This was then diluted to the 50 mL mark with Methylene chloride and labeled 1826-1-1. • Fenarimol standard was made by weighing 0.0506 g of the neat material into a 50 mL volumetric flask. This was then diluted to the 50 mL mark with hexane and labeled 1829B-1. • 4,4' DDE standard was made by weighing 0.0501 g of the neat material into a 50 mL volumetric flask. This was then diluted to the 50 mL mark with hexane and labeled 1832-1a-1. • Methoxychlor standard was made by weighing 0.0513 g of the neat material into a 50 mL volumetric flask. This was then diluted to the 50 mL mark with hexane and labeled 1808-1-3. • Vinclosolin standard was made by weighing 0.0512 g of the neat material into a 50 mL volumetric flask. This was then diluted to the 50 mL mark with hexane and labeled 1779-78. This analysis used an internal standard, in this case 5a androstane, which is made by weighing 0.0511 g of the neat material into a 50 mL volumetric flask. This was then diluted to the 50 mL mark with hexane, this is then labeled REP7. The EDSP Mix 1 series (A through E) was made as follows. • Solution A, 1 ml of 1826-1-1, 1829B-1, 1832-1a-1, 1808-1-3, 1779-78 and 0.02 ml REP7 added to a 10 ml volumetric flask and diluted to the mark with hexane. • Solution B, 1 ml of 1826-1-1, 1829B-1, 1832-1a-1, 1808-1-3, 1779-78 and 1 ml REP7 added to a 50 ml volumetric flask and diluted to the mark with hexane. • Solution C, 0.25 ml of 1826-1-1, 1829B-1, 1832-1a-1, 1808-1-3, 1779-78 and 1 ml REP7 added to a 50 ml volumetric flask and diluted to the mark with hexane. • Solution D, 0.1 ml of 1826-1-1, 1829B-1, 1832-1a-1, 1808-1-3, 1779-78 and 2 ml REP7 added to a 100 ml volumetric flask and diluted to the mark with hexane. • Solution E, 0.05 ml of 1826-1-1, 1829B-1, 1832-1a-1, 1808-1-3, 1779-78 and 2 ml REP7 added to a 100 ml volumetric flask and diluted to the mark with hexane.

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Table C.3. Internal Standards Data for Methoxychlor in Mazola Corn Oil

Sample Name	Date	5A Androstane Recovery
1839-1a-1-1 R-1	6/18/2002	105%
1839-1a-1-1 R-2	6/18/2002	103%
1839-1a-1-1 R-3	6/18/2002	105%
1839-1a-2-1 R-1	6/18/2002	105%
1839-1a-2-1 R-2	6/18/2002	107%
1839-1a-2-1 R-3	6/18/2002	108%
1839-1a-3-1 R-1	6/18/2002	106%
1839-1a-3-1 R-2	6/18/2002	106%
1839-1a-3-1 R-3	6/18/2002	107%
1839-1a-1-2 R-1	6/25/2002	101%
1839-1a-1-2 R-2	6/25/2002	105%
1839-1a-1-2 R-3	6/25/2002	104%
1839-1a-2-2 R-1	6/25/2002	104%
1839-1a-2-2 R-2	6/25/2002	102%
1839-1a-2-2 R-3	6/25/2002	103%
1839-1a-3-2 R-1	6/25/2002	104%
1839-1a-3-2 R-2	6/25/2002	102%
1839-1a-3-2 R-3	6/25/2002	103%
1839-1a-1-3 R-1	7/2/2002	104%
1839-1a-1-3 R-2	7/2/2002	97.7%
1839-1a-1-3 R-3	7/2/2002	100%
1839-1a-2-3 R-1	7/2/2002	104%
1839-1a-2-3 R-2	7/2/2002	102%
1839-1a-2-3 R-3	7/2/2002	102%
1839-1a-3-3 R-1	7/2/2002	102%
1839-1a-3-3 R-2	7/2/2002	102%
1839-1a-3-3 R-3	7/2/2002	101%
1839-1a-1-4 R-1	7/9/2002	103%
1839-1a-1-4 R-2	7/9/2002	103%
1839-1a-1-4 R-3	7/9/2002	101%
1839-1a-2-4 R-1	7/9/2002	99.4%
1839-1a-2-4 R-2	7/9/2002	98.5%
1839-1a-2-4 R-3	7/9/2002	98.7%
1839-1a-3-4 R-1	7/9/2002	100%
1839-1a-3-4 R-2	7/9/2002	97.1%
1839-1a-3-4 R-3	7/9/2002	98.7%
1839-1a-1-5 R-1	7/16/2002	107%
1839-1a-1-5 R-2	7/16/2002	105%
1839-1a-1-5 R-3	7/16/2002	104%
1839-1a-2-5 R-1	7/16/2002	103%
1839-1a-2-5 R-2	7/16/2002	110%
1839-1a-2-5 R-3	7/16/2002	103%
1839-1a-3-5 R-1	7/16/2002	104%
1839-1a-3-5 R-2	7/16/2002	103%
1839-1a-3-5 R-3	7/16/2002	105%
1839-1a-1-6 R-1	7/23/2002	107%
1839-1a-1-6 R-2	7/23/2002	105%
1839-1a-1-6 R-3	7/23/2002	105%

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Table C3. continued

Sample Name	Date	5A Androstane Recovery
1839-1a-2-6 R-1	7/23/2002	106%
1839-1a-2-6 R-2	7/23/2002	103%
1839-1a-2-6 R-3	7/23/2002	106%
1839-1a-3-6 R-1	7/23/2002	106%
1839-1a-3-6 R-2	7/23/2002	104%
1839-1a-3-6 R-3	7/23/2002	105%
1839-1a-1-7 R-1	8/6/2002	102%
1839-1a-1-7 R-2	8/6/2002	102%
1839-1a-1-7 R-3	8/6/2002	102%
1839-1a-2-7 R-1	8/6/2002	103%
1839-1a-2-7 R-2	8/6/2002	102%
1839-1a-2-7 R-3	8/6/2002	102%
1839-1a-3-7 R-1	8/6/2002	103%
1839-1a-3-7 R-2	8/6/2002	101%
1839-1a-3-7 R-3	8/6/2002	102%
1839-1a-1-8 R-1	8/13/2002	103%
1839-1a-1-8 R-2	8/13/2002	105%
1839-1a-1-8 R-3	8/13/2002	105%
1839-1a-2-8 R-1	8/13/2002	106%
1839-1a-2-8 R-2	8/13/2002	102%
1839-1a-2-8 R-3	8/13/2002	103%
1839-1a-3-8 R-1	8/13/2002	104%
1839-1a-3-8 R-2	8/13/2002	107%
1839-1a-3-8 R-3	8/13/2002	111%
1839-1a-1-9 R-1	8/20/2002	102%
1839-1a-1-9 R-2	8/20/2002	105%
1839-1a-1-9 R-3	8/20/2002	104%
1839-1a-2-9 R-1	8/20/2002	106%
1839-1a-2-9 R-2	8/20/2002	104%
1839-1a-2-9 R-3	8/20/2002	103%
1839-1a-3-9 R-1	8/20/2002	104%
1839-1a-3-9 R-2	8/20/2002	107%
1839-1a-3-9 R-3	8/20/2002	108%
1839-1a-1-10 R-1	8/27/2002	106%
1839-1a-1-10 R-2	8/27/2002	110%
1839-1a-1-10 R-3	8/27/2002	111%
1839-1a-2-10 R-1	8/27/2002	108%
1839-1a-2-10 R-2	8/27/2002	108%
1839-1a-2-10 R-3	8/27/2002	108%
1839-1a-3-10 R-1	8/27/2002	109%
1839-1a-3-10 R-2	8/27/2002	110%
1839-1a-3-10 R-3	8/27/2002	110%
1839-1a-1-12 R-1	9/10/2002	105%
1839-1a-1-12 R-2	9/10/2002	105%
1839-1a-1-12 R-3	9/10/2002	105%
1839-1a-2-12 R-1	9/10/2002	102%
1839-1a-2-12 R-2	9/10/2002	105%
1839-1a-2-12 R-3	9/10/2002	107%

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Table C3. continued

Sample Name	Date	5A Androstane Recovery
1839-1a-3-12 R-1	9/10/2002	104%
1839-1a-3-12 R-2	9/10/2002	103%
1839-1a-3-12 R-3	9/10/2002	106%

Table C.4. Peroxide concentration in Mazola Corn Oil (meq/kg) measured on 6/17/02

Sample	Volume of Sodium Thiosulfate (mL)	Normality	Weight of Oil (g)	Peroxide Number	Average Peroxide Number	RSD
Blank	0.75	0.005	5.00	0.75		
Mazola Corn Oil Expiration 9-03 R-1	1.6	0.005	5.43	1.47		
Mazola Corn Oil Expiration 9-03 R-2	1.5	0.005	5.32	1.41	1.38	7.8%
Mazola Corn Oil Expiration 9-03 R-3	1.2	0.005	4.75	1.26		
Mazola Corn Oil Expiration 4-03 R-1	2.0	0.005	5.18	1.93		
Mazola Corn Oil Expiration 4-03 R-2	2.2	0.005	5.09	2.16	2.07	5.9%
Mazola Corn Oil Expiration 4-03 R-3	2.5	0.005	5.21	2.11		

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APPENDIX D

STATISTICAL REPORT

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WA-2-23-02-01
Statistical Analysis conducted by Valerie Cullinan
Using Minitab Version 13.32, Minitab Inc., 1999.

11/25/2002 11:22:30 AM

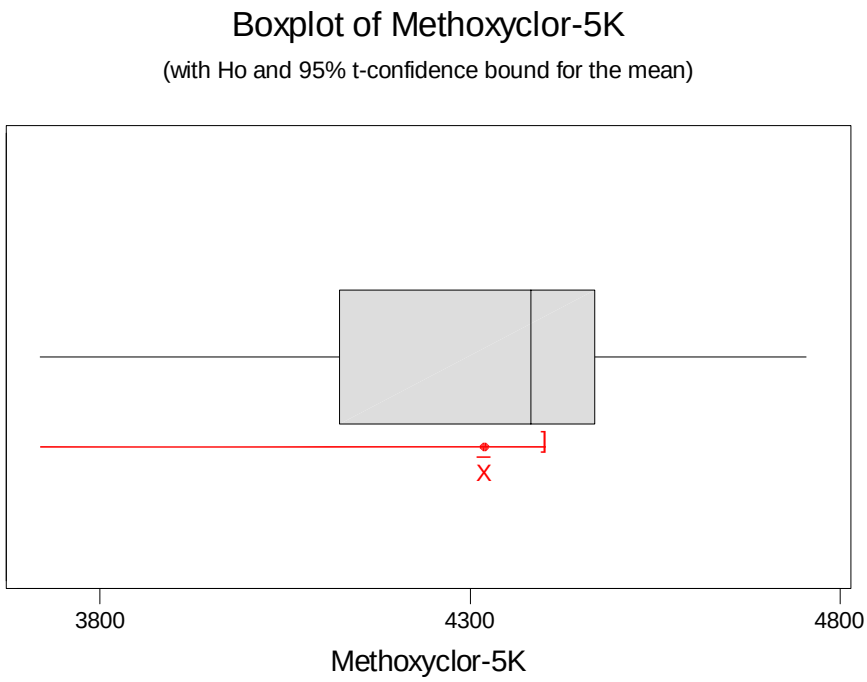
Analysis of Methoxychlor-5k in corn oil

- Test to determine if the data are from a population with mean of 5000.

One-Sample T: Methoxychlor-5K

```
Test of mu = 5000 vs mu < 5000

Variable           N      Mean     StDev   SE Mean
Methoxychlor-     33    4319.0     281.5      49.0

Variable       95.0% Upper Bound        T      P
Methoxychlor-              4402.0   -13.90  0.000
```

t Boxplot of Methoxychlor-5K



- Nonparametric Test for outlier.

```
Outliers are < Median-3*IQD OR > Median+3*IQD
Boundary for outliers are values <    3348.62  and >    5416.88
No outliers
```

US EPA ARCHIVE DOCUMENT

- Transform data to natural logarithm and conduct regression analysis.

Week	Rep	Ln(Concentration)
0	1	8.4428
0	2	8.4667
0	3	8.4388
7	1	8.4246
7	2	8.4587
7	3	8.4034
14	1	8.3925
14	2	8.4529
14	3	8.4654
21	1	8.3965
21	2	8.3687
21	3	8.3985
28	1	8.3740
28	2	8.3957
28	3	8.3854
35	1	8.3266
35	2	8.3441
35	3	8.3504
49	1	8.4063
49	2	8.4030
49	3	8.3945
56	1	8.3651
56	2	8.3669
56	3	8.3945
63	1	8.3225
63	2	8.2743
63	3	8.2983
70	1	8.2245
70	2	8.2212
70	3	8.2430
84	1	8.2996
84	2	8.3106
84	3	8.3559

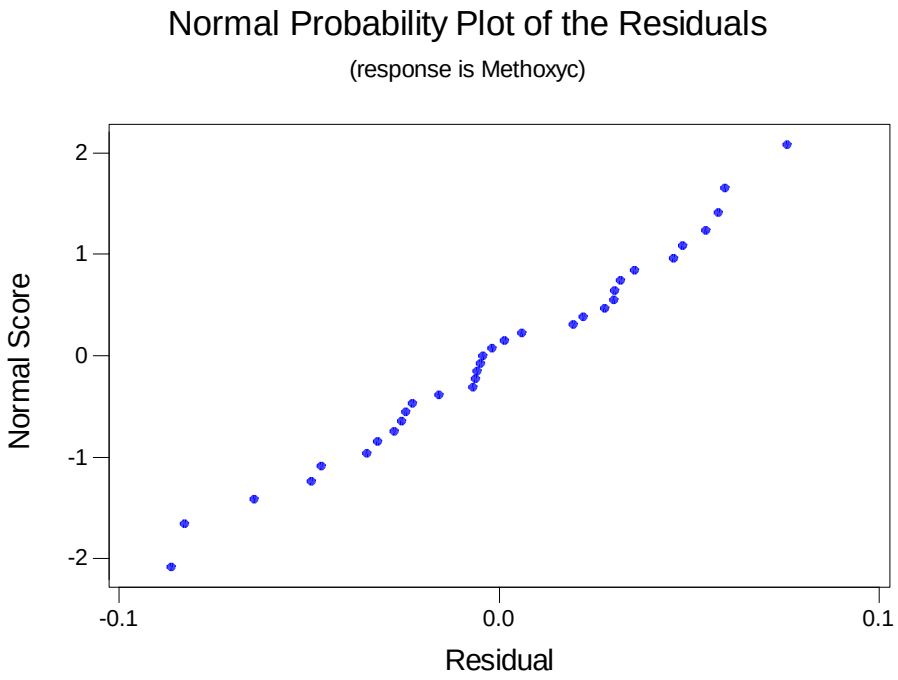
- Conducts Simple Linear Regression

Regression Analysis: Methoxychlor-5K versus Day

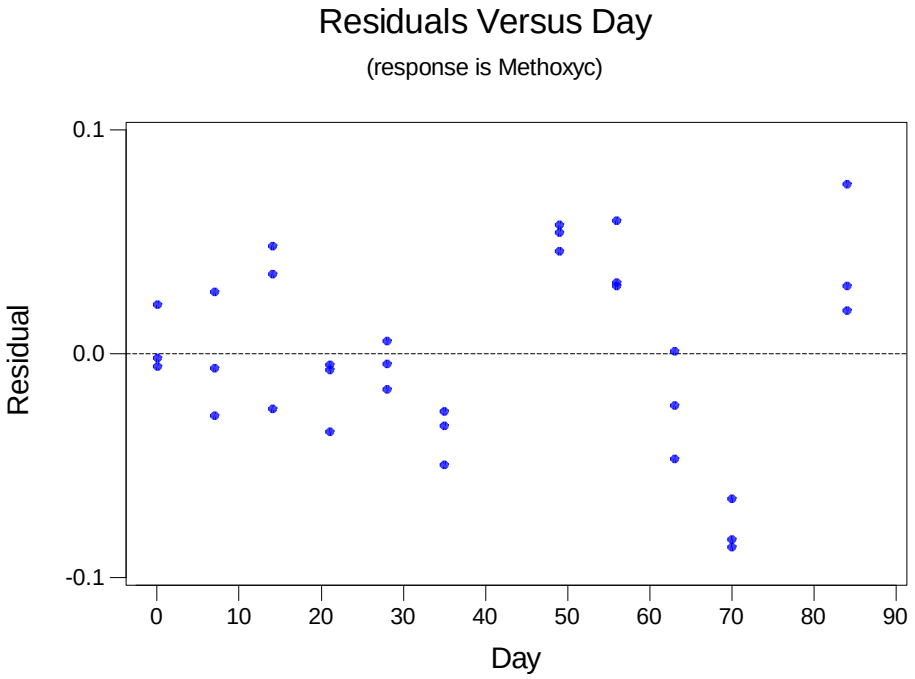
```
The regression equation is
Methoxychlor-5K = 8.44 - 0.00196 Day

Predictor        Coef     SE Coef          T        P
Constant      8.44471     0.01299     650.13    0.000
Day        -0.0019588   0.0002772      -7.07    0.000
S = 0.04180     R-Sq = 61.7%     R-Sq(adj) = 60.5%

Analysis of Variance
Source            DF          SS          MS         F        P
Regression         1    0.087268    0.087268     49.94    0.000
Residual Error    31    0.054171    0.001747
  Lack of Fit      9    0.044193    0.004910     10.83    0.000
  Pure Error      22    0.009978    0.000454
Total             32    0.141440

Unusual Observations
Obs        Day   Methoxyc         Fit      SE Fit    Residual    St Resid
 28       70.0    8.22455     8.30760     0.01130    -0.08305       -2.06R
 29       70.0    8.22122     8.30760     0.01130    -0.08638       -2.15R

R denotes an observation with a large standardized residual
```


