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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Date September 28, 2004 **TXR #** 0052771

MEMORANDUM

SUBJECT: Iodomethane: Reviews for Multigeneration Reproductive Toxicity Study in Rats and Chronic Toxicity/Carcinogenicity Study in Rats *via* the Inhalation Route

DP BARCODE: D304187 MRID No. 46203710 & 46203707
P.C. CODE: 000011

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TO: Mary Waller
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The registrant, Arvesta, submitted a One-Year Interim Report for a Chronic Toxicity/Carcinogenicity Study in Rats and a Multigeneration Reproductive Toxicity Study in Rats with iodomethane exposure *via* the inhalation route . These studies have been reviewed and DER for each study are attached. The citation of the studies and the conclusions of the reviews are presented below:

1) Nemec, M.D. (2001) An inhalation two-generation reproductive toxicity study of iodomethane in rats (comprehensive final report). WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-418004, May 24, 2001. MRID 46203710 Unpublished.

In a two-generation reproduction toxicity study, iodomethane (99.7% a.i.; Lot/batch # 007403/02) was administered via whole-body inhalation to Crl:CD®(SD)IGS BR rats (30/sex/concentration) for 6 hours/day at nominal concentration levels of 0, 5, 20, or 50 ppm (equivalent to analytical concentrations of 0, 5, 21, and 50 ppm). The P animals were exposed to the test article for at least 70 days prior to mating to produce the F_1 litters. Exposure of the P males continued throughout mating and until the day prior to euthanasia. The P females continued to be exposed throughout mating and through gestation day (GD)

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20, at which point exposure was discontinued. Daily exposure of the P females was reinitiated on lactation day (LD) 5 and continued until the day prior to euthanasia. After weaning, F_1 animals (30/sex/concentration) were selected, equalized by sex, to become the parents of the F_2 generation and, beginning on post-natal day (PND) 28, were exposed to the same concentration test atmosphere as their dam.

In adult animals (P and F_1), the majority of the effects noted occurred at the highest concentration tested (HCT; 50 ppm).[1] **In the P generation**, lower body weights, body weight gains, and food efficiencies were noted in males at this concentration relative to control. These differences - though statistically significant - were sporadic (weeks 3 and 9-10 only), and not considered to be toxicologically relevant. In the case of females, body weights were consistently 4-8% lower than control at 50 ppm ($p \leq 0.05$ or 0.01) beginning during the 8th week of premating and throughout gestation and lactation. At 50 ppm, female weight gain during pre-mating and late gestation (GD 14-20) was 13% lower than control ($p \leq 0.05$). However, at 50 ppm overall body weight gain was approximately 10% lower than control during gestation and 31% higher during lactation. Other effects noted at 50 ppm were decreases in organ weights, gross pathology and histopathology findings. The absolute organ weights affected included adrenal gland (↓15%, males and females), and thymus weights which were increased by 18-26% (males only) at concentrations ≥ 20 ppm.. Relative adrenal weights were decreased (↓17 and 8% in males and females, respectively) while relative thymus weights were increased by 20% (males only). During necropsy, animals exposed to iodomethane at concentrations ≥ 20 ppm exhibited slight increases in the incidence of dark red discoloration on the mandibular lymph node (2/30 and 3/30 at 20 and 50 ppm, respectively *vs.* 0 control) and white area(s) on the lungs (2/30 and 3/30 at 20 and 50 ppm, respectively *vs* 0/30 controls). The toxicological relevance of these findings is considered to be equivocal given their low incidence and the lack of histopathological correlates. The histopathological changes occurred primarily in the liver and respiratory tract. At 50 ppm, the following microscopic findings were noted in males: minimal to mild hepatocellular necrosis (4/30 vs 1/30 controls); minimal to mild subacute inflammation in the lungs (14/30 vs 9/30 controls); mild to moderate hemorrhage of the mandibular lymph node (4/30; controls not examined); and minimal to moderate degeneration of the olfactory epithelium at Nasal Levels II (14/30), III (11/30), and IV (10/30) *vs.* none in control. Females treated at the 50 ppm concentration level exhibited minimal to mild degeneration of the olfactory epithelium at Nasal Levels II (11/30), III (10/30), and IV (6/30) *vs* 0/30 in controls. No other histopathological findings were reported for females

In F_1 adults, male body weight was 8-14% ($p \leq 0.05$ or 0.01)lower at 50 ppm than control throughout pre-mating while body weight gain was 10% lower ($p \leq 0.01$) during weeks 3-4 of pre-mating but comparable or higher than controls during the remainder of the pre-mating period. Female body weights were decreased 6-14% during the 2nd and 9th week of premating and 6-8% during gestation and lactation at the 50 ppm concentration. At this concentration, overall female body weight gain was unaffected during pre-mating and lactation but decreased by 21% during gestation. This is consistent with the observation of a 17% decrease in food efficiency noted during gestation. Absolute organ weights affected

[1] Abbreviations: HCT = highest concentration tested

by compound administration at the 50 ppm concentration level are: brain (↓8% ♂ and ♀), kidneys (↓12%♂, ↓7% ♀), adrenal glands (↓20%♂, ↓22%♂), testis (↓9%), epidydimis (↓8%), cauda epidydimis (↓8%), and thymus (↑18%, ♂ only). Testicular weights were also reduced ≈8% at the 20 ppm concentration. Relative organ weights at the 50 ppm concentration were higher than controls for the liver (≈10% in ♂ and ♀), and the thymus (↑19% ♂ only). However, the relative adrenal weights were decreased by 12-19% at ≥ 20 ppm in both males and females. During necropsy, 7/28 males exhibited dilated renal pelvis at the 50 ppm level vs 0 in control. In 50 ppm males, histopathology findings consisted exclusively of minimal to mild degeneration of the olfactory epithelium at Nasal Levels II (5/28), III (4/28), and IV (2/28) *vs* 0 control. Females exposed at the 50 ppm level had a slight (non-statistically significant) increase in the incidence of chronic progressive nephropathy (7/30 *vs* 3/29 control), renal calculi (4/30 *vs* 0 control), and minimal-mild degeneration of the olfactory epithelium at Nasal Level II (7/30), Level III (7/30), and Level IV (3/30) *vs* 0 in control.[2]

Under the conditions of the study, the systemic parental NOAEL is 20 ppm and the LOAEL is established at 50 ppm based on decreases in body weight, body weight gain, changes in organ weights (adrenal glands, testis, cauda epidymis, epidydimis, and thymus) as well as gross pathology and histopathology findings. The port of entry NOAEL is 20 ppm and the LOAEL is 50 ppm based on minimal-mild degeneration of the olfactory epithelium.

In the F_1 generation, post natal survival was decreased at the 50 ppm concentration level as evidenced by the decrease in the mean litter size (relative to control) in conjunction with a lower mean live litter size (↓4 and 12%, respectively). Thus the live birth index at 50 ppm is 90.5% *vs.* 97% in the control group. This trend of decreased survival was maintained from PND 0-1 (83% *vs* 98% control) and PND 0-4 (74.3% *vs* 94.9% control). However, after culling survival was comparable across all treatment groups. Thirty seven of the 77 pups (14/20 litters) that were found dead in the 50 ppm group had no milk in their stomachs in contrast with 8/30 pups (7/14 litters) in the control group.

Beginning on PND 14, pup body weight was 6-10% lower than control in the 50 ppm group. Body weight gain was reduced during PND 7-14 in males (↓18%) and females (16%) and PND 14-21 (↓9% and 7% males and females, respectively) at the 50 ppm concentration. Necropsy evaluation revealed that, for pups sacrificed on PND 21, absolute thymus weights were reduced in males (↓13%) and females (↓17%), however, these organ weight decreases were not statistically significant or corroborated by relative weight measurements. For pups sacrificed on PND 35 the absolute brain, spleen, and thymus weights were reduced at 50 ppm (↓8-13, 21-26, and 8-27%, respectively). As was the case for the animals euthanized on PND 21, these changes were not statistically significant and were not reflected by relative organ weight measures.

In the F_2 generation, mean litter size and mean live litter size were reduced by 23 and 24%, respectively at 50 ppm. Similar to what was noted in the F_1 generation, survival in the 50

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[2] Since F_1 animals were directly exposed only as adults, the nasal histopathology observed was considered a parental effect rather than an offspring effect.

ppm group was reduced on PND 0-1 (82.6% *vs* 98% control) and PND 0-4 (74.3% *vs* 94.9% control) but was comparable across all test groups after culling. At the highest concentration tested, 23/32 pups (10/12 litters) found dead had no milk in their stomachs compared 9/15 pups (4/6 litters) in the control group.

Beginning on PND 7, pup weights were 8-20% lower than control in the 50 ppm group while pup weights in the 20 ppm test group were 10-14% lower than control beginning on PND 14. Body weight gains in the 20 and 50 ppm groups began decreasing on PND 4 by 13-23% and 19-37%, respectively. Pups sacrificed on PND 21 had decreased absolute thymus weights at 20 ppm (↓19% -25%) and 50 ppm (↓24- 28%), spleen weights at 20 ppm (22% ♀ only) and 50 ppm (23-28%), and brain weights at 50 ppm (6% ♂ only). For males, relative organ weights were comparable across all test groups but the relative thymus weight of females was 12-13% lower than control at concentrations ≥ 20 ppm.

Under the conditions of the study, the offspring NOAEL is 5 ppm and the LOAEL is 20 ppm based on decreases in body weight, body weight gain, as well as lower absolute and relative thymus weights.

Reproductive parameters such as sperm count, motility, and morphology, balanopreputial separation, and estrous cyclicity were unaffected by treatment with the test article. Attainment of vaginal patency, however, was delayed at 20 ppm (2 days) and 50 ppm (3 days). Also noted at the 50 ppm concentration was a 19% increase in the number of primordial follicles in conjunction with a 20% decrease in the number of corpora lutea.

Under the conditions of the study, the reproductive NOAEL is 5 ppm and the LOAEL is 20 ppm based on delays in attainment of vaginal patency.

This study is classified as **acceptable/guideline** and it **satisfies** the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

2) Kirkpatrick, D.T. (2003) A 24-month inhalation combined chronic toxicity/carcinogenicity study of iodomethane in rats. Wil Research Laboratories, Inc., Ashland OH. Study Number Wil-418019, December 2, 2003. MRID 46203707. Unpublished

In a combined chronic toxicity/carcinogenicity study in rats (MRID 46203707),iodomethane (99.7% a.i., Batch No. 02/Lot # 007403) was administered to Crl:CD®(SD)IGS BR rats *via* whole body inhalation at concentrations of 0, 5, 20, or 60 ppm for 6 hours/day 5 days/week. Sixty animals/sex/concentration were exposed to 0, 5, or 20 ppm iodomethane while 70/sex were exposed at the 60 ppm level. Animals were observed for moribundity and mortality twice daily and clinical observations once daily. Once a week a detailed physical examination was conducted including but not limited to evaluations of changes in appearance, autonomic activity (*e.g.* lacrimation, piloerection, pupil size, breathing patterns), gait, posture, response to handling, stereotypic and/or bizarre behavior. In addition, evaluations of clinical chemistry, hematology, urinalysis, gross pathology and histopathology parameters were conducted. This robust summary describes the findings reported in the One-Year Interim Report for this study.

The majority of the treatment-related findings were limited to animals in the 60 ppm group. An increase in mortality was reported at the 60 ppm concentration in males (8/70 *vs* 5/60 in control) and females (13/70 *vs* 1/60). Of these deaths, 14 (6 ♂ and 8 ♀) were attributed by the study authors to a malfunction of the inhalation chamber that lead to an overexposure of the animals to the test article.[3] Histopathological evaluation of tissues from decedents revealed a high incidence of salivary gland squamous cell metaplasia (7/8 ♂ and 9/11 ♀ *vs* 0 control), lymphoid depletion in the spleen (5/8 ♂ and 7/13 ♀ *vs* 0 control), lymphoid hystiocytosis of various organs, degeneration of the olfactory epithelium at Nasal Levels III-VI (6-7/8 ♂ and 4-13/13 ♀ *vs* 0 control), ultimobranchial cysts of the thyroid (2/8 ♂ and 5/13 ♀), and follicular cell hyperplasia (2/8 ♂ and 6/13 ♀ *vs* 0 in control group).

Clinical observations and physical examinations revealed a higher incidence of hypoactivity (4/70♂ and 3/70♀ *vs* 0 control), hyper-reactivity to touch (8/70 ♂ *vs* 2/60 control), and thinness (6/70 ♀ *vs* 0 control) at the 60 ppm exposure level. Also noted at this exposure level was a decrease in body weight of males (↓11-23%) and females (↓10-15%) beginning during the fourth week of exposure. Similarly, overall body weight gains were reduced by 24-26% in both sexes at 60 ppm. These decreases in body weight and body weight gain are accompanied by decreases in food consumption in males (↓7-21%) and females (↓5-20%). In general, hematology parameters were unaffected by treatment with the test article. The few changes noted were of minimal magnitude and sporadic rendering their toxicological relevance equivocal. During the week 26 clinical chemistry evaluations, increases in alkaline phosphatase (↑48% and 28% in males and females, respectively) and cholesterol (↑81% ♂ and ↑40% ♀) were noted at 60 ppm. Alterations of thyroid hormone levels and TSH were also observed at this exposure level [see Table 1]. Cholesterol levels were also elevated in females at the 20 ppm exposure level (↑33%). By the week 52 evaluation, however, alkaline phosphatase and cholesterol levels were comparable across treatment groups. Urinalysis parameters were unaffected by treatment with the test article except for a 45% decrease in urine volume noted at the 60 ppm concentration level during the week 52 assessment.

Gross pathology examination of animals sacrificed on schedule (*i.e.* week 52) revealed a 25% incidence of enlarged thyroids in males treated at the 60 ppm exposure level. This observation is consistent with the increased absolute and relative weight of the thyroid/parathyroid (↑83% and 120%, respectively) seen at this concentration level. Also noted at 60 ppm were absolute weight changes in the brain (↓11%♂ and 5%♀), kidneys (↓22%♂ and 16%♀), spleen (↓19%♂), heart (↓14%♂), and adrenal glands (↓17%♂). Organ weights relative to body weight and brain weights were generally comparable across test groups or higher than control suggesting that the decreases noted in the absolute weights were a function of overall decreased body weight rather than organ-specific toxicity. One year exposure to 60 ppm iodomethane elicited various histopathological changes primarily confined to the respiratory tract, thyroid, and salivary glands. Increased incidences of salivary gland squamous cell metaplasia, atrophy of salivary glands, ultimobranchial thyroid cysts, follicular cell hyperplasia, follicular cell adenomas, thyroid cytoplasmic vacuolation, as well as olfactory epithelium degeneration and cysts were reported at the highest concentration tested (60 ppm) [see Table 2]. An increase in the incidence of salivary gland

[3] Symbols: ♂ = male, ♀ = female

squamous cell metaplasia was also seen at the 20 ppm exposure concentration..

Under the conditions of this study, the interim NOAEL is 5 ppm; the LOAEL is established at 20 ppm based on increased incidence of salivary gland squamous cell metaplasia. The NOAEL for port of entry effects (respiratory tract) is 20 ppm and the LOAEL is 60 ppm based on degeneration of the olfactory epithelium.

This combined chronic toxicity/carcinogenicity study is **acceptable/non-guideline** and **does not** satisfy the guideline requirement for a in rats [OPPTS 870.4300); OECD 453].
In a combined chronic toxicity/carcinogenicity study in rats (MRID 46203707),iodomethane (99.7% a.i., Batch No. 02/Lot # 007403) was administered to Crl:CD®(SD)IGS BR rats *via* whole body inhalation at concentrations of 0, 5, 20, or 60 ppm for 6 hours/day 5 days/week. Sixty animals/sex/concentration were exposed to 0, 5, or 20 ppm iodomethane while 70/sex were exposed at the 60 ppm level. Animals were observed for moribundity and mortality twice daily and clinical observations once daily. Once a week a detailed physical examination was conducted including but not limited to evaluations of changes in appearance, autonomic activity (*e.g.* lacrimation, piloerection, pupil size, breathing patterns), gait, posture, response to handling, stereotypic and/or bizarre behavior. In addition, evaluations of clinical chemistry, hematology, urinalysis, gross pathology and histopathology parameters were conducted. This robust summary describes the findings reported in the One-Year Interim Report for this study.

The majority of the treatment-related findings were limited to animals in the 60 ppm group. An increase in mortality was reported at the 60 ppm concentration in males (8/70 *vs* 5/60 in control) and females (13/70 *vs* 1/60). Of these deaths, 14 (6 ♂ and 8 ♀) were attributed by the study authors to a malfunction of the inhalation chamber that lead to an overexposure of the animals to the test article.[4] Histopathological evaluation of tissues from decedents revealed a high incidence of salivary gland squamous cell metaplasia (7/8 ♂ and 9/11 ♀ *vs* 0 control), lymphoid depletion in the spleen (5/8 ♂ and 7/13 ♀ *vs* 0 control), lymphoid hystiocytosis of various organs, degeneration of the olfactory epithelium at Nasal Levels III-VI (6-7/8 ♂ and 4-13/13 ♀ *vs* 0 control), ultimobranchial cysts of the thyroid (2/8 ♂ and 5/13 ♀), and follicular cell hyperplasia (2/8 ♂ and 6/13 ♀ *vs* 0 in control group).

Clinical observations and physical examinations revealed a higher incidence of hypoactivity (4/70♂ and 3/70♀ *vs* 0 control), hyper-reactivity to touch (8/70 ♂ *vs* 2/60 control), and thinness (6/70 ♀ *vs* 0 control) at the 60 ppm exposure level. Also noted at this exposure level was a decrease in body weight of males (↓11-23%) and females (↓10-15%) beginning during the fourth week of exposure. Similarly, overall body weight gains were reduced by 24-26% in both sexes at 60 ppm. These decreases in body weight and body weight gain are accompanied by decreases in food consumption in males (↓7-21%) and females (↓5-20%). In general, hematology parameters were unaffected by treatment with the test article. The few changes noted were of minimal magnitude and sporadic rendering their toxicological relevance equivocal. During the week 26 clinical chemistry evaluations, increases in alkaline phosphatase (↑48% and 28% in males and females, respectively) and cholesterol (↑81% ♂ and ↑40% ♀) were noted at 60 ppm. Alterations of thyroid hormone levels and

[4] Symbols: ♂ = male, ♀ = female

TSH were also observed at this exposure level [see Table 1]. Cholesterol levels were also elevated in females at the 20 ppm exposure level (↑33%). By the week 52 evaluation, however, alkaline phosphatase and cholesterol levels were comparable across treatment groups. Urinalysis parameters were unaffected by treatment with the test article except for a 45% decrease in urine volume noted at the 60 ppm concentration level during the week 52 assessment.

Gross pathology examination of animals sacrificed on schedule (*i.e.* week 52) revealed a 25% incidence of enlarged thyroids in males treated at the 60 ppm exposure level. This observation is consistent with the increased absolute and relative weight of the thyroid/parathyroid (↑83% and 120%, respectively) seen at this concentration level. Also noted at 60 ppm were absolute weight changes in the brain (↓11%♂ and 5%♀), kidneys (↓22%♂ and 16%♀), spleen (↓19%♂), heart (↓14%♂), and adrenal glands (↓17%♂). Organ weights relative to body weight and brain weights were generally comparable across test groups or higher than control suggesting that the decreases noted in the absolute weights were a function of overall decreased body weight rather than organ-specific toxicity. One year exposure to 60 ppm iodomethane elicited various histopathological changes primarily confined to the respiratory tract, thyroid, and salivary glands. Increased incidences of salivary gland squamous cell metaplasia, atrophy of salivary glands, ultimobranchial thyroid cysts, follicular cell hyperplasia, follicular cell adenomas, thyroid cytoplasmic vacuolation, as well as olfactory epithelium degeneration and cysts were reported at the highest concentration tested (60 ppm) [see Table 2]. An increase in the incidence of salivary gland squamous cell metaplasia was also seen at the 20 ppm exposure concentration..

Under the conditions of this study, the interim NOAEL is 5 ppm; the LOAEL is established at 20 ppm based on increased incidence of salivary gland squamous cell metaplasia. The NOAEL for port of entry effects (respiratory tract) is 20 ppm and the LOAEL is 60 ppm based on degeneration of the olfactory epithelium.

This combined chronic toxicity/carcinogenicity study is **acceptable/non-guideline** and **does not** satisfy the guideline requirement for a in rats [OPPTS 870.4300); OECD 453].

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DATA EVALUATION RECORD

IODOMETHANE

Study Type: §83-4; Multigeneration Reproduction Study in Rats

Work Assignment No. 1-01-10 (MRID 45710301)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
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Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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Signature: [signature] **Date** 9/29/04
Signature: [signature] **Date** 9/29/04

TXR#: 0052771

DATA EVALUATION RECORD
See TXR# 0050463 for review of interim report

STUDY TYPE: Reproduction and Fertility Effects Study - [rat] OPPTS 870.3800 [§83-4]; OECD 416.

PC CODE: 000011 **DP BARCODE:** D304187

TEST MATERIAL (PURITY): Iodomethane (99.7% a.i.)

SYNONYMS: CH_3I, Methyl iodide

CITATION: Nemec, M.D. (2001) An inhalation two-generation reproductive toxicity study of iodomethane in rats (comprehensive final report). WIL Research Laboratories, Inc., Ashland, OH. Laboratory Study No.: WIL-418004, May 24, 2001. MRID 46203710 Unpublished.