US EPA ARCHIVE DOCUMENT

Normplot of Residuals for Methoxychlor



Residuals from Methoxychlor vs Day



US EPA ARCHIVE DOCUMENT

- Power analysis for t-test of slope less than zero

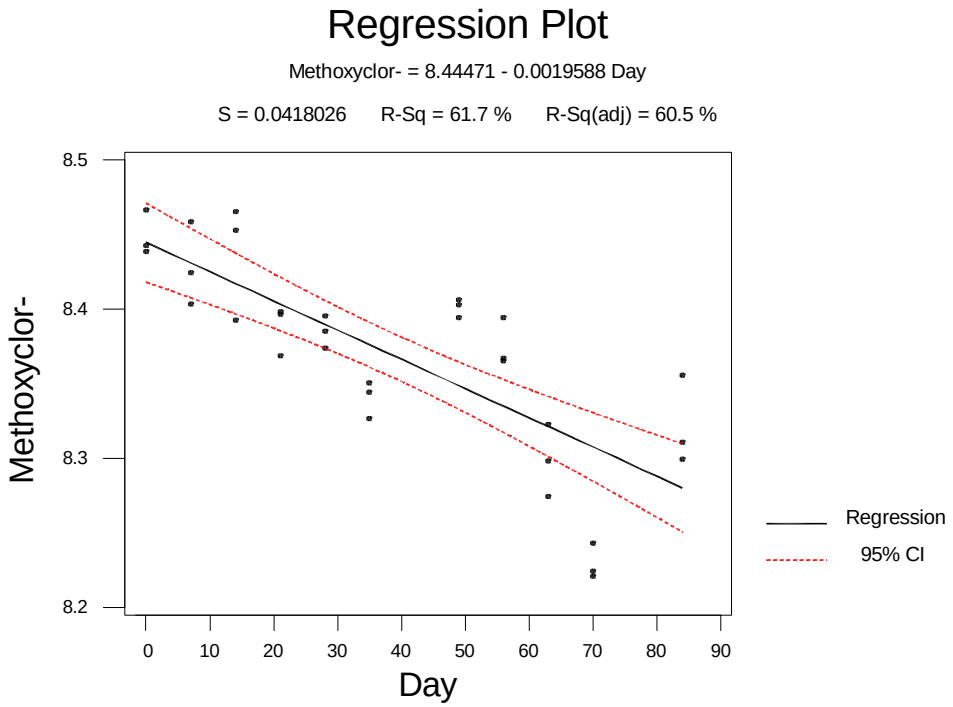
Power and Sample Size

```
1-Sample t Test

Testing mean = null (versus < null)
Calculating power for mean = null + difference
Alpha = 0.05  Sigma = 0.0418026

Sample
  Size   Power  Difference
    31  0.9900     -0.0305
```

- That means we would detect a mean of 8.4867 as significantly less than ln(5000) = 8.5172 or a change of 4850 from 5000 = 3.0% loss.

- Fit 95% confidence bands about the fitted simple linear model

Fitted Line Plot: Methoxychlor- versus Day



- **Conclusion – stable for 1 week from target concentration.**
- **Conclusion – stable for 5 weeks if from average of day 0 concentration (see Excel spreadsheet WA 2-10_WA2-14stability rev 1.xls).**

US EPA ARCHIVE DOCUMENT

WA-2-23-02-01
Statistical Analysis conducted by Valerie Cullinan
Using Minitab Version 13.32, Minitab Inc., 1999.

11/25/2002 11:22:30 AM

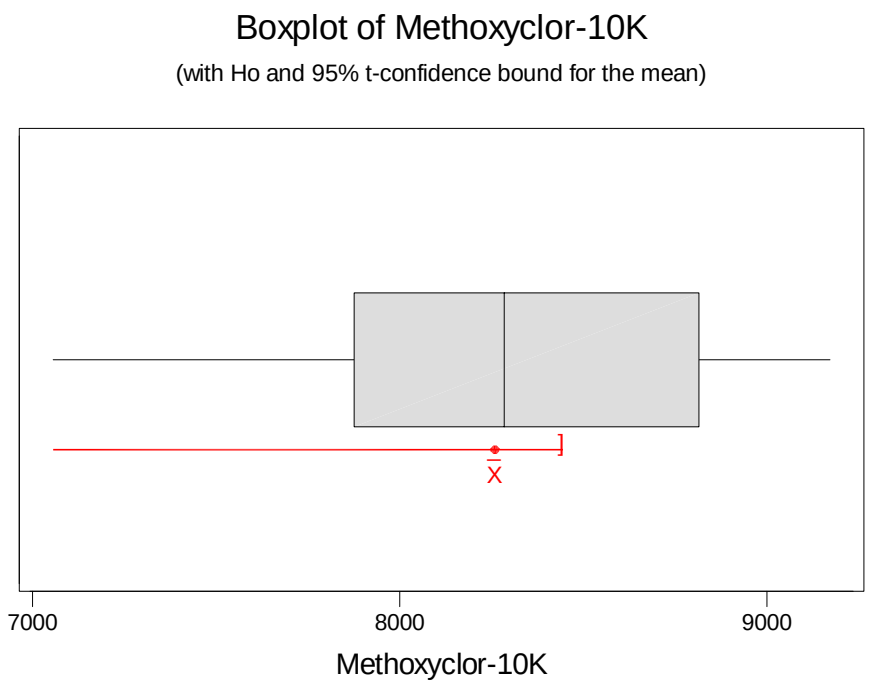
Analysis of Methoxychlor-10k in corn oil

- Test to determine if the data are from a population with mean of 10000.

One-Sample T: Methoxychlor-10K

```
Test of mu = 10000 vs mu < 10000

Variable           N      Mean     StDev   SE Mean
Methoxychlor-     33      8259       630       110

Variable       95.0% Upper Bound        T      P
Methoxychlor-               8445   -15.89  0.000
```

t Boxplot of Methoxychlor-10K



- Nonparametric Test for outlier.

```
Outliers are < Median-3*IQD OR > Median+3*IQD
Boundary for outliers are values <    5469.47  and >    11098.7
No outliers
```

US EPA ARCHIVE DOCUMENT

- Transform data to natural logarithm and conduct regression analysis.

Week	Rep	Ln(Concentration)
0	1	9.1012
0	2	9.1013
0	3	9.1212
7	1	9.0537
7	2	9.1162
7	3	9.0870
14	1	9.0541
14	2	9.0812
14	3	9.0779
21	1	9.1114
21	2	9.1238
21	3	9.1006
28	1	9.0486
28	2	9.0221
28	3	9.0527
35	1	9.0242
35	2	9.0065
35	3	9.0293
49	1	8.9671
49	2	8.9762
49	3	9.0084
56	1	8.9586
56	2	8.9766
56	3	8.9759
63	1	8.9237
63	2	8.9043
63	3	8.9133
70	1	8.8617
70	2	8.8660
70	3	8.8694
84	1	9.0195
84	2	8.9930
84	3	9.0070

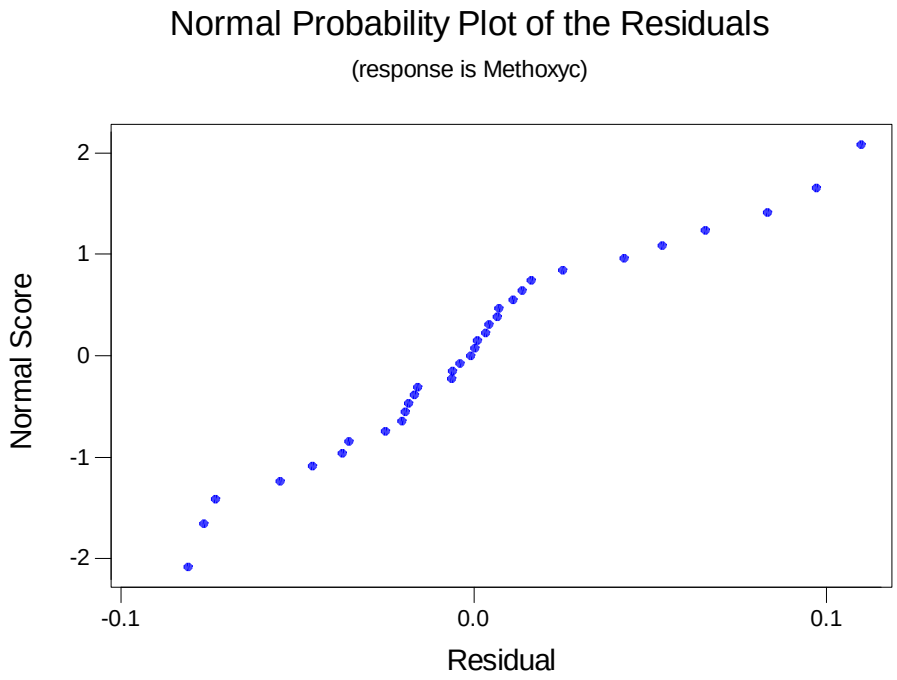
- Conducts Simple Linear Regression

Regression Analysis: Methoxychlor-10K versus Day

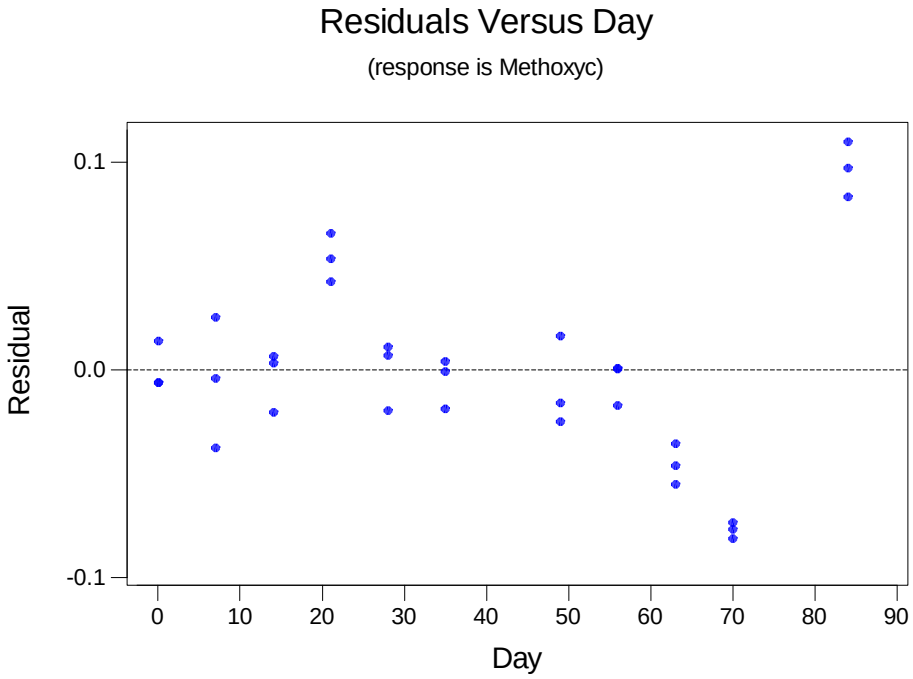
```
The regression equation is
Methoxychlor-10K = 9.11 - 0.00235 Day

Predictor        Coef     SE Coef          T        P
Constant      9.10753     0.01442     631.66    0.000
Day        -0.0023535   0.0003077      -7.65    0.000
S = 0.04640     R-Sq = 65.4%     R-Sq(adj) = 64.2%

Analysis of Variance
Source            DF          SS          MS         F        P
Regression         1     0.12598     0.12598     58.51    0.000
Residual Error    31     0.06675     0.00215
  Lack of Fit      9     0.06127     0.00681     27.33    0.000
  Pure Error      22     0.00548     0.00025
Total             32     0.19273

Unusual Observations
Obs        Day   Methoxyc         Fit      SE Fit    Residual    St Resid
 31       84.0    9.01955     8.90984     0.01608     0.10971        2.52R
 33       84.0    9.00696     8.90984     0.01608     0.09712        2.23R

R denotes an observation with a large standardized residual
```


US EPA ARCHIVE DOCUMENT

Normplot of Residuals for Methoxychlor



Residuals from Methoxychlor vs Day



US EPA ARCHIVE DOCUMENT

- Power analysis for t-test of slope less than zero

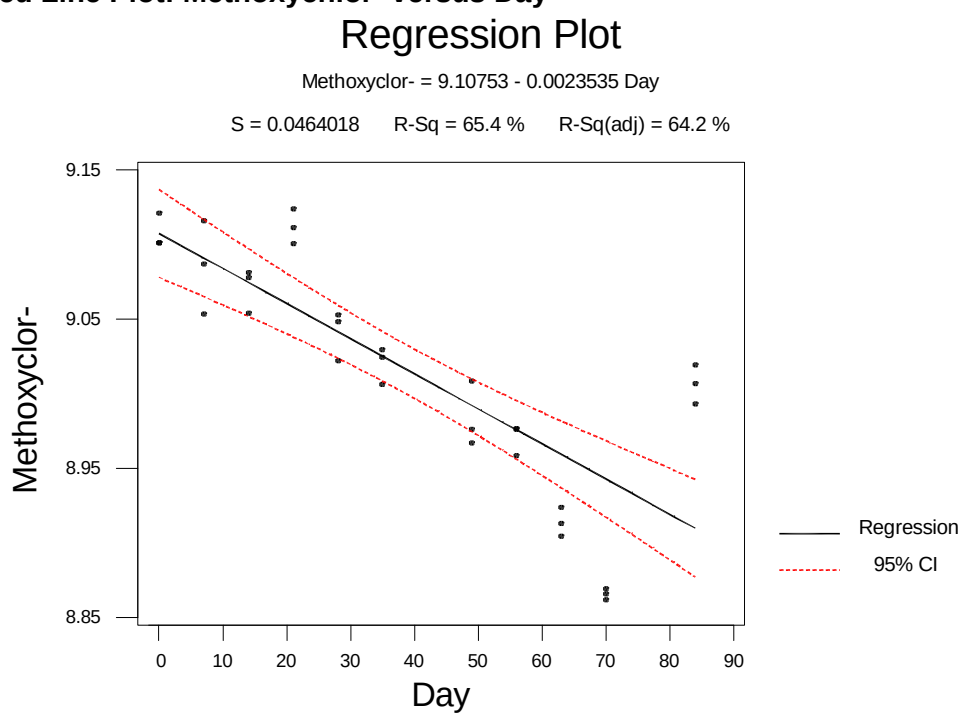
Power and Sample Size

```
1-Sample t Test

Testing mean = null (versus < null)
Calculating power for mean = null + difference
Alpha = 0.05  Sigma = 0.0464018

Sample
  Size   Power  Difference
    31  0.9900     -0.0339
```

- That means we would detect a mean of 9.1764 as significantly less than ln(10000) = 9.2103 or a change of 9667 from 10000 = 3.3% loss.