SPONSOR: Arvesta Corporation, 100 First Street, Suite 1700, San Francisco, CA

EXECUTIVE SUMMARY: In a two-generation reproduction toxicity study, iodomethane (99.7% a.i.; Lot/batch # 007403/02) was administered via whole-body inhalation to Crl:CD®(SD)IGS BR rats (30/sex/concentration) for 6 hours/day at nominal concentration levels of 0, 5, 20, or 50 ppm (equivalent to analytical concentrations of 0, 5, 21, and 50 ppm). The P animals were exposed to the test article for at least 70 days prior to mating to produce the F_1 litters. Exposure of the P males continued throughout mating and until the day prior to euthanasia. The P females continued to be exposed throughout mating and through gestation day (GD) 20, at which point exposure was discontinued. Daily exposure of the P females was reinitiated on lactation day (LD) 5 and continued until the day prior to euthanasia. After weaning, F_1 animals (30/sex/concentration) were selected, equalized by sex, to become the parents of the F_2 generation and, beginning on post-natal day (PND) 28, were exposed to the same concentration test atmosphere as their dam.

In adult animals (P and F_1), the majority of the effects noted occurred at the highest concentration tested (HCT; 50 ppm).[1] **In the P generation,** lower body weights, body weight gains, and food efficiencies were noted in males at this concentration relative to control. These differences -

[1] Abbreviations: HCT = highest concentration tested

though statistically significant - were sporadic (weeks 3 and 9-10 only), and not considered to be toxicologically relevant. In the case of females, body weights were consistently 4-8% lower than control at 50 ppm ($p \leq 0.05$ or 0.01) beginning during the 8th week of premating and throughout gestation and lactation. At 50 ppm, female weight gain during pre-mating and late gestation (GD 14-20) was 13% lower than control ($p \leq 0.05$). However, at 50 ppm overall body weight gain was approximately 10% lower than control during gestation and 31% higher during lactation. Other effects noted at 50 ppm were decreases in organ weights, gross pathology and histopathology findings. The absolute organ weights affected included adrenal gland (↓15%, males and females), and thymus weights which were increased by 18-26% (males only) at concentrations ≥ 20 ppm.. Relative adrenal weights were decreased (↓17 and 8% in males and females, respectively) while relative thymus weights were increased by 20% (males only). During necropsy, animals exposed to iodomethane at concentrations ≥ 20 ppm exhibited slight increases in the incidence of dark red discoloration on the mandibular lymph node (2/30 and 3/30 at 20 and 50 ppm, respectively *vs.* 0 control) and white area(s) on the lungs (2/30 and 3/30 at 20 and 50 ppm, respectively *vs* 0/30 controls). The toxicological relevance of these findings is considered to be equivocal given their low incidence and the lack of histopathological correlates. The histopathological changes occurred primarily in the liver and respiratory tract. At 50 ppm, the following microscopic findings were noted in males: minimal to mild hepatocellular necrosis (4/30 vs 1/30 controls); minimal to mild subacute inflammation in the lungs (14/30 vs 9/30 controls); mild to moderate hemorrhage of the mandibular lymph node (4/30; controls not examined); and minimal to moderate degeneration of the olfactory epithelium at Nasal Levels II (14/30), III (11/30), and IV (10/30) *vs.* none in control. Females treated at the 50 ppm concentration level exhibited minimal to mild degeneration of the olfactory epithelium at Nasal Levels II (11/30), III (10/30), and IV (6/30) *vs* 0/30 in controls. No other histopathological findings were reported for females

In F_1 adults, male body weight was 8-14% ($p \leq 0.05$ or 0.01)lower at 50 ppm than control throughout pre-mating while body weight gain was 10% lower ($p \leq 0.01$) during weeks 3-4 of pre-mating but comparable or higher than controls during the remainder of the pre-mating period. Female body weights were decreased 6-14% during the 2nd and 9th week of premating and 6-8% during gestation and lactation at the 50 ppm concentration. At this concentration, overall female body weight gain was unaffected during pre-mating and lactation but decreased by 21% during gestation. This is consistent with the observation of a 17% decrease in food efficiency noted during gestation. Absolute organ weights affected by compound administration at the 50 ppm concentration level are: brain (↓8% ♂ and ♀), kidneys (↓12%♂, ↓7% ♀), adrenal glands (↓20%♂, ↓22%♂), testis (↓9%), epididymis (↓8%), cauda epididymis (↓8%), and thymus (↑18%, ♂ only). Testicular weights were also reduced ≈8% at the 20 ppm concentration. Relative organ weights at the 50 ppm concentration were higher than controls for the liver (≈10% in ♂ and ♀), and the thymus (↑19% ♂ only). However, the relative adrenal weights were decreased by 12-19% at ≥ 20 ppm in both males and females. During necropsy, 7/28 males exhibited dilated renal pelvis at the 50 ppm level vs 0 in control. In 50 ppm males, histopathology findings consisted exclusively of minimal to mild degeneration of the olfactory epithelium at Nasal Levels II (5/28), III (4/28), and IV (2/28) *vs* 0 control. Females exposed at the 50 ppm level had a slight (non-statistically significant) increase in the incidence of chronic

progressive nephropathy (7/30 *vs* 3/29 control), renal calculi (4/30 *vs* 0 control), and minimal-mild degeneration of the olfactory epithelium at Nasal Level II (7/30), Level III (7/30), and Level IV (3/30) *vs* 0 in control.[2]

Under the conditions of the study, the systemic parental NOAEL is 20 ppm and the LOAEL is established at 50 ppm based on decreases in body weight, body weight gain, changes in organ weights (adrenal glands, testis, cauda epidymis, epidydimis, and thymus) as well as gross pathology and histopathology findings. The port of entry NOAEL is 20 ppm and the LOAEL is 50 ppm based on minimal-mild degeneration of the olfactory epithelium.

In the F_1 generation, post natal survival was decreased at the 50 ppm concentration level as evidenced by the decrease in the mean litter size (relative to control) in conjunction with a lower mean live litter size (↓4 and 12%, respectively). Thus the live birth index at 50 ppm is 90.5% *vs.* 97% in the control group. This trend of decreased survival was maintained from PND 0-1 (83% *vs* 98% control) and PND 0-4 (74.3% *vs* 94.9% control). However, after culling survival was comparable across all treatment groups. Thirty seven of the 77 pups (14/20 litters) that were found dead in the 50 ppm group had no milk in their stomachs in contrast with 8/30 pups (7/14 litters) in the control group.

Beginning on PND 14, pup body weight was 6-10% lower than control in the 50 ppm group. Body weight gain was reduced during PND 7-14 in males (↓18%) and females (16%) and PND 14-21 (↓9% and 7% males and females, respectively) at the 50 ppm concentration. Necropsy evaluation revealed that, for pups sacrificed on PND 21, absolute thymus weights were reduced in males (↓13%) and females (↓17%), however, these organ weight decreases were not statistically significant or corroborated by relative weight measurements. For pups sacrificed on PND 35 the absolute brain, spleen, and thymus weights were reduced at 50 ppm (↓8-13, 21-26, and 8-27%, respectively). As was the case for the animals euthanized on PND 21, these changes were not statistically significant and were not reflected by relative organ weight measures.

In the F_2 generation, mean litter size and mean live litter size were reduced by 23 and 24%, respectively at 50 ppm. Similar to what was noted in the F_1 generation, survival in the 50 ppm group was reduced on PND 0-1 (82.6% *vs* 98% control) and PND 0-4 (74.3% *vs* 94.9% control) but was comparable across all test groups after culling. At the highest concentration tested, 23/32 pups (10/12 litters) found dead had no milk in their stomachs compared 9/15 pups (4/6 litters) in the control group.

Beginning on PND 7, pup weights were 8-20% lower than control in the 50 ppm group while pup weights in the 20 ppm test group were 10-14% lower than control beginning on PND 14. Body weight gains in the 20 and 50 ppm groups began decreasing on PND 4 by 13-23% and 19-37%, respectively. Pups sacrificed on PND 21 had decreased absolute thymus weights at 20 ppm

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[2] Since F_1 animals were directly exposed only as adults, the nasal histopathology observed was considered a parental effect rather than an offspring effect.

(↓19% -25%) and 50 ppm (↓24- 28%), spleen weights at 20 ppm (22% ♀ only) and 50 ppm (23-28%), and brain weights at 50 ppm (6% ♂ only). For males, relative organ weights were comparable across all test groups but the relative thymus weight of females was 12-13% lower than control at concentrations ≥ 20 ppm.

Under the conditions of the study, the offspring NOAEL is 5 ppm and the LOAEL is 20 ppm based on decreases in body weight, body weight gain, as well as lower absolute and relative thymus weights.

Reproductive parameters such as sperm count, motility, and morphology, balanopreputial separation, and estrous cyclicity were unaffected by treatment with the test article. Attainment of vaginal patency, however, was delayed at 20 ppm (2 days) and 50 ppm (3 days). Also noted at the 50 ppm concentration was a 19% increase in the number of primordial follicles in conjunction with a 20% decrease in the number of corpora lutea.

Under the conditions of the study, the reproductive NOAEL is 5 ppm and the LOAEL is 20 ppm based on delays in attainment of vaginal patency.

This study is classified as **acceptable/guideline** and it **satisfies** the guideline requirement for a two-generation reproductive study (OPPTS 870.3800); OECD 416 in rats.

COMPLIANCE: Signed and dated Data Confidentiality, Quality Assurance, GLP, and Flagging statements were provided.

Note: F_1 pups were not directly exposed to iodomethane until PND 28 while F_2 pups received no post-natal exposure. Thus, exposure to the test article during critical windows of development was minimal.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material: Iodomethane

Description:	Deep yellow, translucent liquid
Lot/Batch #:	007403/02
Purity:	99.7% a.i.
Compound Stability:	The test substance was stable in the test atmosphere throughout the study.
CAS # of TGAI:	74-88-4
Structure:	$I\text{-}CH_3$

2. Vehicle and/or positive control: Air

3. Test animals:

Species:	Rat	
Strain:	Crl:CD®(SD)IGS BR	
Age at study initiation:	(P) approximately 6 weeks; (F_1) 28 days	
Wt. at study initiation:	(P) Males: 181-236 g; Females: 148-182 g (F_1 range of group means at PND 28 [Week 17]) Males: 52-60 g; Females: 51-58 g	
Source:	Charles River Laboratories, Raleigh, NC	
Housing:	All male rats were housed individually (except during mating) in suspended, wire-mesh cages. All female rats were housed individually in wire-mesh cages during premating. Following positive evidence of mating, females were housed in plastic maternity cages with nesting material throughout gestation and until weaning on lactation day 21.	
Diet:	Certified Rodent LabDiet® 5002 (PMI Nutrition International, Inc.), *ad libitum*, except during each 6-hour daily exposure.	
Water:	Reverse-osmosis tap water, *ad libitum*, except during each 6-hour daily exposure.	
Environmental conditions:	**Temperature:**	19.3-22.4°C
	Humidity:	36.6-60.3%
	Air changes:	10/hour
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	14 days	

B. PROCEDURES AND STUDY DESIGN

1. Mating procedure: Animals from the same test group were paired (1 female:1 male) for mating in the home cage of the male for a maximum of 14 days until evidence of mating (copulatory plug or presence of sperm in a vaginal smear) was observed. The day on which evidence of mating was found was termed gestation day (GD) 0. After successful mating, each pregnant female was housed individually in a plastic maternity cage with nesting material. If evidence of mating was not found after 14 days' observation, no further matings were attempted, and the female was housed in a plastic maternity cage with nesting material.

2. Study schedule: The P and F_1 animals were exposed to the test atmosphere for 6 hours/day, 7 days/week for at least 70 consecutive days prior to mating. Parental males continued to be exposed throughout mating and until the day prior to euthanasia following selection of the F_1 parental animals. Parental females continued to be exposed throughout mating and gestation

until GD 20 and from lactation day (LD) 5 until the day prior to euthanasia; exposures were discontinued from GD 21 through LD 4. During lactation, dams were removed from their litters for the exposure period. Selection of parents for the F_1 generation (30/sex/group) was made when the pups were weaned at post-natal day (PND) 21. Due to mortalities in the selected F_1 pups (including controls) after initiation of direct exposure to the test atmospheres on PND 22, daily exposures were suspended and not resumed until PND 28. The selected F_1 pups continued to be group housed until PND 35 and were then housed individually until mating to produce the F_2 generation.

3. Animal assignment: P animals were randomly assigned (stratified by body weight) to test groups as seen in Table 1.

TABLE 1. Study design[a]

Test Group	Target Conc. (ppm)	Analytical Conc. (ppm)[b]	Animals/group			
			P Males	P Females	F_1 Males	F_1 Females
Control	0	0	30	30	30	30
Low	5	5	30	30	30	30
Mid	20	21	30	30	30	30
High	50	50	30	30	30	30

a Data were obtained from the study report, page 35
b Analytical concentrations were obtained from pages 3081 and 3113 of the study report.

4. Concentration selection rationale: No concentration rationale was provided.

5. Generation of test atmosphere / chamber description: Each animal was exposed for 6 hours/day, 7 days/week, in a 2.0 m^3 glass and stainless-steel, whole-body inhalation chamber with an air flow of 12 to 15 changes/hour. Chamber ventilation flow rate was 450 LPM (actual group means ranged from 456-457 LPM), and generation flow rate ranged from approximately 5 to 50 mL/min. Group mean chamber temperature averaged 21-24°C, and chamber relative humidity averaged 44-54%. Oxygen content was adequate and averaged 20.2-20.3%. The overall mean nominal concentrations were 7, 25, and 59 ppm for the P generation and 6, 24, and 56 ppm in the F_1 generation, for the 5, 20, and 50 ppm groups, respectively. Actual concentration of the test substance in each chamber was measured by gas chromatography approximately every 35 minutes during each 6-hour exposure period. Stability of the test substance in the test atmosphere was verified from the concentration analyses during each exposure period throughout the duration of the study. Homogeneity of the test substance in the chamber atmosphere was demonstrated immediately prior to the study for the 50 ppm chamber and immediately following the study for the 5 and 20 ppm chambers by measuring the exposure concentration at four different locations within the chamber and comparing these values to a reference location.

Results -

Test atmosphere concentration and stability (mean ppm ± SD; % CV)

P generation:	F_1 generation:
5 ppm: 5 ± 0.5; 10.46	5 ppm: 5 ± 0.5; 9.90
20 ppm: 20 ± 0.9; 4.37	20 ppm: 21 ± 0.8; 4.01
50 ppm: 50 ± 1.5; 3.01	50 ppm: 49 ± 1.8; 3.61

Homogeneity of test atmosphere within chamber (range as % of reference): 89.2-111.9%

C. OBSERVATIONS

1. Parental animals: All animals were examined twice daily (at least 7 hours apart) for mortality, moribundity, and clinical signs of toxicity. Additionally, animals were observed at the midpoint during daily exposure (only animals visible in chambers) and within one hour following exposure. Furthermore, during the period of expected parturition, females were observed twice daily for labor difficulties. Detailed physical examinations were performed weekly. For the males, body weights were measured weekly throughout the study, and food consumption was measured weekly throughout the pre-mating and post-mating periods. For the females, body weights and food consumption were recorded weekly during pre-mating and on GDs 0, 4, 7, 11, 14, and 20 and on LDs 1, 4, 7, 14, and 21. Body weight gains and food efficiency were calculated for each of these intervals and for the overall gestation (GD 0-20) and lactation (LD 1-21) periods. Estrous cycle length was determined from daily vaginal smears of each female from 21 days prior to mating until evidence of mating was determined. Sperm numbers (10^6/g tissue), production rate (10^6/g tissue/day), motility (%), and morphology were evaluated in the testes and epididymides at scheduled sacrifice.

2. Litter observations: The following litter parameters (X) were observed (Table 2):

TABLE 2. F_1 / F_2 Litter observations [a]

Observation	Time of observation (lactation day)					
	Day 0/1	Day 4[b]	Day 4[c]	Day 7	Day 14	Day 21
Number of live pups	X	X	X	X	X	X
Pup weight	X	X		X	X	X
Clinical signs	X	X		X	X	X
External alterations	X	X		X	X	X
Number of dead pups	X	X	X	X	X	X
Anogenital distance	X					
Sex of each pup (M/F)	X	X	X	X	X	X

a Parameters evaluated were obtained from pages 43-44 in the study report.
b Before standardization (culling)
c After standardization (culling)

On PND 4, litters were standardized to a maximum of 8 pups/litter (4/sex/litter, when possible); excess pups were weighed, euthanized, and discarded. In addition to the parameters noted in Table 2, developmental landmarks were recorded in each pup selected to be parents of the F_2 generation. Male pups were observed daily for balanopreputial separation beginning on PND 35; and female pups were observed daily for vaginal patency beginning on PND 25.

3. Postmortem observations:

1) Parental animals: Following selection of the F_1 generation, all P generation parents were given a detailed clinical examination and then euthanized after approximately 126-132 days of exposure. A complete gross necropsy was performed on all animals and included the aorta, bone, bone marrow, eyes, optic nerve, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, heart, lymph node, pancreas, sciatic nerve, salivary gland, skeletal muscle, skin, mammary gland, spinal cord, thyroid, parathyroids, trachea, urinary bladder and the tissues listed in the following table. The checked (X) tissues were evaluated microscopically in all animals in the control and high concentration groups, with the exception of the nasal cavities which were examined in all groups. Additionally, the (XX) organs were weighed in all animals.

XX	Adrenal glands	XX	Cervix
XX	Brain	XX	Ovaries [b]
XX	Kidneys	XX	Uterus (with oviducts)
XX	Liver	X	Vagina
X	Lung		
X	Nasal cavities [a]	XX	Epididymis [c] (caput, corpus, and cauda)
XX	Pituitary	XX	Prostate
XX	Spleen	XX	Seminal vesicles with coagulating gland
XX	Thymus	XX	Testis [c](right)
X	Gross lesions	X	Vas deferens

a The nasal cavities were processed and sectioned (4 levels) according to the method described by Young.
b One section of each ovary was evaluated.
c These paired organs were weighed separately; the total and cauda epididymis were weighed. The right testis (transverse sections) and epididymis were stained with PAS and hematoxylin.

2) Offspring: The F_1 offspring not selected as parental animals were retained as possible replacement animals and were then sacrificed on PND 34 or 35 and subjected to a gross necropsy. One pup/sex/litter (when available) was selected for complete necropsy from the F_1 and F_2 weanlings on PND 21 and, additionally, from the surplus F_1 weanlings on PND 35. Absolute and relative (to body) weights of the brain, spleen, and thymus were obtained from these animals at necropsy. Microscopic examinations were not performed.

D. DATA ANALYSIS

1. Statistical analyses: The following statistical methods were used:

Parameter	Method of Statistical Analysis
Parental mating and fertility indices	Chi-square test with Yates' correction factor
Parental (weekly, gestation, and lactation) and offspring body weight; parental food consumption, food efficiency, estrous cycle length, pre-coital intervals, gestation length, implantation sites, live litter size, unaccounted sites, number of pups born, balanopreputial separation (day of acquisition and body weight), vaginal patency (day of acquisition and body weight), anogenital distance, absolute and relative organ weights, sperm production rate, epididymal and testicular sperm numbers	One-way analysis of variance (ANOVA) followed by Dunnett's test for pair-wise comparisons with control, if appropriate (parametric).
Postnatal pup survival (litter proportions), sex ratios, sperm motility, sperm morphology.	Kruskal-Wallis followed by Mann-Whitney U-test for pair-wise comparisons with control, if appropriate (non-parametric).
Histopathology	Fisher's Exact test

All tests were two-tailed, and significance was denoted at $p \leq 0.05$.

2. Indices:

Reproductive indices: The following reproductive indices were calculated from breeding and parturition records and sperm assessment of animals in the study:

Male (female) mating index (%) = # males (females) with evidence of mating/# males (females) used for mating x 100

Female fertility index (%) = # females with confirmed pregnancy/# used for mating x 100

Male fertility index (%) = # males siring a litter/# used for mating x 100

Motile sperm (%) = Number of motile sperm/number of sperm counted x 100

Offspring viability indices: The following viability indices were calculated:

Live litter size = # viable pups on PND 0/# litters with viable pups on PND 0

Postnatal survival between birth and PND 0 or PND 4 (pre-cull) (% per litter) = $\sum$(# viable pups per litter on PND 0 or PND 4/# pups born per litter)/# litters per group x 100

Postnatal survival for all other intervals (% per litter) = $\sum$(# viable pups per litter at end of interval N/# viable pups per litter at start of interval N)/# litters per group x 100; where N = PND 0-1, 1-4 (pre-cull), 4 (post-cull)-7, 7-14, 14-21, or 4 (post-cull)-21.

3. Historical control data: Historical control data were comprised of 32 studies from 1996-2000 and included the following parameters: reproduction data; sperm measurements; and offspring viability, body weights, anogenital distance, and sexual maturation.