- Fit 95% confidence bands about the fitted simple linear model

Fitted Line Plot: Methoxychlor- versus Day



- **Conclusion – stable for 0 weeks from target concentration.**
- **Conclusion – stable for 5 weeks if from average of day 0 concentration (see Excel spreadsheet WA 2-10_WA2-14stability rev 1.xls).**

US EPA ARCHIVE DOCUMENT

WA-2-23-02-01
Statistical Analysis conducted by Valerie Cullinan
Using Minitab Version 13.32, Minitab Inc., 1999.

11/25/2002 11:22:30 AM

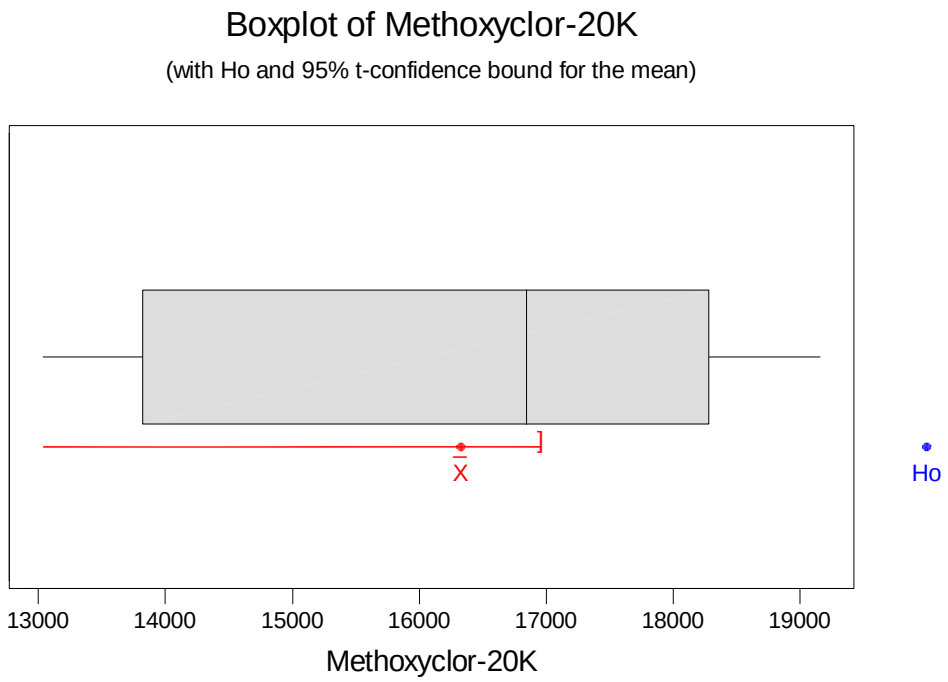
Analysis of Methoxychlor-20k in corn oil

- Test to determine if the data are from a population with mean of 20000.

One-Sample T: Methoxychlor-20K

```
Test of mu = 20000 vs mu < 20000

Variable          N      Mean     StDev   SE Mean
Methoxyclor-     33     16328      2164       377

Variable      95.0% Upper Bound        T      P
Methoxyclor-              16966    -9.75  0.000
```

t Boxplot of Methoxychlor-20K



- Nonparametric Test for outlier.

```
Outliers are < Median-3*IQD OR > Median+3*IQD
Boundary for outliers are values <    3454.31  and >    30236.0
No outliers
```

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- Transform data to natural logarithm and conduct regression analysis.

Week	Rep	Ln(Concentration)
0	1	9.8285
0	2	9.8149
0	3	9.8117
7	1	9.8117
7	2	9.8604
7	3	9.8500
14	1	9.7640
14	2	9.8126
14	3	9.8378
21	1	9.8231
21	2	9.8346
21	3	9.8192
28	1	9.7821
28	2	9.7993
28	3	9.7655
35	1	9.7212
35	2	9.7197
35	3	9.7318
49	1	9.5457
49	2	9.5894
49	3	9.5583
56	1	9.5588
56	2	9.5219
56	3	9.5196
63	1	9.5078
63	2	9.5058
63	3	9.5164
70	1	9.4757
70	2	9.4908
70	3	9.4838
84	1	9.7184
84	2	9.7120
84	3	9.7352

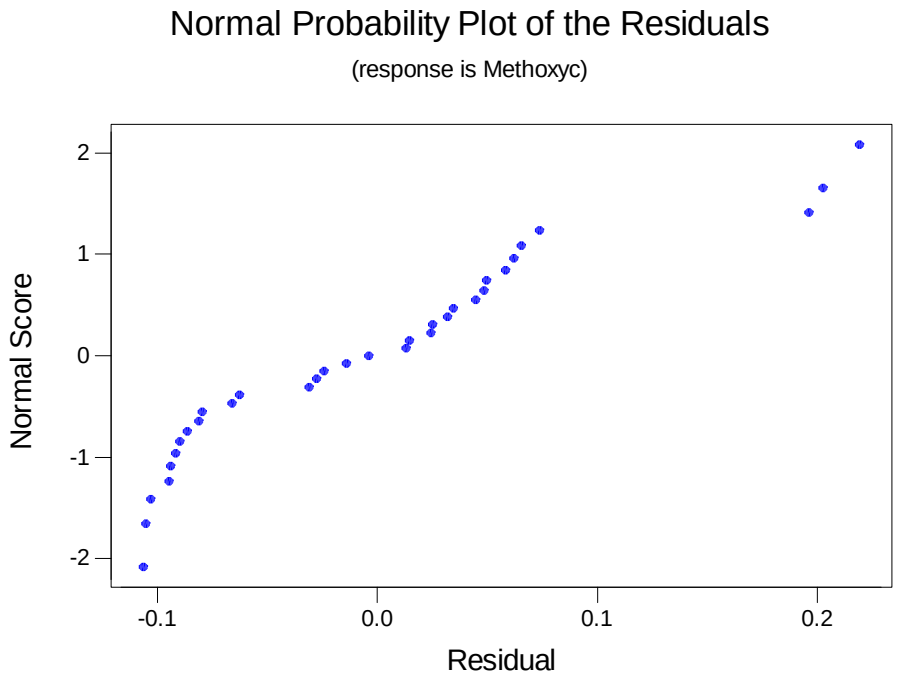
- Conducts Simple Linear Regression

Regression Analysis: Methoxychlor-20K versus Day

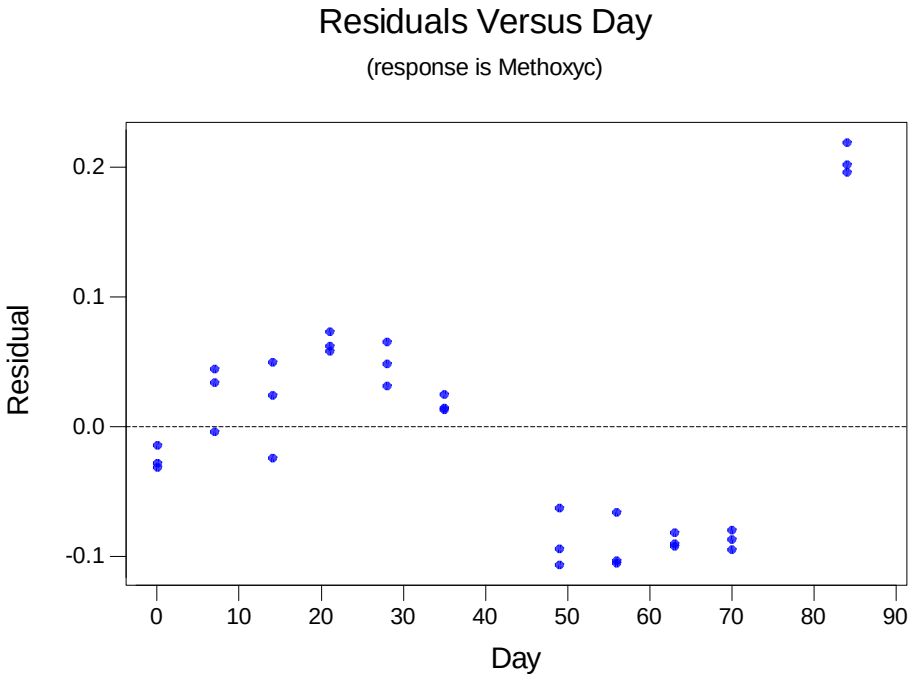
```
The regression equation is
Methoxychlor-20K = 9.84 - 0.00389 Day

Predictor        Coef     SE Coef          T        P
Constant      9.84277     0.02811     350.21    0.000
Day        -0.0038905   0.0005997      -6.49    0.000
S = 0.09045     R-Sq = 57.6%     R-Sq(adj) = 56.2%

Analysis of Variance
Source            DF          SS          MS         F        P
Regression         1     0.34427     0.34427     42.08    0.000
Residual Error    31     0.25361     0.00818
  Lack of Fit      9     0.24609     0.02734     79.97    0.000
  Pure Error      22     0.00752     0.00034
Total             32     0.59788

Unusual Observations
Obs        Day   Methoxyc         Fit      SE Fit    Residual    St Resid
 31       84.0     9.7184      9.5160      0.0313      0.2024        2.39R
 32       84.0     9.7120      9.5160      0.0313      0.1960        2.31R
 33       84.0     9.7352      9.5160      0.0313      0.2192        2.58R
R denotes an observation with a large standardized residual
```


US EPA ARCHIVE DOCUMENT

Normplot of Residuals for Methoxychlor



Residuals from Methoxychlor vs Day



US EPA ARCHIVE DOCUMENT

- Power analysis for t-test of slope less than zero

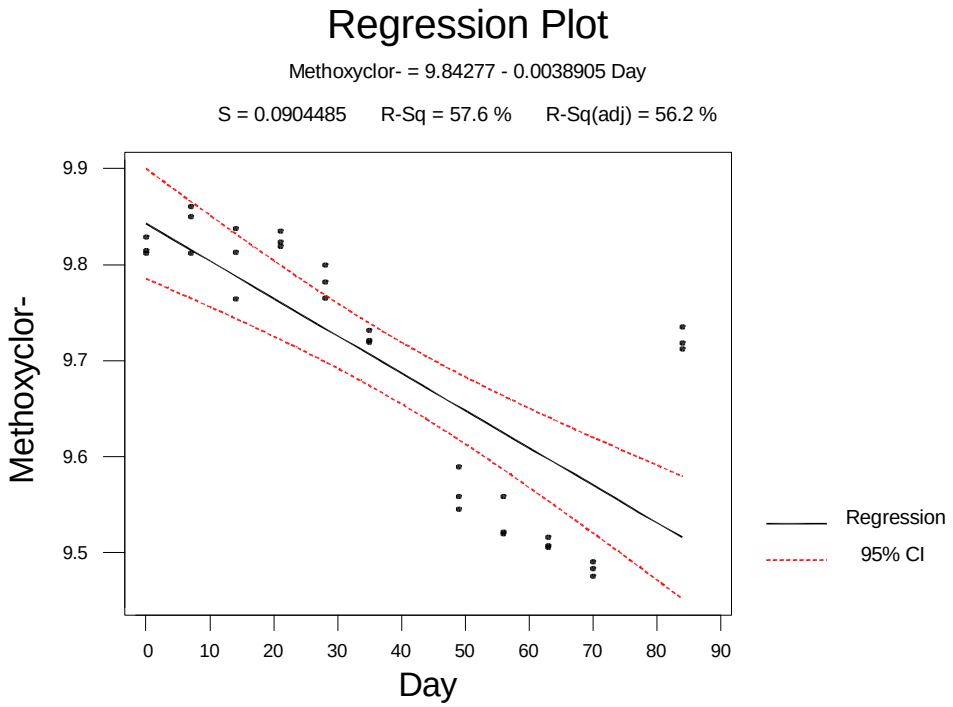
Power and Sample Size

```
1-Sample t Test

Testing mean = null (versus < null)
Calculating power for mean = null + difference
Alpha = 0.05  Sigma = 0.0904485

Sample
  Size   Power  Difference
    31  0.9900     -0.0660
```

- That means we would detect a mean of 9.8375 as significantly less than ln(20000) = 9.9035 or a change of 18723 from 20000 = 6.4% loss.

- Fit 95% confidence bands about the fitted simple linear model

Fitted Line Plot: Methoxychlor- versus Day



- **Conclusion – stable for 1 week from target concentration.**
- **Conclusion – stable for 3 weeks if from average of day 0 concentration (see Excel spreadsheet WA 2-10_WA2-14stability rev 1.xls).**

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APPENDIX E

CHEMISTRY RESULTS
FOR THE ANALYSIS OF IN-LIFE SAMPLES

Chemistry Report for Verification of Formulations and In-Life Sample Results

PROJECT: **EDSP WA 2-23**

PARAMETER: Methoxychlor in-life test solution samples in corn oil

LABORATORY: Battelle Marine Sciences Laboratory
1529 West Sequim Bay Rd.
Sequim, WA 98382

MATRIX: Methoxychlor in corn oil

TEST SOLUTION SAMPLE CUSTODY AND PROCESSING: Test solution samples were prepared by the EDSP Chemical Repository, Sequim, WA using Methoxychlor (CF 1839, Sigma lot # 49H1328, expiration date 6/05) dissolved in Mazola corn oil (corn oil was from containers with the following expiration dates; 6/12/03, 1/1/04, and 4/24/04). A large volume of corn oil was used because many formulations for WA 2-23 were prepared over several months. Formulations were prepared at three concentrations as well as the control. Test concentrations for all replicates and exposures unless noted below; 5 mg/mL, 10 mg/mL and 20 mg/mL. The 5 mg/mL concentration was prepared by dissolving 2.63 g of Methoxychlor in 462 g of corn oil in a pre-cleaned 500 mL amber glass container or 5.25 g in 925 g of corn oil in a one liter container. The 10 and 20 mg/mL concentration were prepared using proportionally greater amounts. Note: the weights used reflect adjustments made for the 95% purity of the Methoxychlor and the density of corn oil.

Formulations were prepared at five different times:
Replicates 1 and 2 – prepared on 1/7/03 and shipped on 1/8/03
Replicate 3- prepared on 1/29/03 and shipped on 1/30/03
Replicate 4- prepared on 2/11/03 and shipped on 2/13/03
Replicate 5- prepared on 2/26/03 and shipped on 2/27/03
Replicate 6- corn oil only shipped on 4/7/03
Replicate 6- three formulations prepared on 4/8/03 and shipped on 4/9/03

The formulations were sampled in triplicate and analyzed to verify that the concentrations were within 90% to 110% of the nominal concentrations. Because Replicates 1 and 2 were prepared at the same time on 1/7/03, only Rep 1 test solutions were analyzed for verification. The concentration determined in the verification analyses ranged from 87% to 108% of the nominal or target concentration (Table 1). Only the low dose (5 mg/mL) of Rep 5 prepared on 2/26/03 was below 90% (87%) and no corrective action was taken.

Unused portions of Rep 2 and Rep 3 formulations were returned to Battelle from RTI after the dosing was completed. These formulations were analyzed and their concentrations, which ranged from 82% to 99% of nominal, are shown in Table 2.