II. RESULTS

A. PARENTAL ANIMALS

1. Mortality and clinical signs: No mortalities were noted in either sex of the P generation. In the F_1 parents, parental males were found dead in the control (1), 5 ppm (1), and 50 ppm (2) groups between study weeks 18 and 36; the cause of death was undetermined. Because of the mortality observed in the control group and the absence of clinical findings prior to death, these deaths were considered incidental and unrelated to treatment. Additionally, one control female was euthanized *in extremis* during study week 29 because of a mass on the right lateral abdominal area. No treatment-related clinical signs were observed in the P or F_1 males or females during the weekly detailed physical examinations or during the observations conducted at the mid-point of exposure or one-hour post-exposure. In the P females, several clinical findings were noted at 50 ppm, such as hair loss, swollen/impaired use of limbs, and dried secretions in the anogenital area; however, these findings were deemed unrelated to treatment because they occurred with minimal incidence and frequency. All other clinical observations were unrelated to concentration.

2. Body weight and food consumption: Selected body weight, body weight gain, food consumption, and food efficiency data are presented in Tables 3a through 3d.

In the 50 ppm P animals, body weights were decreased (↓4-8%; $p \leq 0.05$) in the males during Week 3 and in the females during pre-mating Weeks 8-10, throughout gestation, and during lactation days (LD) 1-7. Weekly body weight gains were decreased ($p \leq 0.05$) in the males during pre-mating Weeks 0-1, 1-2, and 9-10 (↓13-29%) and post-mating Weeks 15-16 (↓45%) and in the females during gestation days (GD) 14-20 (↓13%). Cumulative body weight gains were decreased (↓8-14%; $p \leq 0.05$) in the males during Weeks 1-5 and in the females during Weeks 5 and 8-10. Throughout lactation, weekly and cumulative body weight gains of the females were comparable to controls. Absolute food consumption was increased ($p \leq 0.05$) in the females during pre-mating Weeks 1-2 (↑5%) and in the males during post-mating Weeks 13-15 (↑4-8%). Food efficiency was decreased ($p \leq 0.05$) during pre-mating in the males during Weeks 0-2 and 9-10 and in the females during Weeks 2-3 (↓12-33%); food efficiency was also decreased ($p \leq 0.05$) in the males during post-mating Weeks 15-16 (↓49%).

In the F_1 parents, body weights were decreased ($p \leq 0.05$) in the 50 ppm males during pre-mating (↓8-14%, with the exception of Week 3) and throughout mating and post-mating (↓7-10%). In the 50 ppm females, body weights were decreased (↓6-14%; $p \leq 0.05$) at pre-mating weeks 2 and 9. Body weight gains were decreased ($p \leq 0.05$) in the males at ≥20 ppm during Weeks 3-4 (↓10%) and at 50 ppm during Weeks 2-3 and 8-9 (↓13-26%). Cumulative body weight gains were decreased in the ≥20 ppm males during the first two weeks (↓7-10%), in the 50 ppm males at Week 3 (↓7%), and in the 50 ppm females at Week 5 (↓10%). During gestation, body weights were decreased at 50 ppm on GD 11 and 20 (↓6-8%; $p \leq 0.05$). Body weight gains were decreased (↓21-24%; $p \leq 0.01$) at 50 ppm on GD 14-20 and for the overall (GD 0-20) gestation period. During lactation, body weights remained decreased (↓6-7%; $p \leq 0.05$) at this concentration during LD 4, 7, and 14; however, body weight gains were comparable to controls. There were no effects of treatment on food consumption or food efficiency during pre-mating in the F_1 males or females. During gestation, food efficiency was decreased (↓17%; $p \leq 0.01$) at 50 ppm for the overall (GD 0-20) gestation period, while food consumption was comparable to controls. During lactation, food consumption was decreased ($p \leq 0.01$) at 50 ppm during LD 1-4 (↓16%) and at ≥20 ppm during LD 7-21 (↓11-24%), resulting in decreased food consumption for the overall (LD 1-21) lactation period at ≥20 ppm (↓13-21%). Food efficiency was comparable to controls during lactation.

There were no other treatment-related differences in body weights, body weight gains, food consumption, or food efficiency in the P or F_1 parents.

TABLE 3a. Mean (±SD) body weight, body weight gain, food consumption, and food efficiency - pre-mating, P generation [a]

Observations/study week		Concentration (ppm)			
		Control	5	20	50
P Generation Males - Pre-mating					
Mean body weight (g)	Week 1	269 ± 18.0	267 ± 20.6	266 ± 16.5	260 ± 16.3
Mean body weight (g)	Week 3	354 ± 23.2	349 ± 26.3	349 ± 24.5	337 ± 20.7* (↓5)
Mean body weight (g)	Week 10	503 ± 39.1	502 ± 44.5	508 ± 40.8	485 ± 41.4
Mean weight gain (g)	Week 1-2	48 ± 8.3	44 ± 7.5	45 ± 8.5	42 ± 7.8** (↓13)
Mean weight gain (g)	Week 9-10	17 ± 5.8	14 ± 5.5	15 ± 5.5	12 ± 6.7** (↓29)
Pre-mating (Weeks 0-10) weight gain (g)		283 ± 34.6	283 ± 37.7	289 ± 35.4	266 ± 36.5
Mean food consumption (g/animal/day) Week 0-1		25 ± 2.0	25 ± 2.1	25 ± 1.8	25 ± 2.0
Mean food consumption (g/animal/day) Week 9-10		27 ± 2.3	27 ± 2.5	27 ± 2.3	27 ± 3.0
Mean food efficiency (%)	Week 1-2	27.1 ± 4.41	24.9 ± 3.50	25.6 ± 3.80	23.8 ± 4.26** (↓12)
Mean food efficiency (%)	Week 9-10	8.7 ± 2.88	7.6 ± 2.71	7.8 ± 2.68	5.8 ± 4.07** (↓33)
P Generation Females - Pre-mating					
Mean body weight (g)	Week 1	193 ± 11.7	195 ± 11.2	190 ± 7.2	192 ± 10.9
Mean body weight (g)	Week 8	291 ± 20.8	293 ± 18.3	288 ± 13.0	278 ± 23.0* (↓4)
Mean body weight (g)	Week 10	303 ± 20.5	303 ± 18.5	298 ± 13.5	285 ± 25.0** (↓6)
Pre-mating (Weeks 0-10) weight gain (g)		133 ± 16.6	133 ± 14.5	129 ± 15.4	116 ± 21.0** (↓13)
Mean food consumption (g/animal/day) Week 1-2		19 ± 1.8	20 ± 1.8	19 ± 1.2	20 ± 1.7* (↑5)
Mean food efficiency (%)	Week 2-3	13.5 ± 4.79	12.3 ± 3.62	13.9 ± 4.21	10.5 ± 3.80* (↓22)

a Data obtained from Tables 7 through 9 on pages 113-136, Table14 on pages 141-148, and Table 16 on pages 157-164 in the study report; n=30. Percent difference from controls is presented parenthetically.

* Significantly different from control at $p \leq 0.05$.

** Significantly different from control at $p \leq 0.01$.

TABLE 3b. Mean (±SD) body weight, body weight gain, food consumption, and food efficiency - pre-mating, F_1 generation [a]

Observations/study week [b]	Concentration (ppm)			
	Control	5	20	50
F_1 Generation Males - Pre-mating				
Mean body weight (g) Week 2	95 ± 18.5	98 ± 17.3	95 ± 17.5	82 ± 16.3* (↓14)
Mean body weight (g) Week 10	445 ± 36.3	453 ± 36.3	441 ± 48.5	411 ± 40.9** (↓8)
Mean weight gain (g) Week 3-4	60 ± 6	58 ± 6.1	54 ± 8.4** (↓10)	54 ± 7.1** (↓10)
Mean weight gain (g) Week 8-9	19 ± 6.7	21 ± 7.7	22 ± 6.4	24 ± 4.8* (↑26)
Pre-mating (Weeks 0-10) weight gain (g)	287 ± 28.2	292 ± 37.2	286 ± 37.1	273 ± 38.9
Mean food consumption (g/animal/day) Week 0-1	26 ± 2.5	25 ± 2.0	25 ± 3.3	25 ± 2.4
Mean food consumption (g/animal/day) Week 9-10	28 ± 1.8	29 ± 2.6	28 ± 2.8	28 ± 2.5
Mean food efficiency (%) Week 0-1	36.1 ± 5.27	35.2 ± 4.78	34.9 ± 6.66	32.6 ± 3.66
Mean food efficiency (%) Week 9-10	7.2 ± 3.68	7.2 ± 3.75	6.9 ± 2.69	7.1 ± 2.21
F_1 Generation Females - Pre-mating				
Mean body weight (g) Week 2	88 ± 15.5	86 ± 17.6	88 ± 18.0	76 ± 16.2* (↓14)
Mean body weight (g) Week 9	262 ± 18.6	269 ± 30.1	270 ± 19.5	247 ± 17.3* (↓6)
Pre-mating (Weeks 0-10) weight gain (g)	126 ± 18.8	138 ± 25.3	133 ± 18.8	121 ± 23.1
Mean food consumption (g/animal/day) Week 0-1	20 ± 2.2	20 ± 2.2	21 ± 2.2	21 ± 2.4* (↑5)
Mean food consumption (g/animal/day) Week 9-10	21 ± 2.3	22 ± 3.0	21 ± 2.0	21 ± 2.4
Mean food efficiency (%) Week 0-1	22.8 ± 8.04	27.5 ± 8.60	24.6 ± 5.90	24.4 ± 5.94
Mean food efficiency (%) Week 9-10	2.0 ± 6.19	4.3 ± 4.41	3.5 ± 3.20	4.6 ± 2.74

a Data obtained from Tables 60 through 62 on pages 262-289 and Tables 67 through 69 on pages 294-317 in the study report; n=18-30. Percent difference from controls is presented parenthetically.

b Note that Study Weeks 17-26 in MRID 45710301 correspond to pre-mating weeks 1-10 in the F_1 generation.

* Significantly different from control at $p \leq 0.05$.

** Significantly different from control at $p \leq 0.01$.

TABLE 3c. Mean (±SD) body weight and food consumption - gestation and lactation, P generation [a]

Observations/study interval		Concentration (ppm)			
		Control	5	20	50
P Generation: Gestation					
Mean body weight (g)	GD 0	302 ± 23.2	303 ± 19.6	296 ± 17.2	285 ± 25.7* (↓6)
Mean body weight (g)	GD 4	321 ± 22.8	316 ± 21.3	311 ± 19.8	304 ± 27.2* (↓5)
Mean body weight (g)	GD 20	430 ± 28.6	429 ± 32.1	419 ± 32.2	399 ± 28.7** (↓7)
Mean weight gain (g)	GD 14-20	70 ± 11.6	73 ± 10.2	72 ± 15.4	61 ± 12.1* (↓13)
Overall weight gain (g)	GD 0-20	128 ± 22.0	126 ± 17.2	123 ± 23.0	115 ± 12.7
Mean food consumption (g/animal/day) GD 0-20		23 ± 2.3	23 ± 1.9	23 ± 2.4	22 ± 1.7
Mean food efficiency (%)	GD 0-20	27.5 ± 3.56	27.7 ± 2.43	27.3 ± 4.27	25.8 ± 3.22
P Generation: Lactation					
Mean body weight (g)	LD 1	328 ± 25.1	325 ± 22.3	319 ± 20.6	301 ± 23.1** (↓8)
Mean body weight (g)	LD 7	339 ± 24.4	338 ± 19.1	334 ± 20.1	314 ± 24.0** (↓7)
Overall weight gain (g)	LD 1-21	35 ± 20.4	29 ± 19.8	36 ± 19.9	46 ± 24.3
Mean food consumption (g/animal/day) LD 1-21		47 ± 6.8	48 ± 4.6	47 ± 6.2	46 ± 4.2
Mean food efficiency (%)	LD 1-21	3.9 ± 2.33	3.2 ± 2.08	3.9 ± 1.95	5.0 ± 2.47

a Data obtained from Tables 10 through 13 on pages 137-140, Table17 on page 165, Tables 19-20 on page 167-168, and Table 22 on page 170 in the study report; n=23-29. Percent difference from controls is presented parenthetically.

* Significantly different from control at $p \leq 0.05$.

** Significantly different from control at $p \leq 0.01$.

TABLE 3d. Mean (±SD) body weight and food consumption - gestation and lactation, F_1 generation [a]

Observations/study interval		Concentration (ppm)			
		Control	5	20	50
P Generation - Gestation					
Mean body weight (g)	GD 11	338 ± 25.9	352 ± 34.2	344 ± 23.1	319 ± 20.1* (↓6)
Mean body weight (g)	GD 20	419 ± 27.1	439 ± 41.0	424 ± 27.0	385 ± 33.4** (↓8)
Mean weight gain (g)	GD 14-20	72 ± 12.3	77 ± 26.1	67 ± 11.1	55 ± 21.2** (↓24)
Overall weight gain (g)	GD 0-20	130 ± 13.7	134 ± 28.0	124 ± 14.7	103 ± 29.3** (↓21)
Mean food consumption (g/animal/day) GD 0-20		24 ± 1.8	25 ± 2.1	23 ± 2.5	23 ± 3.1
Mean food efficiency (%)	GD 0-20	27.6 ± 2.44	27.6 ± 6.35	27.1 ± 3.08	22.9 ± 6.57** (↓17)
F_1 Generation - Lactation					
Mean body weight (g)	LD 4	333 ± 25.1	343 ± 31.3	333 ± 23.4	310 ± 24.2** (↓7)
Mean body weight (g)	LD 7	337 ± 25.4	342 ± 31.8	336 ± 22.3	318 ± 20.6* (↓6)
Mean body weight (g)	LD 14	357 ± 26.8	363 ± 31.3	356 ± 29.6	333 ± 23.3* (↓7)
Overall weight gain (g)	LD 1-21	37 ± 16.3	23 ± 21.9	25 ± 24.7	34 ± 18.0
Mean food consumption (g/animal/day) LD1-21		52 ± 3.0	50 ± 3.4	45 ± 3.4** (↓13)	41 ± 6.6** (↓21)
Mean food efficiency (%)	LD 1-21	3.6 ± 1.53	2.4 ± 2.29	2.8 ± 2.71	4.1 ± 1.98

a Data obtained from Tables 63 through 66 on pages 290-293 and Tables 70-75 on pages 318-323 in the study report; n=23-26. Percent difference from controls is presented parenthetically.

* Significantly different from control at $p \leq 0.05$.

** Significantly different from control at $p \leq 0.01$.

3. Reproductive function

a. Estrous cycle length and periodicity: Estrous cycle length in the treated females was comparable to controls in both generations.

b. Sperm measures: There were no effects of treatment on sperm numbers, production rate, percent motile, or morphology in the P or F_1 parental males.

4. Reproductive performance: No treatment-related effects on reproductive performance were observed (Tables 4a and 4b). The mating and fertility indices were comparable between the treated groups and controls in both generations. Gestation length was increased ($p \leq 0.01$) in the 50 ppm P females (22.1 days treated vs 21.6 days in controls); however, this difference was within the range of historical controls (21.6-22.3 days) and was not observed in the F_1 females.

TABLE 4a. Reproductive performance in the P generation [a]

Observation	Concentration (ppm)				Historical Controls [b]
	Control	5	20	50	
P generation - males					
Number mated	30	30	30	30	24-40
Number fertile (Fertility index; %)	29 (96.7)	28 (93.3)	27 (90.0)	27 (90.0)	56.7-100.0
Number (%) males with evidence of mating Number (%) that sired a litter Number (%) that did not sire a litter	28 (93.3) 27 (96.4) 1 (3.6)	28 (93.3) 27 (96.4) 1 (3.6)	28 (93.3) 25 (89.3) 3 (10.7)	27 (90.0) 26 (96.3) 1 (3.7)	NP
Number (%) males with no evidence of mating Number (%) that sired a litter Number (%) that did not sire a litter	2 (6.7) 2 (100.0) 0 (0.0)	2 (6.7) 1 (50.0) 1 (50.0)	2 (6.7) 2 (100.0) 0 (0.0)	3 (10.0) 1 (33.3) 2 (66.7)	NP
Intercurrent deaths	0	0	0	0	NP
Mating Index (%)	100.0	96.7	100.0	93.3	72.0-100.0
P generation - females					
Number mated	30	30	30	30	22-40
Number fertile (Fertility index; %)	29 (96.7)	28 (93.3)	27 (90.0)	27 (90.0)	56.7-100.0
Number (%) females with evidence of mating Number (%) that delivered Number (%) that did not deliver	28 (93.3) 27 (96.4) 1 (3.6)	28 (93.3) 27 (96.4) 1 (3.6)	28 (93.3) 25 (89.3) 3 (10.7)	27 (90.0) 26 (96.3) 1 (3.7)	NP
Number (%) females with no evidence of mating Number (%) that delivered Number (%) that did not deliver	2 (6.7) 2 (100.0) 0 (0.0)	2 (6.7) 1 (50.0) 1 (50.0)	2 (6.7) 2 (100.0) 0 (0.0)	3 (10.0) 1 (33.3) 2 (66.7)	NP
Intercurrent deaths	0	0	0	0	NP
Mating Index (%)	100.0	96.7	100.0	93.3	84.0-100.0
Gestation duration (days)	21.6 ± 0.57	21.8 ± 0.40	21.6 ± 0.51	22.1 ± 0.49**	21.6-22.3

a Data obtained from Table 5 on pages 109-111 and Table 23 on page 171 in the study report.
b Historical control data were obtained from Appendix E on page 3140 of the study report.
** Significantly different from control at $p \leq 0.01$
NP Not provided

TABLE 4b. Reproductive performance in the F_1 generation [a]

Observation	Concentration (ppm)				Historical Controls [b]
	Control	5	20	50	
F_1 generation - males					
Number mated [c]	29[d]	30	30	28	24-40
Number fertile (Fertility index; %)	25 (86.2)	26 (86.7)	23 (76.7)	23 (82.1)	56.7-100.0
Number (%) males with evidence of mating Number (%) that sired a litter Number (%) that did not sire a litter	27 (93.1) 24 (88.8) 3 (11.1)	30 (100.0) 26 (86.7) 4 (13.3)	26 (86.7) 23 (88.5) 3 (11.5)	26 (92.9) 23 (88.5) 3 (11.5)	NP
Number (%) males with no evidence of mating Number (%) that sired a litter Number (%) that did not sire a litter	2 (6.9) 1 (50.0) 1 (50.0)	0 (0.0) 0 (0.0) 0 (0.0)	4 (13.3) 0 (0.0) 4 (100.0)	2 (7.1) 0 (0.0) 2 (100.0)	NP
Intercurrent deaths	0	0	0	2[e]	NP
Mating Index (%)	96.6	100.0	86.7	92.9	72.0-100.0
F_1 generation - females					
Number mated [c]	29[d]	30	30	30	22-40
Number fertile (Fertility index; %)	25 (86.2)	26 (86.7)	23 (76.7)	24 (80.0)	56.7-100.0
Number (%) females with evidence of mating Number (%) that delivered Number (%) that did not deliver	27 (93.1) 24 (88.8) 3 (11.1)	30 (100.0) 26 (86.7) 4 (13.3)	26 (86.7) 23 (88.5) 3 (11.5)	28 (93.3) 23 (82.1) 5 (17.9)	NP
Number (%) females with no evidence of mating Number (%) that delivered Number (%) that did not deliver	2 (6.9) 1 (50.0) 1 (50.0)	0 (0.0) 0 (0.0) 0 (0.0)	4 (13.3) 0 (0.0) 4 (100.0)	2 (6.7) 0 (0.0) 2 (100.0)	NP
Intercurrent deaths	1[d]	0	0	0	NP
Mating Index (%)	96.6	100.0	86.7	93.3	84.0-100.0
Gestation duration (days)	21.8 ± 0.38	21.7 ± 0.49	21.9 ± 0.34	22.0 ± 0.37	21.6-22.3

a Data obtained from Table 58 on page 258-260 and Table 76 on page 324 in the study report.
b Historical control data were obtained from Appendix E on page 3140 of the study report.
c Calculated by the reviewers from data presented in this table.
d In the control groups, one female died prior to pairing, and thus one male was not mated because it was paired with this female. These two animals were not included in calculations.
e Two 50 ppm males died prior to pairing and are not included in calculations.
NP Not provided

5. Parental postmortem results

a) Organ weights: Selected organ weights are presented in Table 5. Absolute and relative (to body) adrenal weights were decreased (↓8-22%; $p \leq 0.05$) at 50 ppm in both sexes and both generations. Relative adrenal weights were also decreased (↓12%; $p \leq 0.05$) in the 20 ppm F_1 females. Additionally in the males, absolute and relative thymus weights were increased at ≥20 ppm (↑18-29%; $p \leq 0.05$, except not significant in 50 ppm P males). These weight changes were considered treatment-related because they were consistent between sexes and generations and could not be accounted for by the decreased terminal body weights; however, they were not considered adverse because they were not corroborated by macroscopic or microscopic findings.

Numerous other differences ($p \leq 0.05$) from controls were noted in absolute and relative organ weights but were considered unrelated to treatment because they were uncorroborated by gross or microscopic findings and were likely related to the decreased terminal body weight.