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In-life samples were collected five times (1/13/03, 1/29/03, 2/5/03, 2/12/03, and 2/19/03) by RTI and returned to Battelle for chemical analysis. Table 3 provides results of the in-life samples which ranged from 83% to 101% of the nominal. Of the 15 in-life samples (five sampling times 3 dosing concentrations), five of the samples were below the target range of 90% to 110%, and the nominal recovery for these five samples were 85%, 85%, 83%, 87%, and 89%.

Processing

Test Solution Samples for Concentration Verification Prior to Shipping:

The container was sampled prior to shipment. 1 mL triplicate samples were removed and each placed in a tared 60 mL amber glass bottle. The weight of the sample was determined gravimetrically. A 1 g sub sample was removed, placed in a 30 mL amber glass, ashed vial, and 25 mL of hexane (JT Baker lot number X40E12) was added and the bottle agitated to mix. Then, 0.1 mL sample and 0.02 internal standard, 5a androstane, and 0.88 mL hexane were transferred to an auto sampler vial.

In-life and Returned Container Samples:

In-life and returned containers were analyzed the same way. Some of the returned containers were returned empty, so only containers with sufficient material were analyzed.

The samples were removed from the refrigerator and allowed to warm to room temperature. About 1 mL was sampled and placed in a tared 30 mL amber glass bottle. The weight of the sample was determined gravimetrically. 25 mL of hexane was added and the bottle agitated to mix. Then 0.1ml was transferred to a 1.8 ml vial with 0.02 ml of internal standard solution containing 5a Androstane, and 0.88 mL hexane.

SAMPLE ANALYSIS

The samples were analyzed by GC with a flame ionization detector (FID). The GC was set up with an auto sampler and a 30 m x 0.25 mm, DB-5 capillary column. The temperature program was set to start at 50 ºC, and ramped at 20 ºC/min to a final temperature of 320 ºC. The injection port temperature was set at 270 ºC and the detector temperature at 320 ºC. The auto sampler was set to inject 1 µL of the matrix dilution.

Data Quality Objectives:	Control Limits
Procedural Blank	< 5 x MDL
Blank Spike Recovery	40-120%
Continuing Standard Recovery	75 – 125%

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QC SUMMARY

METHODS:	GC-FID
CALIBRATION:	Calibration was performed using dilutions prepared from standard EDSP Mix 1 (see Appendix C), A through E (a 5-point curve), with a CCV analyzed every 10 samples.
CONTINUING STANDARD RECOVERY:	Percent recovery results for initial and continuing calibration verification samples analyzed with the in-life sample data set ranged from 94 to 108% with a mean recovery of 101%. There were no occurrences of recoveries exceeding the 75-125% acceptability criteria.
BLANK	Two control corn oil formulation samples, returned from RTI, were analyzed for Methoxychlor to verify the concentration in the blank, see Table 2. One sample had no discernable peak and the other was 186 ug/mL, less than 5 times the MDL of 115 ug/mL, the acceptance criterion.
DETECTION LIMIT:	The Methoxychlor detection limit in corn oil was 115 ug/mL as determined by an MDL study.
BLANK SPIKE SAMPLES	Blank spike samples were not analyzed. In this analysis, sampling was performed by taking the sample material from flask through to analysis. Analyzing a spiked sample would be no different than analyzing a CCV.
INTERNAL STANDARD	5a androstane was spiked into each sample and analyzed as the internal standard. Average percent recovery result for 1-8-03 was 90%, for 2/3/03 89%, for 2/5/03 100%, for 2/13/03 100%, for 2/28/03 98%, 3/10/03 106%, for 3/26/03 95%, and for 4/10/03 94%. There were no cases where the percent recovery of the internal standard exceeded the acceptance criteria of 40-120%.
REPLICATE ANALYSIS:	Relative standard deviations (RSD) for the analysis of the triplicate samples for verification of the formulations were in the range of 1% to 8%, Table 1. Replicate samples were not submitted for the in-life sample set.

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TABLE 1: Verification of Methoxychlor Formulations Shipped to RTI

Bottle Code	Nominal Conc (mg/mL)	Preparation Replicate	Preparation Date at MSL	Date Shipped to RTI	Sample Replicate	Analysis Date	Measured Conc (ug/mL)	Mean	RSD	**Mean Percent Recovery of Nominal**
2-23-A	0	Rep 1	1/7/03	1/8/03		1/8/03	115 U			
2-23-B	5	Rep 1	1/7/03	1/8/03	R-1	1/8/03	5619			
2-23-B	5	Rep 1	1/7/03	1/8/03	R-2	1/8/03	5118			
2-23-B	5	Rep 1	1/7/03	1/8/03	R-3	1/8/03	4953	5230	7%	**105%**
2-23-C	10	Rep 1	1/7/03	1/8/03	R-1	1/8/03	10469			
2-23-C	10	Rep 1	1/7/03	1/8/03	R-2	1/8/03	9708			
2-23-C	10	Rep 1	1/7/03	1/8/03	R-3	1/8/03	9671	9949	5%	**99%**
2-23-D	20	Rep 1	1/7/03	1/8/03	R-1	1/8/03	19506			
2-23-D	20	Rep 1	1/7/03	1/8/03	R-2	1/8/03	19516			
2-23-D	20	Rep 1	1/7/03	1/8/03	R-3	1/8/03	20170	19731	2%	**99%**
2-23-A	0	Rep 3	1/29/03	1/30/03		2/3/03	115 U			
2-23-B	5	Rep 3	1/29/03	1/30/03	R-1	2/3/03	5053			
2-23-B	5	Rep 3	1/29/03	1/30/03	R-2	2/3/03	5231			
2-23-B	5	Rep 3	1/29/03	1/30/03	R-3	2/3/03	5621	5302	5%	**106%**
2-23-C	10	Rep 3	1/29/03	1/30/03	R-1	2/3/03	11100			
2-23-C	10	Rep 3	1/29/03	1/30/03	R-2	2/3/03	9735			
2-23-C	10	Rep 3	1/29/03	1/30/03	R-3	2/3/03	11210	10682	8%	**107%**
2-23-D	20	Rep 3	1/29/03	1/30/03	R-1	2/3/03	21263			
2-23-D	20	Rep 3	1/29/03	1/30/03	R-2	2/3/03	20161			
2-23-D	20	Rep 3	1/29/03	1/30/03	R-3	2/3/03	20885	20770	3%	**104%**
2-23-A	0	Rep 4	2/11/03	2/13/03		2/13/03	115 U			
2-23-B	5	Rep 4	2/11/03	2/13/03	R-1	2/13/03	4595			
2-23-B	5	Rep 4	2/11/03	2/13/03	R-2	2/13/03	4721			
2-23-B	5	Rep 4	2/11/03	2/13/03	R-3	2/13/03	4540	4619	2%	**92%**
2-23-C	10	Rep 4	2/11/03	2/13/03	R-1	2/13/03	9366			
2-23-C	10	Rep 4	2/11/03	2/13/03	R-2	2/13/03	9698			
2-23-C	10	Rep 4	2/11/03	2/13/03	R-3	2/13/03	9556	9540	2%	**95%**
2-23-D	20	Rep 4	2/11/03	2/13/03	R-1	2/13/03	18149			
2-23-D	20	Rep 4	2/11/03	2/13/03	R-2	2/13/03	18604			
2-23-D	20	Rep 4	2/11/03	2/13/03	R-3	2/13/03	17811	18188	2%	**91%**
2-23-A	0	Rep 5	2/26/03	2/27/03		2/28/03	115 U			
2-23-B	5	Rep 5	2/26/03	2/27/03	R-1	2/28/03	4311			
2-23-B	5	Rep 5	2/26/03	2/27/03	R-2	2/28/03	4338			
2-23-B	5	Rep 5	2/26/03	2/27/03	R-3	2/28/03	4364	4337	1%	**87%**
2-23-C	10	Rep 5	2/26/03	2/27/03	R-1	2/28/03	9661			
2-23-C	10	Rep 5	2/26/03	2/27/03	R-2	2/28/03	10334			
2-23-C	10	Rep 5	2/26/03	2/27/03	R-3	2/28/03	9458	9818	5%	**98%**
2-23-D	20	Rep 5	2/26/03	2/27/03	R-1	2/28/03	18953			
2-23-D	20	Rep 5	2/26/03	2/27/03	R-2	2/28/03	19783			
2-23-D	20	Rep 5	2/26/03	2/27/03	R-3	2/28/03	19235	19324	2%	**97%**
2-23-A	0	Rep 6	4/7/03	4/7/03		4/11/03	115 U			
2-23-B	5	Rep 6	4/8/03	4/9/03	R-1	4/11/03	5639			
2-23-B	5	Rep 6	4/8/03	4/9/03	R-2	4/11/03	5273			
2-23-B	5	Rep 6	4/8/03	4/9/03	R-3	4/11/03	5281	5398	4%	**108%**
2-23-C	10	Rep 6	4/8/03	4/9/03	R-1	4/11/03	10199			
2-23-C	10	Rep 6	4/8/03	4/9/03	R-2	4/11/03	10357			
2-23-C	10	Rep 6	4/8/03	4/9/03	R-3	4/11/03	10152	10236	1%	**102%**
2-23-D	20	Rep 6	4/8/03	4/9/03	R-1	4/11/03	18448			
2-23-D	20	Rep 6	4/8/03	4/9/03	R-2	4/11/03	19970			
2-23-D	20	Rep 6	4/8/03	4/9/03	R-3	4/11/03	19853	19424	4%	**97%**
2-23-B	5	Rep 6	4/8/03	4/9/03	Verification		5304	NA	NA	**NA**

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Table 2. Methoxychlor Concentrations in Formulations Returned to Battelle from RTI after Dosing Formulation Prepared

Bottle Code	Nominal Conc (mg/mL)	Preparation Replicate	Preparation Date at MSL	Date Shipped to RTI	Analysis Date	Measured Conc (ug/mL)	Percent Recovery of Nominal
2-23-A	0	Rep 2	1/7/03	1/8/03	2/6/03	**115 U**	
2-23-B	5	Rep 2	1/7/03	1/8/03	2/6/03	**4268**	**85%**
2-23-C	10	Rep 2	1/7/03	1/8/03	2/6/03	**8932**	**89%**
2-23-D	20	Rep 2	1/7/03	1/8/03	2/6/03	**17522**	**88%**
2-23-A	0	Rep 3	1/29/03	1/30/03	3/26/03	**186**	
2-23-B	5	Rep 3	1/29/03	1/30/03	3/26/03	**4957**	**99%**
2-23-C	10	Rep 3	1/29/03	1/30/03	3/26/03	**9132**	**91%**
2-23-D	20	Rep 3	1/29/03	1/30/03	3/26/03	**16423**	**82%**

Table 3. In-life Sample Methoxychlor Formulation Concentrations

Date Sample Collected	Date Sample Received	Date Sample Analyzed	Nominal Conc. (mg/mL)	Sample ID Number	Replicate	Dosing Period	Values (ug/mL)	Percent Recovery of Nominal
1/13/03	2/5/03	2/6/03	5	2-23-B	Rep 1	GESTATIONAL DAY 6	4447	89%
1/29/03	2/5/03	2/6/03	5	2-23-B	Rep 1	POSTNATAL DAY 0	4573	91%
2/5/03	2/28/03	3/26/03	5	2-23-B	Rep 3	POSTNATAL DAY 7	5035	101%
2/12/03	2/28/03	3/26/03	5	2-23-B	Rep 3	POSTNATAL DAY 14	4922	98%
2/19/03	2/28/03	3/26/03	5	2-23-B	Rep 3	POSTNATAL DAY 21	4912	98%
1/13/03	2/5/03	2/6/03	10	2-23-C	Rep 1	GESTATIONAL DAY 6	9290	93%
1/29/03	2/5/03	2/6/03	10	2-23-C	Rep 1	POSTNATAL DAY 0	9103	91%
2/5/03	2/28/03	3/26/03	10	2-23-C	Rep 3	POSTNATAL DAY 7	9387	94%
2/12/03	2/28/03	3/26/03	10	2-23-C	Rep 3	POSTNATAL DAY 14	8529	85%
2/19/03	2/28/03	3/26/03	10	2-23-C	Rep 3	POSTNATAL DAY 21	9949	99%
1/13/03	2/5/03	2/6/03	20	2-23-D	Rep 1	GESTATIONAL DAY 6	17382	87%
1/29/03	2/5/03	2/6/03	20	2-23-D	Rep 1	POSTNATAL DAY 0	18045	90%
2/5/03	2/28/03	3/26/03	20	2-23-D	Rep 3	POSTNATAL DAY 7	18194	91%
2/12/03	2/28/03	3/26/03	20	2-23-D	Rep 3	POSTNATAL DAY 14	16651	83%
2/19/03	2/28/03	3/26/03	20	2-23-D	Rep 3	POSTNATAL DAY 21	16926	85%

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APPENDIX F

DEVIATIONS

US EPA ARCHIVE DOCUMENT

ENDOCRINE DISRUPTOR SCREENING PROGRAM DEVIATION FORM

STUDY NUMBER: WA 2-23		DATE: 10/30/03
DEVIATION NUMBER: WA 2-23-D-001, Methoxychlor in corn oil		WAL/Study DIRECTOR: Michael Blanton/Eric Crecelius
NOTEBOOK NUMBER: NA		
TITLE OF STUDY: WA 2-23		
QAPP/PROTOCOL ID:		

DEVIATION RELATING TO:

[ ]	QAPP	[ ]	QMP	[ ]	Protocol
[ ]	SOP	[ ]	Method	[X]	Miscellaneous Documentation

ORIGINAL DOCUMENT SPECIFICATIONS: The protocol for WA 2-23 does not provide holding times for analysis of in-life samples. The stability of formulations was determined to be adequate for the period of time that animals would be dosed.

DEVIATION: In-life samples were not analyzed within the stability time determined during the testing of the stability of the formulation.

REASON/IMPACT: No impact. The formulations were shown to be within the acceptable target range based on established preparation procedures and were used within the known stability time periods determined for each formulation.
PROPOSED CORRECTIVE ACTION AND SCHEDULE FOR COMPLETION: No corrective action required beyond this documentation.

ACTIONS TO PREVENT RECURRENCE: Upper management will review testing schedules for return shipments and analysis.

Approval:

Michael Blanton, WAL — Date 11/3/03

Eric Crecelius, Study Director, Chemical Repository — Date 11/3/03

Deborah Coffey, MSL QA Manager — Date 11/3/03

Richard Ecker, MSL Laboratory Director — Date 11/3/03

David Houchens, EDSP Program Management — Date 10/31/03

Terri Pollock, EDSP Battelle QAM — Date 10-31-03

US EPA ARCHIVE DOCUMENT

Deviation Documentation Form

Project No. EDSP WA 3-2/2-23
Deviation No. WA 2-23-02-01-D-001
Project Manager: Eric Crecelius

EDSP WA 2-23 and the EDSP Chemical Repository

Entered by: Eric Crecelius Date: 4/17/03

The following information is (check one)
[x] a miscellaneous documentation
[ ] a deviation from Protocol, Work Plan or QA Plan (give title)

[ ] a deviation from SOP
(give number and title)

Description: Battelle was notified by RTI on 4/8/03 that additional formulation was needed because the rats had grown larger than anticipated. Battelle prepared additional formulations on 4/8/03 and shipped the formulations of Methoxychlor in corn oil on 4/9/03 to RTI. Splits of the formulations were retained at Sequim and were analyzed for verification of the concentrations. When Battelle, analytically verified the concentrations of these split samples, the results indicated that the bottles WA 2-23-B and WA 2-23-D may have been reversed or that the chemistry splits were mislabeled. To resolve this issue, a sample of the shipped formulations (5 mL of WA 2-23-B rep 6) was returned from RTI to Battelle for analysis, which verified that the bottles shipped to RTI were correctly labeled and the labels of the split samples retained for analysis had been reversed.

Corrective Action: No corrective action.

Action to Prevent Recurrence: In the future management will schedule analysis to be completed before formulations are shipped.

Impact on Project: No impact.