TABLE 5. Selected mean (±SD) absolute (g) and relative to body (%) organ weights [a]

Organ	Concentration (ppm)			
	Control	5	20	50
P generation - males				
Final body weight (g)	560 ± 48.2	569 ± 55.4	575 ± 47.8	548 ± 44.5
Adrenal glands				
absolute	0.066 ± 0.009	0.067 ± 0.012	0.062 ± 0.009	0.056 ± 0.007** (↓15)
relative to body	0.012 ± 0.002	0.012 ± 0.002	0.011 ± 0.002	0.010 ± 0.001** (↓17)
Thymus				
absolute	0.226 ± 0.048	0.241 ± 0.071	0.284 ± 0.093** (↑26)	0.267 ± 0.043 (↑18)
relative to body	0.041 ± 0.010	0.043 ± 0.013	0.050 ± 0.015* (↑22)	0.049 ± 0.008* (↑20)
P generation - females				
Final body weight (g)	335 ± 24.1	332 ± 17.5	323 ± 18.5	312 ± 26.0** (↓7)
Adrenal glands				
absolute	0.080 ± 0.011	0.079 ± 0.011	0.079 ± 0.009	0.068 ± 0.010** (↓15)
relative to body	0.024 ± 0.004	0.024 ± 0.003	0.024 ± 0.003	0.022 ± 0.004* (↓8)
F_1 generation - males				
Final body weight (g)	576 ± 48.0	584 ± 46.3	575 ± 65.0	526 ± 52.0** (↓9)
Brain				
Absolute	2.06 ± 0.107	2.06 ± 0.106	2.00 ± 0.119	1.89 ± 0.122** (↓8%)
Relative	0.360 ± 0.031	0.355 ± 0.031	0.351 ± 0.033	0.361 ± 0.029
Adrenal glands				
absolute	0.062 ± 0.008	0.062 ± 0.009	0.058 ± 0.010	0.049 ± 0.006** (↓20)
relative to body	0.011 ± 0.002	0.011 ± 0.002	0.010 ± 0.002	0.009 ± 0.002** (↓18)
Thymus				
absolute	0.238 ± 0.059	0.261 ± 0.076	0.286 ± 0.072* (↑20)	0.281 ± 0.065* (↑18)
relative to body	0.042 ± 0.010	0.045 ± 0.014	0.050 ± 0.013* (↑19)	0.054 ± 0.014** (↑29)
Kidneys				
Absolute	3.85 ± 0.393	3.88 ± 0.312	3.65 ± 0.485	3.36 ± 0.383** (↓12%)
Right Testis				
Absolute	1.84 ± 0.151	1.87 ± 0.127	1.71 ± 0.120** (↓7%)	1.69 ± 0.158** (↓8%)
Relative	0.320 ± 0.032	0.322 ± 0.034	0.301 ± 0.032	0.325 ± 0.044
Left Testis				
Absolute	1.87 ± 0.145	1.93 ± 0.289	1.71 ± 0.133** (↓9%)	1.70 ± 0.178** (↓9%)
Relative	0.327 ± 0.033	0.332 ± 0.049	0.299 ± 0.034** (↓9%)	0.326 ± 0.048
Right Cauda Epid				
Absolute	0.3364 ± 0.285	0.3424 ± 0.039	0.3215 ± 0.035	0.3117 ± 0.041** (↓7%)
Relative	0.059 ± 0.007	0.059 ± 0.008	0.056 ± 0.007	0.059 ± 0.008
Left Cauda Epid				
Absolute	0.3489 ± 0.027	0.3514 ± 0.049	0.3192 ± 0.036** (↓9%)	0.3220 ± 0.033** (↓8%)
Relative	0.061 ± 0.008	0.060 ± 0.009	0.056 ± 0.008*(↓8%)	0.062 ± 0.008
F_1 generation - females				
Final body weight (g)	326 ± 26.2	341 ± 30.1	332 ± 29.8	308 ± 21.0* (↓6)

Brain				
Absolute	1.93 ± 0.085	1.93 ± 0.100	1.89 ± 0.118	1.78 ± 0.102** (↓8%)
Relative	0.596 ± 0.048	0.570 ± 0.050	0.573 ± 0.050	0.581 ± 0.049
Kidneys				
Absolute	2.27 ± 0.250	2.22 ± 0.244	2.15 ± 0.198	2.10 ± 0.249* (↓7%)
Relative	0.700 ± 0.085	0.655 ± 0.068* (↓6%)	0.649 ± 0.048* (↓7%)	0.681 ± 0.064
Adrenal glands				
absolute	0.080 ± 0.010	0.080 ± 0.013	0.074 ± 0.013	0.063 ± 0.007** (↓22)
relative to body	0.025 ± 0.004	0.024 ± 0.003	0.022 ± 0.004* (↓12)	0.021 ± 0.002** (↓16)

a Data obtained from Tables 31 and 32 on pages 184-194 and Tables 85-86 on pages 340-350 in the study report; n=28-30. Percent difference from control is presented in parentheses.
* Significantly different from control at p≤0.05
** Significantly different from control at p≤0.01

b) Pathology

1) **Macroscopic examination**: In the P males, dark red discoloration on the mandibular lymph node and white area(s) on the lungs were observed at 20 and 50 ppm (2-3/30 treated vs 0/30 controls; Table 6). In the F_1 males and females, dilated kidney pelvis was observed at 20 and 50 ppm (2-6/30 treated vs 0/30 controls). The Sponsor stated that the incidences of dilated renal pelvis were usually unilateral and could not be confirmed microscopically. Thus, the reviewers consider this finding to be equivocal. There were no other macroscopic observations that could be attributed to treatment.

TABLE 6. Selected gross pathological findings (# affected animals) [a]

Macroscopic observation	Concentration (ppm)			
	0	5	20	50
P generation - males				
Number examined	30	30	30	30
Lymph node, mandibular - dark red discoloration	0	0	2	3
Lungs - white area(s)	0	1	2	3
F_1 generation - males				
Number examined	29	29	30	28
Kidneys - dilated pelvis	0	3	6	6
F_1 generation - females				
Number examined	29	30	30	30
Kidneys - dilated pelvis	0	0	3	2

a Data obtained from Table 29 on page 179 and Table 82 on pages 334 and 337 in the study report.

2) **Microscopic examination:** At 50 ppm, the following histopathological findings were noted (Tables 7a and 7b): (i) minimal to mild hepatocellular necrosis in 4/30 males vs 1/30 controls in the P generation; (ii) minimal to mild subacute inflammation in the lungs in 14/30 males vs 9/30 controls in

the P generation; (iii) mild to moderate hemorrhage of the mandibular lymph node in 4/30 males vs 0/30 controls in the P generation; and (iv) degeneration of Levels II, III, and IV of the olfactory epithelium at minimal to moderate severity in the P males (10-14/30 treated vs 1/30 controls), minimal to mild severity in P females (6-11/30 treated vs 0/30 controls), minimal to mild severity in the F_1 males (2-5/28 treated vs 0/29 controls), and minimal to mild severity in the F_1 females (3-7/30 treated vs 0/29 controls). There were no other treatment-related microscopic findings.

At the 20 ppm concentration level, 2/30 females in the F_1 generation exhibited indications of minimal degeneration of the olfactory epithelium at Nasal level II.

TABLE 7a. Selected microscopic findings (# affected animals) in the P generation [a]

Organ	Microscopic observation		Concentration (ppm)			
			Control	5	20	50
P generation - males						
Liver	Hepatocellular necrosis -	Total	1	–	–	4
		Minimal	1	–	–	3
		Mild	0	–	–	1
Lungs	Subacute inflammation-	Total	9	0	0	14
		Minimal	7	–	–	8
		Mild	2	–	–	6
Lymph node, mandibular	Hemorrhage -	Total	–	1	2	4
		Minimal	–	1	1	0
		Mild	–	0	1	2
		Moderate	–	0	0	2
Olfactory epithelium	Degeneration, Level II -	Total	0	0	0	14*
		Minimal	0	0	0	7
		Mild	0	0	0	7
	Degeneration, Level III -	Total	1	0	0	11*
		Minimal	0	0	0	6
		Mild	1	0	0	4
		Moderate	0	0	0	1
	Degeneration, Level IV -	Total	0	0	0	10*
		Minimal	0	0	0	4
		Mild	0	0	0	6
P generation -females						
Olfactory epithelium	Degeneration, Level II -	Total	0	0	0	11*
		Minimal	0	0	0	3
		Mild	0	0	0	8
	Degeneration, Level III -	Total	0	0	0	10*
		Minimal	0	0	0	5
		Mild	0	0	0	5
	Degeneration, Level IV -	Total	0	0	0	6*
		Minimal	0	0	0	3
		Mild	0	0	0	3

a Data were obtained from Table 33 on pages 195-211 in the study report; n = 30.
– No animals examined in this group
* Significantly different from control at $p \leq 0.05$.

TABLE 7b. Selected microscopic findings (# affected animals) in the F_1 generation [a]

Organ	Microscopic observation		Concentration (ppm)			
			Control	5	20	50
F_1 generation - males						
Number examined			29	29	30	28
Olfactory epithelium	Degeneration, Level II -	Total	0	0	0	5*
		Minimal	0	0	0	3
		Mild	0	0	0	2
	Degeneration, Level III -	Minimal	0	0	0	4
	Degeneration, Level IV -	Mild	0	0	0	2
F_1 generation -females						
Number examined			29	30	30	30
Olfactory epithelium	Degeneration, Level II -	Total	0	0	2	7*
		Minimal	0	0	2	1
		Mild	0	0	0	6
	Degeneration, Level III -	Total	0	0	0	7*
		Minimal	0	0	0	6
		Mild	0	0	0	1
	Degeneration, Level IV -	Minimal	0	0	0	3

a Data were obtained from Table 8 on pages 365-366 and 374-375 in the study report; n = 28-30.
– No animals examined in this group
* Significantly different from control at $p \leq 0.05$.

B. OFFSPRING

1. Viability and clinical signs: In the F_1 generation, the mean number of pups born alive was decreased at 50 ppm (12.5) compared to controls (14.2) as reflected in the decreased ($p \leq 0.05$) live birth index at this concentration (90.5% treated vs 97.3% controls; Table 8). Furthermore at this concentration, there was an increase in the number of deaths during PND 0-4 (47 treated vs 8 controls) as reflected in the decreased ($p \leq 0.01$) survival for PND 0-1 and 1-4 (82.6-87.2% treated vs 98.0-99.6% controls) and the decreased ($p \leq 0.01$) viability index for PND 0-4 (74.3% treated vs 94.9% controls). In instances where historical control data were provided, these findings were outside of the range, further confirming that these occurrences were treatment-related.

In the F_2 generation at 50 ppm, the effect appeared even earlier with an increase ($\uparrow$ 19%; $p \leq 0.05$) in the number of primordial follicles and decreases ($\downarrow$ 20-23%; $p \leq 0.05$) in the numbers of corpora lutea and implantations. Consequently, the number born were decreased ($\downarrow$ 23%; $p \leq 0.05$). Furthermore at this concentration, the number born live was decreased ($\downarrow$ 24%; $p \leq 0.01$), and survival for PND 0-1 was decreased (92.2% treated vs 99.5% controls; $p \leq 0.01$), as reflected in decreased viability index for PND 0-4 (86.1% treated vs 95.7% controls). Again, where historical control data were provided, these findings were outside of the range.