APPROVED BY: E Crecelius 4/17/03

Eric Crecelius, Study Manager or Study Director — Date

File in project notebook or study archive
Send a copy to the MSL QA Officer

US EPA ARCHIVE DOCUMENT

APPENDIX IV

HISTOPAHTOLOGY REPORT

VALIDATION OF THE *IN UTERO/* LACTATIONAL EXPOSURE SCREENING PROTOCOL WITH METHOXYCHLOR

65U-08055.001.017

EPL PROJECT NO. 237-005

PATHOLOGY REPORT

Submitted to

Research Triangle Institute
P.O. Box 12194
Research Triangle Park, NC 27709

Submitted by

Experimental Pathology Laboratories, Inc.
P.O. Box 12766
Research Triangle Park, NC 27709

January 14, 2004

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Validation of the In Utero/Lactational Exposure Screening Protocol with Methoxychlor

Client Study: RTI Protocol No. RTI-839; Rt02-ED04; 65U-08055.001.017

EPL Project Coordinator: Dr. John Curtis Seely

EPL Project Number: 237-005

EPL Pathologist: Dr. John Curtis Seely

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	April 4, 2003	April 4, 2003
Project Setup	April 14, 2003; April 30, 2003	April 14, 2003; April 30, 2003
Histology Setup	April 18, 2003; May 1, 2003	April 18, 2003; May 1, 2003
Data Review	May 20. 2003; May 22, 2003; May 27, 2003; May 28, 2003; May 30, 2003; June 3, 2003	May 20. 2003; May 22, 2003; May 27, 2003; May 28, 2003; May 30, 2003; June 3, 2003
Phase/Data Review	April 16, 2003; April 18, 2003	April 16, 2003; April 18, 2003
Draft Report	November 13 & 14, 2003	November 14, 2003
Final Report	January 14, 2004	January 14, 2004

Date Reported to Study Director/Management: December 3, 2004; January 14, 2004; November 29, 2005

Date of last quarterly facility inspection: October 2005

Jane J. Hollingsworth
EPL Quality Assurance Unit

November 29, 2005
Date

Form No. 6-2 (09/10/99)

TABLE OF CONTENTS

	Page
INTRODUCTION	1
SUMMARY	1
DESIGN OF STUDY	2
RESULTS	4
REFERENCES	9
F1 Undosed	
Pubertal Males and Females	
SUMMARY INCIDENCE TABLES	10
HISTOPATHOLOGY INCIDENCE TABLES	12
CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES	24
F1 Dosed	
Pubertal Males and Females	
SUMMARY INCIDENCE TABLES	32
HISTOPATHOLOGY INCIDENCE TABLES	34
CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES	46
F1 Uterotrophic Cohort	
Females	
SUMMARY INCIDENCE TABLES	53
HISTOPATHOLOGY INCIDENCE TABLES	54
QUALITY ASSURANCE CERTIFICATION	56

VALIDATION OF THE *IN UTERO/* LACTATIONAL EXPOSURE SCREENING PROTOCOL WITH METHOXYCHLOR

65U-08055.001.017

EPL PROJECT NO. 237-005

NARRATIVE SUMMARY

INTRODUCTION

The objective of this study was to detect reproductive and developmental effects in male and female rat offspring mediated by alterations in the Estrogen, Androgen, and Thyroid (EAT) signaling pathways, resulting from exposure to the dam during gestation and lactation or from direct exposure to the offspring from weaning through puberty. The test chemical selected for this study was Methoxychlor (MXC).

For both the F1 male and female pubertal cohorts, the pituitary and thyroids were examined microscopically in addition to the testes, epididymides, uterus, and ovaries. For the F1 female uterotrophic cohorts, only the uteri were examined microscopically.

SUMMARY

Administration of MXC by oral gavage to CD® (Sprague-Dawley) F1 male and female pubertal undosed and dosed cohorts or by subcutaneous (SC) injection to female uterotrophic cohorts, under the conditions of this study, was associated with the following histopathologic changes:

1. The presence of ovarian hypoplasia in the mid-and high-dose female undosed and dosed pubertal cohorts. Several follicle cysts were also noted in these animals.
2. The increased incidence of uterine epithelial hyperplasia in the mid-and high-dose female undosed and dosed pubertal cohorts. In addition, several cases of squamous metaplasia and/or epithelial degeneration were also noted in these animals.

DESIGN OF THE STUDY

MXC was dosed by oral gavage to F0 maternal animals from gd 6 through pnd 21 and by oral gavage to the dosed F1 male and female pubertal cohorts (pnd 21-42 for females, pnd 42-70 for males). Undosed F1 male and female pubertal cohorts were exposed to MXC only from gd 6 through pnd 21. MXC was also administered by subcutaneous (SC) injection on pnd 21-24 to the female F1 uterotrophic cohort. The exact study conditions are outlined in the study protocol (RTI Master Protocol No.: RTI-839).

The study design and target dose levels are presented in Table 1.

Table 1 – Study Design and Target Doses

	Group Number			
	1[a]	**2**	**3**	**4**
F0 Females				
No.	15	15	15	15
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	gavage	gavage	gavage	gavage
F1 Pubertal Females				
No.	≥10	≥10	≥10	≥10
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	gavage	gavage	gavage	gavage
F1 Pubertal Males				
No.	≥10	≥10	≥10	≥10
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	gavage	gavage	gavage	gavage
F1 Uterotrophic Cohort				
No.	≥10	≥10	≥10	≥10
Dose (mg/kg/day)	0	25.0	50.0	100.0
Concentration (mg/ml)	0	5.0	10.0	20.0
Dose Volume (ml/kg)	5	5	5	5
Route	sc injection	sc injection	sc injection	sc injection

[a] Corn oil, vehicle control

Individual treatment groups were given unique five digit codes that are presented in Table 2.

Table 2 – Treatment Group Designations

Dose Group (mg/kg)	Code
0	93766
25.0	66560
50.0	18661
100.0	79638

For F1 females, the pituitary, ovaries, uterus, and thyroids with attached portion of trachea were dissected out. The ovaries and uterus were fixed in Bouin's solution for 24 hours and stored in 70% alcohol while the thyroids and pituitary were fixed in 10% neutral buffered formalin.

For F1 males, the testes, epididymides, pituitary, and thyroids with attached portion of trachea were dissected out. The testes and epididymides were fixed in Bouin's solution for 24 hours and stored in 70% alcohol while the thyroids and pituitary were fixed in 10% neutral buffered formalin.

Selected tissues were weighed either prior to fixation or following fixation. The thyroids were weighed post-fixed by EPL. All tissues were trimmed, embedded in paraffin, sectioned and stained with Hematoxylin and Eosin (H&E).

Histopathological examination of selected organs was conducted on the protocol-required tissues. The protocol-required tissues were: F1 male pubertal cohort – testis, epididymis, pituitary and thyroids; F1 female pubertal cohort – ovaries, uterus, pituitary and thyroids; F1 female uterotrophic cohort – uterus only.

The gross and histopathologic data were entered in the Experimental Pathology Laboratories, Inc. Computerized Pathology Reporting System. Each lesion was graded according to a four-grade severity scale (1-4). Developmental Malformation, Pars Nervosa" of the pituitary was designated only as "Present".

RESULTS

The individual animal and group summary data for each exposure period are presented by dose and group in the Histopathology Incidence Table (HIT) and the Summary Incidence Tables (SIT). Gross necropsy findings were correlated to the microscopic findings, whenever possible. These findings are presented in the section "Correlation of Gross and Microscopic Findings Tables".

A limited number of histopathologic changes were observed during the study which did not appear to be related to chemical administration and can be seen in this strain and age of rat.

Biologically-significant organ weight changes which were related to histological changes were limited to the relative and adjusted ovarian weight decreases in both the mid- and high-dose F1 pubertal undosed and dosed animals. Ovary weights were also decreased in the uterotrophic females, but ovaries were not examined in these animals. No changes in the uterine weights were apparent in the uterotrophic animals.

Treatment-related histologic changes were not observed in the undosed or dosed F1 male pubertal animals.

TREATMENT-RELATED FINDINGS IN F1 PUBERTAL FEMALES

Ovary

Administration of MXC was associated with the presence of ovarian hypoplasia and cystic follicles in both the undosed and dosed animals.

Ovarian hypoplasia was characterized by a significant or complete absence of corpora lutea (CL's) accompanied by a reduction or absence of the large pre-ovulatory follicles (Graffian Follicles). Minimal hypoplasia was used when a significant reduction in CL's were observed. Mild ovarian hypoplasia had no CL's and seemingly fewer large follicles while moderate hypoplasia was used when both CL's and large follicles were not present. This appearance suggested that some inhibition or delay of follicle development (maturation) and/or ovulation had occurred. Hypoplasia was used in this context since evidence of complete ovarian maturity and subsequent atrophy was not observed (Davis et al., 1999).

Cystic follicles were also present in several of the animals with ovarian hypoplasia. These follicles were slightly enlarged and lined by only a thin layer of granulosa cells.

The incidence and severity of ovarian hypoplasia and follicle cysts in the F1 undosed and dosed females are presented in Table 3.

Table 3 – Incidence and Severity of Ovarian Hypoplasia and Follicle Cysts

F1 Undosed Females

Dose (mg/kg)	0	25	50	100
Animals (No. Examined)	(23)	(18)	(23)	(16)
Hypoplasia	0	0	11	2
Minimal	0	0	4	0
Mild	0	0	4	2
Moderate	0	0	3	0
Cyst, Follicle	0	0	1	1
Minimal	0	0	1	1

F1 Dosed Females

Dose (mg/kg)	0	25	50	100
Animals (No. Examined)	(23)	(18)	(22)	(16)
Hypoplasia	0	0	13	6
Minimal	0	0	1	1
Mild	0	0	11	5
Moderate	0	0	1	0
Cyst, Follicle	0	0	2	1
Minimal	0	0	1	0
Mild	0	0	1	1

Treatment-related lesions were observed only in the 50 and 100 mg/kg dosed groups. The "No-Effect Level" (NOEL) was 25 mg/kg for both the undosed and dosed groups. The incidence of ovarian hypoplasia seemed to be higher in the dosed F1 animals.

Uterus

Administration of MXC was associated with the presence of epithelial hyperplasia and, on occasion, degeneration and squamous metaplasia of the uterine epithelium in both the undosed and dosed animals.

In most control and treated animals, the uterine surface epithelial lining was characterized by having a single layer of columnar cells with a cytoplasmic

to nuclear ratio of around 1:5. The height and presence of vacuolar to necrotic changes and the presence of inflammatory cells depended upon the stage of the estrous (reproductive) cycle. In addition, mitotic figures were common in the diestrus portion of the cycle (Yuan and Foley, 2002).

Some animals had changes of the uterine surface epithelium that were diagnosed as epithelial hyperplasia. Although one low-dose animal was diagnosed with hyperplasia, the incidence was clearly increased in the mid- and high-dosed animals. In these cases, the lining epithelium was either focally or diffusely affected. In focal lesions, areas of hyperplasia were composed of multilayered cells which were more irregular in shape. In the more common diffuse change, the columnar cells appeared taller and more numerous recognized by nuclear crowding. Furthermore, in the diffuse change, the epithelial cells appeared to have more cytoplasm (hypertrophy) which appeared lightly basophilic. Mitotic figures were occasionally noted, however, vacuolar to necrotic changes normally associated with the estrous cycle were not observed.

Most cases of epithelial hyperplasia were diagnosed as minimal which was a change barely detectable. Mild cases consisted of small papillary projections within the hyperplastic epithelium. No moderate or marked cases were observed.

On occasion, large clear vacuoles were noted in the hyperplastic epithelium which were clearly different in appearance to the smaller vacuoles preceding epithelial necrosis associated with the estrous cycle. This change was diagnosed as degeneration as these vacuoles were often apparent in areas which appeared focally hyperplastic with increased cellular disorganization. In several animals, focal hyperplastic areas were composed of flattened cells several layers thick with increased cytoplasmic eosinophilia compatible with non-keratinizing squamous metaplasia.

Most cases of epithelial hyperplasia were present in animals with ovarian hypoplasia suggesting a hormonal imbalance as a possible mechanism of the changes noted. However, not all ovaries with hypoplasia had uterine epithelial changes.

The incidence and severity of uterine epithelial hyperplasia, degeneration and squamous metaplasia in the F1 undosed and dosed females are presented in Table 4.

Table 4 – Incidence and Severity of Uterine Lesions

F1 Undosed Females

Dose (mg/kg)	0	25	50	100
Animals (No. Examined)	(23)	(18)	(23)	(14)
Hyperplasia, Epithelium	0	0	9	6
Minimal	0	0	6	6
Mild	0	0	3	0
Metaplasia, Squamous, Epithelium	0	0	2	0
Minimal	0	0	2	0

F1 Dosed Females

Dose (mg/kg)	0	25	50	100
Animals (No. Examined)	(23)	(17)	(20)	(16)
Hyperplasia, Epithelium	0	1	6	5
Minimal	0	1	6	5
Mild	0	0	0	0
Metaplasia, Squamous, Epithelium	0	0	2	1
Minimal	0	0	1	1
Mild	0	0	1	0
Degeneration, Epithelium	0	0	2	2
Minimal	0	0	2	1
Mild	0	0	0	1

Treatment-related lesions were observed only in the 50 and 100 mg/kg dose groups. The NOEL was 25 mg/kg for both the undosed and dosed groups. The incidence of the uterine changes seemed to be slightly higher in the dosed animals.

Uterotrophic Component

Changes associated with MXC exposure were not observed in any of the uteri examined. For the most part, uterine sections from these animals, control and treated, were smaller than those examined in the F1 pubertal component of the study. The surface epithelial lining was mainly composed of cuboidal cells

with occasional mitotic figures. Few endometrial glands were present and the endometrial stroma was unremarkable. Overall, these uterine sections were compatible with an immature appearance with little to no histological changes associated with estrous cyclicity.

John Curtis Seely, DVM

JOHN CURTIS SEELY, D.V.M.
Diplomate, ACVP
Senior Pathologist

January 14, 2004
Date

REFERENCES

Davis BJ, et al. Ovary, Oviduct, Uterus, Cervix and Vagina. In. Pathology of the Mouse. Maronpot RR (ed.). Cache River Press, Chapter 16, 1999.

Yuan Y-D and Foley GL (2002). Female Reproductive System. In. Handbook of Toxicologic Pathology (2nd Ed). Haschek WM, Rousseaux CG, and Wallig MA (Eds). Academic Press, Chapter 43.

F1 UNDOSED
PUBERTAL MALES AND FEMALES

SUMMARY INCIDENCE TABLES

SUMMARY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

	GROUP 93766U	GROUP 66560U	GROUP 18661U	GROUP 79638U		
EPIDIDYMIS (NO. EXAMINED)	(23)	(17)	(24)	(18)		
Exfoliated Germ Cells, Lumen	2		1			
PITUITARY (NO. EXAMINED)	(23)	(17)	(24)	(18)		
Cyst, Pars Distalis		1		1		
Developmental Malformation,						
Pars Nervosa		1				
TESTIS (NO. EXAMINED)	(23)	(17)	(23)	(18)		
Degeneration, Seminiferous						
Tubule	4		1	1		
Dilatation, Lumen,						
Seminiferous Tubule			1			
THYROID (NO. EXAMINED)	(22)	(17)	(23)	(17)		

SUMMARY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

	GROUP 93766U	GROUP 66560U	GROUP 18661U	GROUP 79638U		
OVARY (NO. EXAMINED)	(23)	(18)	(23)	(16)		
Cyst, Follicle			1	1		
Hypoplasia			11	2		
PITUITARY (NO. EXAMINED)	(23)	(18)	(22)	(16)		
Cyst, Pars Distalis						
Developmental Malformation, Pars Nervosa			1			
THYROID (NO. EXAMINED)	(23)	(18)	(23)	(16)		
UTERUS (NO. EXAMINED)	(23)	(18)	(23)	(14)		
Degeneration, Epithelium						
Dilatation, Lumen, Bilateral	1		1			
Dilatation, Lumen, Unilateral				1		
Hyperplasia, Epithelium			9	6		
Metaplasia, Squamous, Epithelium			2			

HISTOPATHOLOGY INCIDENCE TABLES

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
93766U

ANIMAL	102	103	111	112	120	121	193	194	202	203	211	212	229	230	353	354	362	363	371	372
EPIDIDYMIS	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Exfoliated Germ Cells, Lumen							2	2												
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X		X				X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule				1		1	2	2												
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

GROUP
93766U

RTI-839
F1 Sacrifice
Male Rat

ANIMAL	380	381	490
EPIDIDYMIS	X	X	X
Exfoliated Germ Cells, Lumen			
PITUITARY	X	X	X
Cyst, Pars Distalis			
Developmental Malformation, Pars Nervosa			
TESTIS	X	X	X
Degeneration, Seminiferous Tubule			
Dilatation, Lumen, Seminiferous Tubule			
THYROID	X	X	X

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
66560U

ANIMAL	128	135	136	238	239	247	248	255	256	264	265	393	394	402	403	411	412			
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X			
Cyst, Pars Distalis							1													
Developmental Malformation, Pars Nervosa					P															
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Degeneration, Seminiferous Tubule																				
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
18661U

ANIMAL	152	153	161	162	169	170	177	178	184	185	318	319	327	328	336	337	344	345	465	466
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
Exfoliated Germ Cells, Lumen																1				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X		X	N	X	X	X	X	X	X	X	X	X		X	X	X	X
Degeneration, Seminiferous Tubule				1																
Dilatation, Lumen, Seminiferous Tubule																2				
THYROID	X	X	X	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X	X

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

GROUP
18661U

RTI-839
F1 Sacrifice
Male Rat

ANIMAL	474	475	483	484
EPIDIDYMIS	X	X	X	X
Exfoliated Germ Cells, Lumen				
PITUITARY	X	X	X	X
Cyst, Pars Distalis				
Developmental Malformation, Pars Nervosa				
TESTIS	X	X	X	X
Degeneration, Seminiferous Tubule				
Dilatation, Lumen, Seminiferous Tubule				
THYROID	X	X	X	X

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
79638U

ANIMAL	273	274	282	283	291	292	300	301	309	310	429	430	438	439	456	457	496	497		
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X		
Cyst, Pars Distalis										1										
Developmental Malformation, Pars Nervosa																				
TESTIS	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Degeneration, Seminiferous Tubule		1																		
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	N	X	X	X	X	X	X	X		

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
93766U

ANIMAL	106	107	115	116	124	125	197	198	206	207	215	216	233	234	357	358	366	367	375	376
OVARY	Xm	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Follicle																				
Hypoplasia																				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UTERUS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral	1																			
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium																				
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
93766U

ANIMAL	384	385	492
OVARY	X	X	X
Cyst, Follicle			
Hypoplasia			
PITUITARY	X	X	X
Cyst, Pars Distalis			
Developmental Malformation, Pars Nervosa			
THYROID	X	Xm	X
UTERUS	X	X	X
Degeneration, Epithelium			
Dilatation, Lumen, Bilateral			
Dilatation, Lumen, Unilateral			
Hyperplasia, Epithelium			
Metaplasia, Squamous, Epithelium			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
66560U

ANIMAL	131	132	139	140	242	243	251	252	259	260	268	269	397	398	406	407	415	416		
OVARY	X	X	X	X	X	Xm	X	X	X	X	X	X	X	X	X	X	X	X		
Cyst, Follicle																				
Hypoplasia																				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
UTERUS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium																				
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

GROUP
18661U

RTI-839
F1 Sacrifice
Female Rat

ANIMAL	156	157	165	166	173	174	180	188	189	322	323	331	332	340	341	348	349	469	470	478
OVARY					X	X	X		X		X	X		X	X	X	X			
Cyst, Follicle			1																	
Hypoplasia	3	3		2				3		2			2					1	1	2
PITUITARY	X	X	X	X	X	X	X	X		X	X	X	X	N	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa									P											
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UTERUS			X		X	X			X		X	X		X	X	X	X	X		X
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral	1																			
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium	1	1		1			2	1		2			1						1	
Metaplasia, Squamous, Epithelium	1												1							

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

GROUP
18661U

RTI-839
F1 Sacrifice
Female Rat

ANIMAL	479	487	488
OVARY	X		
Cyst, Follicle			
Hypoplasia		1	1
PITUITARY	X	X	X
Cyst, Pars Distalis			
Developmental Malformation, Pars Nervosa			
THYROID	X	Xm	X
UTERUS	X		X
Degeneration, Epithelium			
Dilatation, Lumen, Bilateral			
Dilatation, Lumen, Unilateral			
Hyperplasia, Epithelium		2	
Metaplasia, Squamous, Epithelium			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
79638U

ANIMAL	277	278	286	287	294	304	305	313	314	433	434	441	460	461	500	501				
OVARY		m	X	X	X	X	X	X		X	X	X	X	X	Xm	Xm				
Cyst, Follicle									1											
Hypoplasia	2	2																		
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
UTERUS			X	X	N	X	X		X			X	X	X		N				
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral								1												
Hyperplasia, Epithelium	1	1						1		1	1				1					
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 93766U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
120	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
193	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
202	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled
212	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled
354	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
380	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
381	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 66560U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
128	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
135	LARGE INTESTINES	Air	Intentionally Not Sampled
	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
394	COWPER'S GLAND	Lacks right	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 18661U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
319	INTESTINE-LARGE, CECUM	Gas	Intentionally Not Sampled
344	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
345	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
483	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
484	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 79638U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
273	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
	SKIN	Face, alopecia	Intentionally Not Sampled
274	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
282	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
283	LARGE INTESTINES	Air	Intentionally Not Sampled
	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
456	KIDNEY	Right, two 2mm clear cysts on surface	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 93766U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
358	THYMUS	Enlarged	Intentionally Not Sampled
492	ABDOMINAL MUSCLE	Umbilicus, 3x3mm hole (no protrusion of visera; noted umbilical hernia in life on 03/11/03)	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 66560U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
131	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
132	KIDNEY	Right, hydronephrosis, slight	Intentionally Not Sampled

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 18661U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
156	KIDNEY	Left, hydronephrosis, slight	Intentionally Not Sampled
	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
166	UTERUS	Fluid	No Correlating Lesion
180	UTERUS	Bilateral, fluid-filled	Hyperplasia, Epithelium
189	UTERUS	Bilateral, fluid-filled	No Correlating Lesion
322	UTERUS	Filled with fluid	No Correlating Lesion
341	UTERUS	Bilateral, fluid	No Correlating Lesion
487	UTERUS	Bilateral, filled with fluid	Hyperplasia, Epithelium

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 79638U

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
277	UTERUS	Bilateral, fluid	No Correlating Lesion
294	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
313	UTERUS	Fluid-filled	Dilatation, Lumen, Unilateral
433	UTERUS	Bilateral, fluid filled	No Correlating Lesion

F1 DOSED
PUBERTAL MALES AND FEMALES

SUMMARY INCIDENCE TABLES

SUMMARY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

	GROUP 93766D	GROUP 66560D	GROUP 18661D	GROUP 79638D		
EPIDIDYMIS (NO. EXAMINED)	(22)	(17)	(23)	(18)		
Exfoliated Germ Cells, Lumen						
PITUITARY (NO. EXAMINED)	(22)	(17)	(23)	(17)		
Cyst, Pars Distalis	2					
Developmental Malformation, Pars Nervosa						
TESTIS (NO. EXAMINED)	(22)	(17)	(23)	(18)		
Degeneration, Seminiferous Tubule		1	1	1		
Dilatation, Lumen, Seminiferous Tubule						
THYROID (NO. EXAMINED)	(22)	(17)	(23)	(18)		

SUMMARY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

	GROUP 93766D	GROUP 66560D	GROUP 18661D	GROUP 79638D		
OVARY (NO. EXAMINED)	(23)	(18)	(22)	(16)		
Cyst, Follicle			2	1		
Hypoplasia			13	6		
PITUITARY (NO. EXAMINED)	(23)	(18)	(22)	(15)		
Cyst, Pars Distalis						
Developmental Malformation, Pars Nervosa						
THYROID (NO. EXAMINED)	(23)	(18)	(22)	(16)		
UTERUS (NO. EXAMINED)	(23)	(17)	(20)	(16)		
Degeneration, Epithelium			2	2		
Dilatation, Lumen, Bilateral				1		
Dilatation, Lumen, Unilateral			1			
Hyperplasia, Epithelium		1	6	5		
Metaplasia, Squamous, Epithelium			2	1		

HISTOPATHOLOGY INCIDENCE TABLES

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
93766D

ANIMAL	101	109	110	118	119	191	192	200	201	209	210	227	228	351	352	360	361	369	370	378
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	X	X	X
Cyst, Pars Distalis											1			1						
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule																				
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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HISTOPATHOLOGY INCIDENCE TABLE

GROUP
93766D

RTI-839
F1 Sacrifice
Male Rat

ANIMAL	379	489																		
EPIDIDYMIS	X	X																		
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X																		
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X																		
Degeneration, Seminiferous Tubule																				
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X																		

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
66560D

ANIMAL	127	133	134	236	237	245	246	253	254	262	263	391	392	400	401	409	410			
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X			
Degeneration, Seminiferous Tubule							1													
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Male Rat

GROUP
18661D

ANIMAL	150	151	159	160	167	168	175	176	182	183	316	317	325	326	334	335	342	343	463	464
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Degeneration, Seminiferous Tubule												1								
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
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HISTOPATHOLOGY INCIDENCE TABLE

GROUP
18661D

RTI-839
F1 Sacrifice
Male Rat

ANIMAL	473	481	482																	
EPIDIDYMIS	X	X	X																	
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X																	
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X																	
Degeneration, Seminiferous Tubule																				
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X																	

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
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P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

GROUP
79638D

RTI-839
F1 Sacrifice
Male Rat

ANIMAL	271	272	280	281	289	290	298	299	307	308	427	428	436	437	454	455	494	495		
EPIDIDYMIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Exfoliated Germ Cells, Lumen																				
PITUITARY	X	X	X	X	X	X	N	X	X	X	X	X	X	X	X	X	X	X		
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
TESTIS	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		
Degeneration, Seminiferous Tubule															1					
Dilatation, Lumen, Seminiferous Tubule																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
93766D

ANIMAL	104	105	113	114	122	123	195	196	204	205	213	214	231	232	355	356	364	365	373	374
OVARY	X	X	X	X	X	X	X	Xm	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Follicle																				
Hypoplasia																				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UTERUS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium																				
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

GROUP
93766D

RTI-839
F1 Sacrifice
Female Rat

ANIMAL	382	383	491																	
OVARY	X	X	X																	
Cyst, Follicle																				
Hypoplasia																				
PITUITARY	X	X	X																	
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X																	
UTERUS	X	X	X																	
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium																				
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
66560D

ANIMAL	129	130	137	138	240	241	249	250	257	258	266	267	395	396	404	405	413	414		
OVARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Cyst, Follicle																				
Hypoplasia																				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
UTERUS	X	X	N	X	X	X	X	X		X	X	X	X	X	X	X	X	X		
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium									1											
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
18661D

ANIMAL	154	155	163	164	171	172	179	186	187	320	321	330	338	339	346	347	467	468	476	477
OVARY	X				X	X	X					X	X			X				
Cyst, Follicle									1								2			
Hypoplasia		1	2	2				2	2	2	2			2	2		2	3	2	2
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cyst, Pars Distalis																				
Developmental Malformation,																				
Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	Xm	X	X	X	X	X	X	X	X	X	X
UTERUS	N	X		X	X	X	X		X			N	X	X	X	X	X	X		
Degeneration, Epithelium			1								1									
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																			1	
Hyperplasia, Epithelium			1					1		1									1	1
Metaplasia, Squamous,																				
Epithelium			2								1									

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

GROUP
18661D

RTI-839
F1 Sacrifice
Female Rat

ANIMAL	485	486																		
OVARY	X	X																		
Cyst, Follicle																				
Hypoplasia																				
PITUITARY	X	X																		
Cyst, Pars Distalis																				
Developmental Malformation,																				
Pars Nervosa																				
THYROID	X	X																		
UTERUS	X																			
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium		1																		
Metaplasia, Squamous,																				
Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

GROUP
79638D

ANIMAL	275	276	284	285	293	302	303	311	312	431	432	440	458	459	498	499				
OVARY	X	X	X	X		X	X	X	X	X			X							
Cyst, Follicle					2															
Hypoplasia					2						2	1		2	2	2				
PITUITARY	X	X	X	X	X	X	X	X	X	X	X	X	X	N	X	X				
Cyst, Pars Distalis																				
Developmental Malformation, Pars Nervosa																				
THYROID	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
UTERUS		X	X	X	X	X		X	X	X			X	X						
Degeneration, Epithelium											1					2				
Dilatation, Lumen, Bilateral							1													
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium	1										1	1			1	1				
Metaplasia, Squamous, Epithelium											1									

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 93766D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
119	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
209	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
489	TESTIS	Bilateral, undescended	No Correlating Lesion

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 66560D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
236	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
245	SKIN	Front limbs, bilateral, alopecia of fur	Intentionally Not Sampled
262	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
263	SKIN	Face, alopecia	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 18661D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
150	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
151	LARGE INTESTINES	Air	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	PROSTATE	Reduced in size	Intentionally Not Sampled
	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
167	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
317	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
335	KIDNEY	Left, hydronephrosis	Intentionally Not Sampled
464	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Males Group Identification: 79638D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
289	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	PROSTATE	Reduced in size	Intentionally Not Sampled
	LEVATOR ANI PLUS BULBOCAVERNOSUS	Reduced in size	Intentionally Not Sampled
290	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	PROSTATE	Reduced in size	Intentionally Not Sampled
	LEVATOR ANI PLUS BULBOCAVERNOSUS	Reduced in size	Intentionally Not Sampled
299	PROSTATE	Reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled
	LARGE INTESTINES	Air	Intentionally Not Sampled
428	TESTIS	Left, undescended	No Correlating Lesion
494	PROSTATE	Ventral, reduced in size	Intentionally Not Sampled
	PROSTATE	Dorsolateral, reduced in size	Intentionally Not Sampled
	SEMINAL VESICLE	Reduced in size	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 93766D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
491	UTERINE HORN	Fluid-filled, bilateral	No Correlating Lesion (UTERUS)

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 66560D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
266	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled

RTI-839
F1 Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rat Sex: Females Group Identification: 18661D

Animal Number	Client Topography / Site	Client Gross Observations	Microscopic Observations
154	KIDNEY	Bilateral, hydronephrosis	Intentionally Not Sampled
155	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
338	KIDNEY	Right, hydronephrosis	Intentionally Not Sampled
486	UTERUS	Bilateral, fluid	No Correlating Lesion

F1 UTEROTROPHIC COHORT
FEMALES

SUMMARY INCIDENCE TABLES

SUMMARY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

	GROUP 93766	GROUP 66560	GROUP 18661	GROUP 79638		
UTERUS (NO. EXAMINED)	(12)	(6)	(8)	(9)		
Degeneration, Epithelium						
Dilatation, Lumen, Bilateral						
Dilatation, Lumen, Unilateral						
Hyperplasia, Epithelium			1			
Metaplasia, Squamous, Epithelium						

HISTOPATHOLOGY INCIDENCE TABLES

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

ANIMAL	GROUP 93766													GROUP 66560					
	108	117	126	199	208	217	235	359	368	377	386	493		244	261	270	399	408	417
UTERUS	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Degeneration, Epithelium																			
Dilatation, Lumen, Bilateral																			
Dilatation, Lumen, Unilateral																			
Hyperplasia, Epithelium																			
Metaplasia, Squamous, Epithelium																			

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

HISTOPATHOLOGY INCIDENCE TABLE

RTI-839
F1 Sacrifice
Female Rat

ANIMAL	GROUP 18661									GROUP 79638										
	158	181	190	324	333	350	471	480		279	288	295	306	315	435	442	462	502		
UTERUS		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X		
Degeneration, Epithelium																				
Dilatation, Lumen, Bilateral																				
Dilatation, Lumen, Unilateral																				
Hyperplasia, Epithelium	1																			
Metaplasia, Squamous, Epithelium																				

Key : X=Not Remarkable N=No Section I=Incomplete A=Autolysis
1=minimal 2=mild 3=moderate 4=severe
P=Present B=Benign M=Malignant
m=missing one paired organ u=unscheduled sac./death

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE FINAL CERTIFICATION

Study Title: Validation of the In Utero/Lactational Exposure Screening Protocol with Methoxychlor

Client Study: RTI Protocol No. RTI-839; Rt02-ED04; 65U-08055.001.017

EPL Project Coordinator: Dr. John Curtis Seely

EPL Project Number: 237-005

EPL Pathologist: Dr. John Curtis Seely

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Project Coordinator and Management are indicated below.

Area Inspected	Dates: Inspection	Dates: Reporting
EPL Project Sheets	April 4, 2003	April 4, 2003
Project Setup	April 14, 2003; April 30, 2003	April 14, 2003; April 30, 2003
Histology Setup	April 18, 2003; May 1, 2003	April 18, 2003; May 1, 2003
Data Review	May 20. 2003; May 22, 2003; May 27, 2003; May 28, 2003; May 30, 2003; June 3, 2003	May 20. 2003; May 22, 2003; May 27, 2003; May 28, 2003; May 30, 2003; June 3, 2003
Phase/Data Review	April 16, 2003; April 18, 2003	April 16, 2003; April 18, 2003
Draft Report	November 13 & 14, 2003	November 14, 2003
Final Report	January 14, 2004	January 14, 2004

Date Reported to Study Director/Management: January 14, 2004

Date of last quarterly facility inspection: October 2003

James J. Hollingsworth
(EPL Quality Assurance Unit)

January 14, 2004
Date

Form No. 6-2 (09/10/99)

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APPENDIX V

LETTER FROM DR. R.W. TYL
TO
DR. D.P. HOUCHENS

November 24, 2003

Dr. David P. Houchens
Battelle
505 King Avenue
Columbus, OH 43201-2693

RE: RTI Project 65U-8055.003.028

Dear Dr. Houchens:

At Gary Timm's request, this correspondence will serve to document my discussions with Chris Myers and my oral report in the conference call with Gary Timm, Jerry Johnson, and you on Thursday, November 11, 2003.

As we reported, the mid and high doses formulated by the Battelle repository were inadvertently mislabeled at RTI. The error was discovered early in the study and confirmed by the repository (we sent back samples of the dosing solutions in question for reanalysis). We continued to dose, based on the color codes and the data were entered and analyzed based on the correct doses. When direct dosing of the F1 weanlings began, we continued with the same process so as not to confuse the technicians, but also entered the data based on the correct doses.

Chris and I went through each summary table in the report to determine if there was any evidence of an error in reporting the results (i.e., presenting/analyzing mid dose data as high dose data and vice versa).

My examination is summarized in the following 10 tables: four (Tables 1-4) for F0 females, four (Tables 5-8) for F1 female offspring, and two (Tables 9-10) for F1 male offspring. My conclusions from this examination are as follows:

1. All of the F0 maternal data through gestation and lactation exhibited a clear dose-response curve, indicating in fact, the high dose was high, and the mid dose was mid (Tables 1 and 2), except for the body weight change during lactation, postnatal day (pnd) 0-21, where the low dose ($p<0.01$) and the high dose ($p<0.001$) values were significantly increased and the mid dose value was unaffected.

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2. The F0 reproductive and lactational indices for the F1 litters (Table 3) and the hormone data (Table 4) were unaffected for all parameters at all doses.

3. The F1 litter parameters during lactation (Table 5) were all unaffected, except for a decrease in female (but not the sexes combined, or male) pup body weights per litter on pnd 2, significantly reduced at 100 mg/kg/day consistent with appropriate maternal administrations of the correct doses.

4. At weaning, the F1 offspring were distributed into a female uterotrophic cohort (with direct dosing by sc injections; Table 6), female (Table 7) and male (Table 9) undosed pubertal cohorts, and female (Table 8) and male (Table 10) dosed (direct gavage dosing) pubertal cohorts. The Rx codes and color codes of all groups were kept the same as for the F0 females and the data presented under the correct dose levels.

F1 Females

1. The F1 female uterotrophic cohort (Table 6). The body weights and weight changes exhibited a clear dose-response pattern. Ovarian weights were significantly reduced at both the mid and high doses, with greater effects at the mid dose. TSH was elevated in all three dosed groups, with the greatest effect at 50 mg/kg/day. However, it is unlikely that there was an error in dosing, since these parameters were the only ones so affected.

2. The undosed F1 female pubertal cohort (Table 7) exhibited most (or the greatest) effects at 50 mg/kg/day but these females were not dosed directly from pnd 21 to termination on pnd 52. Vaginal patency was affected at both 50 and 100 mg/kg/day and onset of estrous cyclicity was delayed/affected only at 50 mg/kg/day; therefore, these effects at 50 mg/kg/day would not be due to an error in dosing on pnd 21-42, since these animals were not dosed after weaning.

3 In the F1 female dosed pubertal cohort (Table 8), body weights, weight changes, and necropsy parameters all exhibited a dose-response pattern except for paired ovary weight, which was significantly reduced at both 50 and 100 mg/kg/day, but more so at 50 mg/kg/day) and thyroid weights (increased only at 50 mg/kg/day). There were no effects on circulating levels of T4, T3, or TSH. Overall, the responses of this dosed group were similar to the responses of the undosed group of pubertal females. The effects were consistent, and this implies that the effects were due to maternal exposures during gestation and/or lactation. It does not support a mix-up in dosing solutions. The possibility exists that absorption and/or metabolism is saturated at 50 mg/kg/day, so there is no larger effect at 100 mg/kg/day since there is no dose-related increase in absorption and/or metabolism at the highest dose. It does not explain effects observed only at 50 mg/kg/day.

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F1 Males

1. The F1 male undosed pubertal cohort (Table 9) exhibited no effects on body weights for pnd 21-74, with reductions in weight change at both 50 and 100 mg/day for pnd 36-38 and 40-42. Age at preputial separation (PPS) was delayed only at 50 mg/kg/day. Adjusted (for pnd 21 body weight) thyroid weights were significantly increased at 25 and 50 (but not at 100 mg/kg/day), and absolute and adjusted (for terminal body weight) thyroid weights were unaffected at any dose. Absolute and adjusted (for pnd 21 body weight) paired testes weights were significantly reduced only at 100 mg/kg/day and unaffected when adjusted for terminal body weight. LABC was significantly increased at 50 and 100 mg/kg/day only when adjusted for necropsy body weight. Hormones were not affected, and andrology was assessed only at 0 and 100 mg/kg/day (and increased at 100 mg/kg for SHC and efficiency of DSP [but not DSP]; the DSP parameters are calculated from SHC). There is no evidence of misdosing of the F0 generation, and these F1 males were not dosed from pnd 21-74.

2. The F1 male dosed pubertal cohort (Table 10) exhibited clear dose-response patterns for body weights and body weight changes. PPS was delayed at 50 and 100 mg/kg/day with a greater effect at 50 mg/kg/day. At scheduled necropsy, almost all organ weights were affected at all doses, with a clear dose-response pattern. The exception was adjusted paired kidney weights (adjusted for terminal body weight) where effects (reductions) were greatest at 50 mg/kg/day, less at 25 mg/kg/day, and least at 100 mg/kg/day. Absolute and adjusted (for body weight on pnd 21) paired kidney weights were affected at all three doses, with the least effect at 25 mg/kg/day and approximately equivalent effects at 50 and 100 mg/kg/day for both parameters. Andrology (assessed only at 0 and 100 mg/kg/day) exhibited significant reductions in epididymal sperm concentrations and DSP (but not efficiency of DSP) at 100 mg/kg/day. Hormone levels for T3 and TSH were equivalent across all doses; T4 concentration was affected (increased) only at 50 mg/kg/day. The effects on this dosed cohort were similar to the effects on the undosed male cohort, so they could not be due to postwean errors in dosing, especially since the body weight data are so clearly dose related, and the undosed cohort was not treated after pnd 21. The effects are most likely due to maternal exposures during gestation and/or lactation.

CONCLUSIONS

There is no evidence from the data that a dosing mix-up between mid and high doses occurred during F0 gestation, F0 lactation, or during administration to the F1 postwean dosed cohorts. The vast majority of parameters assessed exhibited appropriate dose-response patterns. The presence of significant effects only at, or greatest at 50 mg/kg/day for only very specific endpoints, e.g., ovarian weights (females), circulating thyroid-related hormones for both sexes, estrous cyclicity effects (females), and effects on PPS (males), also occurred in the F1 female and male undosed cohorts.

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Those cases where there were effects at both 50 and 100 mg/kg/day, but a greater effect at 50 mg/kg/day, may be due to saturation of absorption and/or metabolic capability at 50 mg/kg/day, i.e., no greater effects would occur at 100 mg/kg/day. Other than biological variability (which is unlikely), I have no explanation for the effects on a few, very specific, and consistent endpoints only at (or greater at) 50 mg/kg/day. These effects are observed in both dosed and undosed cohorts. In the females, altered ovarian weights may be responsible for hormone-mediated estrous cyclicity effects. In the F1 males, testes weights were reduced at all doses and this could be responsible for the delay in hormone-mediated PPS. The effects on circulating thyroid-related hormones, especially elevated TSH, may indicate that there were reductions in T4 and T3 (not detected analytically but detected by the organism) and may also impact (delay) pubertal (PPS) and post pubertal (estrous cyclicity) endpoints.

Sincerely,

Rochelle W. Tyl, Ph.D., DABT
Program Toxicologist/Research Director
Center for Life Sciences & Toxicology

RWT/db

Table 1. F0 Females – Gestation

Parameter	Methoxychlor (mg/kg/day; po)			
	0	25	50	100
F0 Body Weights				
gd 0		—	—	—
gd 6		—	—	—
gd 9		—	—	***
gd 12		↓**	↓**	↓***
gd 15		↓**	↓**	↓***
gd 18		↓*	↓***	↓***
gd 20		—	↓*	↓***
F0 Body Weight Changes				
gd 0-6		—	—	↓*
gd 6-9		↓*	↓**	↓**
gd 9-12		↓***	↓**	↓***
gd 12-15		—	—	↓*
gd 15-18		—	—	—
gd 18-20		—	—	—
gd 6-20		—	↓**	↓***
gd 0-20		—	↓**	↓***

Note: All exhibiting a clear dose response from 0 through 100 mg/kg/day (Report Table 3).

F0 Feed Consumption					
g/day:	gd 0-6		—	—	—
	gd 6-9		↓*	↓*	↓***
	gd 9-12		—	—	↓**
	gd 12-15		—	↓***	↓***
	gd 15-18		—	↓***	↓***
	gd 18-20		—	—	—
g/kg/day:	gd 0-6		—	—	—
	gd 6-9		—	↓*	↓***
	gd 9-12		—	—	↓*
	gd 12-15		—	↓**	↓***
	gd 15-18		—	—	↓***
	gd 18-20		—	—	—
	gd 6-20		—	↓***	↓***
	gd 0-20		—	↓*	↓***

Note: All exhibiting a clear dose response for 0 through 100 mg/kg/day (Report Table 4).

Key: ↓ = statistically significantly reduction
*, **, *** = $p<0.05$, 0.01, 0.001

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Table 2. F0 Females – Lactation

Parameter		Methoxychlor (mg/kg/day; po)			
		0	25	50	100
F0 Body Weights					
pnd 0			↓**	↓**	↓***
pnd 4			↓**	↓***	↓***
pnd 5			↓**	↓**	↓***
pnd 14			—	—	↓**
pnd 21			—	—	↓*
F0 Body Weight Change					
pnd 0-4			—	—	—
pnd 4-7			—	—	—
pnd 7-14			—	↓*	↓**
pnd 14-21			—	—	—
pnd 0-21			↑**	—	↑***

Note: All exhibiting a clear dose response, except pnd 0-21 where the low and high dose (but not the mid dose) exhibited significant increases (Report Table 6).

F0 Feed Consumption					
g/day)	pnd 0-4		—	—	—
	pnd 4-7		—	—	—
	pnd 7-14		—	—	—
	pnd 14-21		—	—	—
	pnd 0-21		—	—	—
g/kg/day	pnd 0-4		—	—	—
	pnd 4-7		—	—	—
	pnd 7-14		—	—	—
	pnd 14-21		—	—	—
	pnd 0-21		—	—	—

Note: No effects on relative feed consumption (g/kg/day) for any dose or interval (Report, Table 7).

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Table 3. F0 Reproductive and Lactational Indices for F1 Litters

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Fertility Index		—	—	—
Gestational Index		—	—	—
Gestational Length		—	—	—
No. Total Pups/Litter (pnd 0)		—	—	—
No. Dead Pups/Litter (pnd 0)		—	—	—
No. Live Pups/Litter (pnd 0)		—	—	—
Stillbirth Index		—	—	—
Live birth Index		—	—	—
Survival Indices		—	—	—

Note: No statistically significant effects in any parameter for any interval (Report, Table 9).

Table 4. F0 Female Hormone Data at Necropsy

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
T4 (µg/dL)		—	—	—
TSH (ng/ml)		—	—	—

Note: No effects in either hormone at any dose.

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Table 5. F1 Litter Parameters During Lactation

Parameter		Methoxychlor (mg/kg/day, po)			
		0	25	50	100
No. F1 Live Pups/Litter					
from pnd 0-pnd 21			—	—	—
F1 AGD (pnd 0) (Absolute or Adjusted)					
Male			—	—	—
Female			—	—	—
Pup Body Weight/Litter					
pnd 0			—	—	—
pnd 2	All Male Female		—	—	↓**
pnd 4	All Male Female		—	—	—
pnd 7	All Male Female		—	—	—
pnd 10	All Male Female		—	—	—
pnd 14	All Male Female		—	—	—
pnd 17	All Male Female		—	—	—
pnd 21	All Male Female		—	—	—
Sex ratio (% males) per litter					
pnd 0			—	—	—
pnd 4 (precull)			—	—	—
No. Nipples/Male (all 0.0)			—	—	—
No. Males with ≥1 nipple (all 0.0)			—	—	—
No. Areolae/Male			—	—	—
No. Males with ≥1 Areolae			—	—	—

Note: Report, Table 10

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Table 6. F1 Female Uterotrophic Cohort

Parameter	Methoxychlor (sc, injection)			
	0	25	50	100
In Life				
Body Weight				
pnd 21		—	—	—
pnd 22		—	—	—
pnd23		—	—	—
pnd24		—	—	—
Body Weight Changes				
pnd 21-22		—	—	↓*
pnd 22-23		—	—	—
pnd 23-24		—	—	—
pnd 21-24		—	—	—
Necropsy				
Terminal body weight		—	—	—
Paired ovarian weight		—	↓***	↓**
Uterus weight (with fluid)		—	—	—
Adjusted (by necropsy wts.) organ weights				
Paired ovary		—	↓***	↓**
Uterus (with fluid)		—	—	—
Adjusted (by pnd 21 wt.) Organ wts.				
Paired Ovary		—	↓***	↓**
Uterus (with fluid)		—	—	—
Estradiol (pg/ml)		—	—	—
T4 (µg/dL)		—	—	—
TSH (ng/ml)		↑*	↑**	↑*

Note: The absolute and adjusted paired ovarian weights and TSH levels at necropsy exhibited greater effects at the mid dose than at the high dose (Report, Table 18).

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Table 7. F1 Undosed Pubertal Females

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. on study	25	23	23	20
No. at Scheduled Sacrifice	23	18	23	16
In-Life				
AGD (pnd 21) Absolute/Adjusted		—	—	—
Body Weights pnd 21 - 42		—	—	—
Body Weight Change				
pnd 21-34		—	—	—
pnd 34-36		↓**	—	—
pnd 36-38		—	—	—
pnd 38-40		↓*	—	—
pnd 40-42		—	—	—
pnd 21-42		—	—	—
(Report Tables 20 and 21, only the low dose exhibited effects and body weight for pnd 34-36 and pnd 38-40).				
pnd at VP		—	↓***	↓***
BW at VP Acquisition		—	↓***	↓***
Adjusted VP		—	↓***	↓***
Days for VP to first estrus		—	↑***	—
pnd of first estrus		—	↓**	↓*
No./% cycling		—	—	—
No. days from VP to start of first cycle		—	↑***	—
Pnd at start of first cycle		—	↓***	—
No. days from VP to end of first cycle		—	↑***	—
pnd at end of first cycle		—	—	—
% with prolonged estrus		—	↑***	—
% with prolonged diestrus		—	—	—
(From Report Tables 22 and 23, the mid dose exhibited greater or the only effects for vaginal patency [VP] and for estrous cyclicity, but these females were not directly dosed from weaning to termination on pnd 42.				
Sacrifice		—	—	—

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Table 7. F1 Undosed Pubertal Females
(Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Body Weight		—	—	—
Absolute/Adj. ACD		—	—	—
No. Areolae/female		—	—	—
No. Nipples/female		—	—	—
U-V distance (mm)		—	↓**	↓*
Organ Weights				
Absolute Pituitary		—	—	—
Thyroid		—	—	—
Liver		—	—	—
Paired Adrenals		—	—	—
Paired Kidneys		—	—	—
Paired Ovaries		—	↓***	—
Uterus with fluid		—	↑**	—
Uterus without fluid		—	↑**	—
Adjusted for Terminal Body Weight				
Pituitary		—	—	—
Thyroid		—	—	—
Liver		—	—	—
Paired Adrenals		—	—	—
Paired Kidneys		—	—	—
Paired Ovaries		—	↓***	—
Uterus with fluid		—	↑*	—
Uterus without fluid		—	↑*	—
Adjusted for pnd 21 Body Weight				
Pituitary		—	—	—
Thyroid		—	—	—
Liver		—	—	—
Paired Adrenals		—	—	—

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Table 7. F1 Undosed Pubertal Females (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Paired Kidneys		—	—	—
Paired Ovaries		—	↓***	—
Uterus with fluid		—	↑**	—
Uterus without fluid		—	↑*	—
T4 (µg/dL)		—	↑**	—
T3 (ng/ml)		—	—	—
TSH (ng/ml)		—	↑***	—

(From Report Table 24, only the mid dose exhibited effects on paired ovary and uterus [with and without fluid] weights, and on T4 and TSH, but this cohort was not directly dosed for pnd 21-42).

U-V - Urethral-vaginal distance (in mm)
VP = vaginal patency

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Table 8. F1 Dosed Pubertal Females

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. on study	25	23	23	20
No. at Scheduled Sacrifice	23	18	23	16
In-Life				
AGD (pnd 21) Absolute/Adjusted		—	—	—
Body Weights pnd 21		—	—	—
pnd 22		—	—	↓***
pnd 21 - 42		—	—	↓**, ***
Body Weight Change				
pnd 21-22		—	—	—
pnd 22-24		—	—	↓**
pnd 24-26		—	—	—
pnd 26-28		—	—	↓***
pnd 28-30		—	↑*	—
pnd 30-36		—	—	—
pnd 36-38		—	↓**	↓*
pnd 38-40		—	—	↓**
pnd 40-42		—	—	—
pnd 21-42		—	—	↓***
(Report Tables 26 and 27; almost all effects limited to high dose, [except body weight changes for pnd 28-30] and increased only at mid at pnd 36-38 [reduced at mid and high with greater effect at mid dose]).				
pnd at VP		↓***	↓***	↓***
Weight at Acquisition		↓***	↓***	↓***
No. days for VP to first estrus		—	—	—
Age at first estrus		↓**	↓***	↓***
% Females cycling		—	—	—
No. days from VP to start of first cycle		—	—	↑**
Age at start of first cycle		↓***	↓***	↓***
No. days from VP to end of first cycle		—	—	↑***
Age at end of first cycle		↓**	↓***	↓**

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Table 8. F1 Dosed Pubertal Females (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. females with prolonged estrus		—	↑***	↑***
No. females with prolonged diestrus		—	—	—
(Report Table 21, clear dose response with the high dose value the only one affected or the most affected except for age at start and end of first cycle and % females with prolonged estrus, more affected at mid dose. The days from VP to start and end of first cycle are increased only at the high dose.)				
At Necropsy				
Body Weight		—	—	↓***
Absolute AGD		—	—	—
Adjusted AGD		—	—	↑**
No. Areolae/female		—	—	—
No. Nipples/female		—	—	—
U-V distance (mm)		—	↓***	↓**
Absolute Organ Weights				
Pituitary		—	—	—
Thyroid		—	↑**	—
Liver		—	—	↓**
Paired Adrenals		—	—	—
Paired Kidneys		—	—	↓***
Paired Ovaries		—	↓***	↓***
Uterus with fluid		—	—	—
Uterus without fluid		—	—	—
Organ Weights Adjusted for Terminal Body Weight				
Pituitary		—	—	—
Thyroid		—	↑**	—
Liver		—	—	—
Paired Adrenals		—	—	—
Paired Kidneys		—	—	—
Paired Ovaries		—	↓***	↓***
Uterus with fluid		—	—	—

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Table 8. F1 Dosed Pubertal Females (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Uterus without fluid		—	—	—
Organ Weights Adjusted for pnd 21 Body Weight				
Pituitary		—	—	—
Thyroid		—	↑**	—
Liver		—	—	↓*
Paired Adrenals		—	—	—
Paired Kidneys		—	—	↓***
Paired Ovaries		—	↓***	↓***
Uterus with fluid		—	—	—
Uterus without fluid		—	—	—
T4 (µg/dL		—	—	—
T3 (ng/ml)		—	—	—
TSH (ng/ml)		—	—	—

(Report Table 30; body weights, weight change and necropsy parameters exhibited an appropriate dose response pattern, again except for thyroid and ovaries).

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Table 9. F1 Undosed Pubertal Males

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. on study	25	22	24	19
No. at Scheduled Sacrifice	23	17	24	18
In-Life				
Abs./Adj/AGD (pnd 21)		—	—	—
Body Weights pnd 21 - 74		—	—	—
Body Weight Change				
pnd 21-36		—	—	—
pnd 36-38		—	↓*	↓*
pnd 38-40		—	—	—
pnd 40-42		—	↓*	↓**
pnd 42-74		—	—	—
pnd 21-74		—	—	—
(Report Tables 32 and 33; any effects clearly dose related).				
Age (pnd of PPS)		—	↑*	—
Body Weight at PPS		—	—	—
Adjusted PPS		—	↑*	—
(Table 36; only effects at mid dose; absolute age + 1.2 days at 50 mg/kg/day; adjusted age + 1.1 days at 50 mg/kg/day; most other parameters exhibit a dose response pattern.)				
Necropsy				
No. Nipples/Male		—	—	—
Necropsy Body Weight		—	—	—
Absolute Organ Weights				
Pituitary		—	—	—
Thyroid		—	—	—
Liver		—	—	—
Paired Adrenals		—	—	—
Paired Kidneys		—	—	—
Glans Penis		—	—	—
Paired Testes		—	—	↓**

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Table 9. F1 Undosed Pubertal Males (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Right Epididymis		—	—	—
Left Epididymis		—	—	—
SV + CG		—	—	—
Ventral Prostrate		—	—	—
Dorsolateral Prostate		—	—	—
Prostate		—	—	—
LABC		—	—	—
Cowper's Glands		—	—	—
Organ Weights Adjusted for Necropsy Body Weights				
Pituitary		—	—	—
Thyroid		↑*	↑*	—
Liver		—	—	—
Paired Adrenals		—	—	—
Paired Kidneys		—	—	—
Glans Penis		—	—	—
Paired Testes		—	—	—
Right Epididymis		—	—	—
Left Epididymis		—	—	—
SV + CG		—	—	—
Ventral Prostrate		—	—	—
Dorsolateral Prostate		—	—	—
Prostate		—	—	—
LABC		—	↑*	↑*
Cowper's Glands		—	—	—
Organ Weights Adjusted for pnd 21 Weight				
Pituitary		—	—	—
Thyroid		—	—	—

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Table 9. F1 Undosed Pubertal Males (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Liver		—	—	—
Paired Adrenals		—	—	—
Paired Kidneys		—	—	—
Glans Penis		—	—	—
Paired Testes		—	—	↓**
Right Epididymis		—	—	—
Left Epididymis		—	—	—
SV + CG		—	—	—
Ventral Prostrate		—	—	—
Dorsolateral Prostate		—	—	—
Prostate		—	—	—
LABC		—	↑*	↑*
Cowper's Glands		—	—	—
Andrology				
% Motile Sperm	—			—
% Progressively Motile Sperm	—			—
Epididymal Sperm Conc.	—			—
SHC	—			↑*
DSP	—			—
Efficiency of DSP	—			↑*
Hormones				
T4 (µg/dL)		—	—	—
T3 (ng/ml)		—	—	—
TSH (ng/ml)		—	—	—

(From Report Tables 32-36; all effects exhibited a dose response pattern except PPS [only at 50 mg/kg/day] and adj. thyroid weight, at 25 mg/kg/day and at 50/mg/day. These males were not directly dosed after weaning).

DSP = daily sperm production
SHC = Testicular homogenization resistant spermatid head counts
PPS = prepupital separation
SV + CG = seminal vesicles plus coagulating glands
LABC = Levator Ani plus Bulbcavernosus Muscle Complex

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Table 9. F1 Undosed Pubertal Males
(Continued)

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Table 10. F1 Dosed Pubertal Males

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
No. on study	25	22	24	19
No. at Scheduled Sacrifice	22	17	23	18
In-Life				
Abs./Adj./AGD (pnd 21)		—	—	—
Body Weights				
pnd 21-28		—	—	—
pnd 30		—	—	↓**
pnd 32-38		—	—	↓**,***
pnd 40		—	↓*	↓***
pnd 42		—	↓**	↓***
pnd 44		—	↓**	↓***
pnd 46		↓*	↓***	↓***
pnd 48-52		↓**	↓***	↓***
pnd 54-74		↓***	↓***	↓***
Body Weight Change				
pnd 21-24		—	—	—
pnd 24-28		—	—	↓*
pnd 28-30		↓*	—	↓***
pnd 30-32		—	—	↓*
pnd 32-34		—	—	↓***
pnd 34-36		↓*	—	↓***
pnd 36-38		—	↓**	↓**
pnd 38-40		—	↓*	↓***
pnd 40-42		↓*	↓***	↓**
pnd 42-44		—	↓*	↓*
pnd 44-46		↓*	↓*	↓***
pnd 46-48		↓***	↓***	↓***
pnd 48-50		—	↓*	↓*
pnd 50-52		—	↓***	↓***

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Table 10. F1 Dosed Pubertal Males
(Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
pnd 52-54		↓***	↓***	↓***
pnd 54-56		—	↓***	↓**
pnd 56-60		↓***	↓***	↓***
pnd 60-62		↓**	↓***	↓***
pnd 62-64		↓***	↓***	↓***
pnd 64-66		—	—	↓*
pnd 66-68		↓*	↓***	↓**
pnd 68-70		↓**	↓***	↓**
pnd 70-72		—	↓*	—
pnd 72-74		—	—	↓**
pnd 74-76		—	—	—
pnd 21-74		↓***	↓***	↓***
(From Report Tables 38 and 39; all with clear dose response paths except for weight change on 28-32 and 34-36 when the low and high dose levels (but not the mid dose levels) exhibited dose related significant reductions.				
Age (pnd of PPS)		—	↑***	↑***
Body Weight at PPS		—	—	—
Adjusted PPS		—	↑***	↑**
(Report Table 41).				
Necropsy				
No. Nipples/Male		—	—	—
Terminal Body Weight		↓***	↓***	↓***
Absolute Organ Weights				
Pituitary		—	—	↓**
Thyroid		—	—	—
Liver		↓***	↓***	↓***
Paired Adrenals		—	—	—
Paired Kidneys		↓**	↓***	↓***
Glans Penis		—	—	—
Paired Testes		↓**	↓***	↓***

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Table 10. F1 Dosed Pubertal Males (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Right Epididymis		—	↓**	↓***
Left Epididymis		—	↓***	↓***
SV + CG		↓*	↓***	↓***
Ventral Prostrate		—	↓***	↓***
Dorsolateral Prostate		↓**	↓***	↓***
Prostate		↓*	↓***	↓***
LABC		—	↓***	↓***
Cowper's Glands		—	↓***	↓***
Organ Weights Adjusted for Terminal Body Weights				
Pituitary		—	—	—
Thyroid		—	—	—
Liver		—	↑**	↑**
Paired Adrenals		—	↑*	↑***
Paired Kidneys		↑**	↑***	↑*
Glans Penis		—	—	—
Paired Testes		—	—	—
Right Epididymis		—	—	—
Left Epididymis		—	—	—
SV + CG		—	—	—
Ventral Prostrate		—	—	—
Dorsolateral Prostate		—	—	—
Prostate		—	—	—
LABC		—	—	—
Cowper's Glands		—	—	—
Organ Weights Adjusted for BW on pnd 21				
Pituitary		—	—	↓**
Thyroid		—	—	—

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Table 10. F1 Dosed Pubertal Males (Continued)

Parameter	Methoxychlor (mg/kg/day, po)			
	0	25	50	100
Liver		↓***	↓***	↓***
Paired Adrenals		—	—	—
Paired Kidneys		↓**	↓***	↓***
Glans Penis		—	—	—
Paired Testes		↓*	↓***	↓***
Right Epididymis		—	↓**	↓***
Left Epididymis		—	↓***	↓***
SV + CG		↓*	↓***	↓***
Ventral Prostrate		—	↓***	↓***
Dorsolateral Prostate		↓**	↓***	↓***
Prostate			↓***	↓***
LABC			↓***	↓***
Andrology				
% Motile Sperm	—			—
% Progressively Motile Sperm	—			—
Epididymal Sperm Conc.	—			↓**
SHC	—			—
DSP	—			↓**
Efficiency of DSP	—			—
Hormones				
T4 (µg/dL)		—	↑***	—
T3 (ng/ml)		—	—	—
TSH (ng/ml)		—	—	—

(From Report Tables 38, 39, 41, and 42; all values for all parameters exhibited appropriate dose-response curves except for T4 levels, elevated only at 50 mg/kg/day).

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E-mail From L. Earl Gray

Below are my comments sent to Gary on 11/25/03 on the protocol and results, sent after reading Shelly's letter.

I would add. This first trial was not a total failure. It was not deemed worthy of presentation to the EDVMS however. We had suggested a list of chemicals for RTI to run, but that was pared to methoxychlor. We learned that the protocol can be executed as written. I do not think the dosing error would be likely to occur again and, regardless, it did detect the correct effects for methoxychlor which is the purpose of a screen.

Work would be needed to get the uterotropic component to work if this remained in the protocol; this part failed to produced expected results. The control uterine weights were too large, indicating that the females were being stimulated by there own estrogen so the effect of methoxychlor was masked.

Earl

----- Forwarded by Earl Gray/RTP/USEPA/US on 08/26/2005 01:11 PM -----

Earl Gray/RTP/USEPA/US

11/25/2003 04:17 PM

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APPENDIX VI

E-MAIL FROM DR. L.E. GRAY

E-mail From L. Earl Gray

Below are my comments sent to Gary on 11/25/03 on the protocol and results, sent after reading Shelly's letter.

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Earl

----- Forwarded by Earl Gray/RTP/USEPA/US on 08/26/2005 01:11 PM -----

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11/25/2003 04:17 PM

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