No treatment-related clinical signs of toxicity were noted. Increased incidences of uneven hair growth were observed in the 50 ppm F_1 and F_2 pups; however, these increases were attributed primarily to pups from one P dam (#70167) and one F_1 dam (70223-12).

TABLE 8. Litter parameters [a]

Observation	Concentration (ppm)				Historical Controls [b]
	Control	5	20	50	
F_1 generation					
Mean (± SD) implantation sites	15.6 ± 2.56	16.0 ± 1.63	15.6 ± 3.22	15.4 ± 3.00	13.7-16.7
Mean (± SD) born	14.4 ± 2.57	15.0 ± 1.75	14.4 ± 3.04	13.8 ± 2.91	12.0-16.3
Mean (± SD) born live	14.2 ± 2.87	14.8 ± 1.79	14.1 ± 3.08	12.5 ± 3.61	11.6-15.9
Mean (± SD) unaccounted sites	1.2 ± 0.94	1.0 ± 0.96	1.2 ± 1.24	1.6 ± 1.74	0.5-1.2
Mean (±SD) % ♂ Day 0 (sex ratio)	51.2 ± 13.01	51.4 ± 14.64	58.3 ± 13.98	48.5 ± 14.53	44.0-56.4
# Deaths Days 0-4[c]	8	19	17	47	NP
Days 4-21[d]	18	26	7	9	NP
Post-natal survival (%) Day 0-1	98.0 ± 4.49	99.0 ± 3.08	98.2 ± 3.54	82.6 ± 23.09**	NP
Day 1-4[e]	99.6 ± 1.62	96.5 ± 6.86*	98.1 ± 5.18	87.2 ± 31.58**	NP
Day 4-7[f]	96.6 ± 16.33	99.6 ± 2.36	97.2 ± 8.72	100.0 ± 0.00	NP
Day 7-14	94.4 ± 21.54	92.9 ± 19.96	99.3 ± 3.85	100.0 ± 0.00	NP
Day 14-21	95.9 ± 18.99	92.9 ± 26.23	100.0 ± 0.00	95.3 ± 20.46	NP
Birth index (%)	NP	NP	NP	NP	NP
Live birth index (%)	97.3 ± 9.41	99.0 ± 2.40	97.6 ± 6.35	90.5 ± 17.65*	NP
Viability index (Days 0-4)	94.9 ± 9.97	94.7 ± 7.83	94.1 ± 8.86	74.3 ± 30.54**	91.3-99.3
Lactation index (Days 4-21)	92.2 ± 25.97	88.4 ± 29.05	96.8 ± 10.74	95.3 ± 20.46	95.4-100
F_2 generation					
Mean (± SD) primordial follicles	132.9 ± 42.66	NP	NP	158.4 ± 52.84* (↑19)	54.4-98.1
Mean (± SD) corpora lutea	172.1 ± 52.45	NP	NP	138.4 ± 61.18* (↓20)	NP
Mean (± SD) implantation sites	15.2 ± 1.26	16.2 ± 3.17	14.9 ± 2.97	11.7 ± 4.93** (↓23)	13.7-16.7
Mean (± SD) born	14.3 ± 1.43	15.3 ± 3.40	13.8 ± 2.79	11.0 ± 4.59** (↓23)	12.0-16.3
Mean (± SD) born live	13.9 ± 1.85	14.9 ± 3.50	13.6 ± 2.74	10.5 ± 4.19** (↓24)	11.6-15.9
Mean (± SD) unaccounted sites	0.9 ± 1.00	0.9 ± 0.82	1.1 ± 1.28	0.7 ± 0.83	0.5-1.2
Mean (±SD) % ♂ Day 0 (sex ratio)	49.2 ± 17.41	53.1 ± 16.02	50.7 ± 12.57	46.5 ± 14.38	44.0-56.4
# Deaths Days 0-4[c]	14	15	6	24	NP
Days 4-21[d]	3	1	2	4	NP
Post-natal survival (%) Day 0-1	99.5 ± 1.86	99.3 ± 1.99	99.4 ± 2.78	92.2 ± 13.41**	NP
Day 1-4[e]	98.8 ± 5.09	98.6 ± 2.82	99.7 ± 1.49	95.8 ± 12.37	NP
Day 4[f]-7	100.0 ± 0.00	100.0 ± 0.00	99.5 ± 2.61	99.5 ± 2.61	NP
Day 7-14	99.0 ± 3.46	99.5 ± 2.50	99.5 ± 2.61	98.3 ± 5.89	NP
Day 14-21	99.5 ± 2.50	100.0 ± 0.00	100.0 ± 0.00	100.0 ± 0.00	NP
Birth index (%)	NP	NP	NP	NP	NP
Live birth index (%)	97.5 ± 8.21	94.1 ± 19.84	98.5 ± 2.94	96.5 ± 5.94	NP
Viability index (Days 0-4)	95.7 ± 9.28	92.2 ± 19.92	97.6 ± 3.93	86.1 ± 19.68*	91.3-99.3
Lactation index (Days 4-21)	98.5 ± 4.15	99.5 ± 2.50	98.9 ± 3.60	97.8 ± 7.20	95.4-100

(footnotes follow next page)

a Data obtained from Tables 30, 34, 35, 84, 89 through 91on pages 183, 212-214, 339, 377-380 in the study report. Percent difference from controls, calculated by reviewers, is included in parentheses.
b Historical control data were obtained from Appendix E on page 3140-3141 of the study report.
c Tabulated by the reviewers from individual data presented in Table 133 on pages 1235-1242 in the study report.
d Tabulated by the reviewers from individual data presented in Table 185 on pages 2506-2509 in the study report.
e Before standardization (culling)
f After standardization (culling)
NP Not provided

2. Body weight: F_1 pup body weights were comparable between treated groups and controls throughout lactation (Table 9). In the F_2 pups, body weights were decreased compared to concurrent controls beginning on PND 7 in the 50 ppm males (↓8%; $p \leq 0.05$) and beginning on PND 14 at ≥20 ppm in both sexes (↓10-20%; $p \leq 0.01$). A transient decrease in body weights was observed in the 5 ppm females on PND 14 (↓7%; $p \leq 0.05$) but was considered unrelated to treatment because a similar decrease, unrelated to dose, was noted in these animals on PND 1 (↓7%; $p \leq 0.05$). These values fell at the lower end of the historical control ranges. Body weight gains were decreased (↓13-37%; $p \leq 0.05$) in both sexes at ≥20 ppm beginning on PND 4.

TABLE 9. Mean (±SD) F_1 pup weights (g) [a]

Post-natal Day	Concentration (ppm) 0	5	20	50	Historical Controls [b]
F_1 Pups - male					
1	6.8 ± 0.76	7.1 ± 0.61	6.8 ± 0.84	6.9 ± 0.75	6.5-7.4
4 [b]	9.4 ± 1.56	10.1 ± 1.22	9.6 ± 1.74	10.0 ± 1.30	8.6-10.7
7	12.8 ± 2.41	13.7 ± 2.56	12.9 ± 2.36	12.8 ± 1.92	11.7-17.8
14	24.8 ± 5.02	25.6 ± 5.28	24.7 ± 3.85	22.6 ± 3.41	22.5-36.5
21	39.1 ± 6.05	40.0 ± 7.46	39.1 ± 5.93	35.2 ± 5.25	34.9-58.0
F_1 Pups - female					
1	6.5 ± 0.81	6.6 ± 0.54	6.4 ± 0.77	6.5 ± 1.03	6.1-6.9
4 [b]	8.9 ± 1.53	9.4 ± 1.22	9.1 ± 1.66	9.7 ± 1.28	8.1-10.0
7	11.8 ± 2.65	12.8 ± 2.38	12.3 ± 2.38	12.4 ± 1.99	11.0-16.8
14	23.6 ± 5.38	23.5 ± 5.71	23.4 ± 4.46	22.1 ± 3.60	21.2-34.7
21	37.3 ± 6.26	37.4 ± 7.67	36.8 ± 6.78	34.4 ± 5.65	33.3-54.8
F_2 Pups - male					
1	7.2 ± 0.49	6.9 ± 0.56	7.1 ± 0.58	7.2 ± 0.80	6.5-7.4
4 [c]	10.5 ± 1.12	10.1 ± 0.80	10.5 ± 1.28	10.7 ± 1.68	8.6-10.7
7	15.0 ± 1.77	14.8 ± 1.29	14.5 ± 1.58	13.6 ± 2.18* (↓8)	11.7-17.8
14	29.7 ± 3.09	28.7 ± 2.82	26.8 ± 2.00** (↓10)	24.3 ± 3.24** (↓18)	22.5-36.5
21	45.1 ± 5.15	44.4 ± 4.18	38.7 ± 4.69** (↓14)	36.2 ± 5.41** (↓20)	34.9-58.0
F_2 Pups - female					
1	6.9 ± 0.60	6.4 ± 0.57* (↓7)	6.6 ± 0.59	6.8 ± 0.80	6.1-6.9
4 [c]	9.9 ± 1.07	9.2 ± 0.94	9.7 ± 1.25	10.0 ± 1.50	8.1-10.0
7	14.3 ± 1.76	13.4 ± 1.43	13.4 ± 1.64	13.0 ± 2.03	11.0-16.8
14	28.3 ± 2.98	26.4 ± 3.09* (↓7)	25.3 ± 2.21** (↓11)	23.3 ± 2.69** (↓18)	21.2-34.7
21	42.9 ± 4.64	40.6 ± 4.12	37.2 ± 5.05** (↓13)	35.0 ± 4.06** (↓18)	33.3-54.8

(footnotes follow next page)

a Data obtained from Table 40 on pages 222-223 and Table 96 on pages 386-387 in the study report.
b Historical control data were obtained from Appendix E on page 3141 of the study report.
c Before standardization (culling)

3. Sexual maturation (F_1): Time to vaginal patency was concentration-dependently increased in the 20 and 50 ppm F_1 females compared to concurrent controls (↑5-8%; $p \leq 0.05$) and exceeded the range of historical controls at 50 ppm (Table 10). Body weights of the F_1 females on the day of vaginal patency were comparable to controls. There were no effects of treatment on time to balanopreputial separation. However, body weights of the F_1 males on the day of balanopreputial separation were decreased compared to concurrent controls (↓7%; $p \leq 0.01$) and fell below the range of historical controls. Anogenital distances (absolute, relative to pup body weight, and relative to the cube root of the pup body weight) in the F_1 and F_2 treated groups were comparable to controls.

TABLE 10. Mean (±SD) F_1 developmental landmarks [a]

Developmental Landmark	Concentration (ppm)				Historical Controls [b]
	0	5	20	50	
Males					
Day of BP separation	46.5 ±2.58	45.1 ± 2.97	46.4 ± 2.82	47.0 ± 2.82	41.6-49.0
BW on day of BP separation	219.5 ± 20.62	218.5 ± 16.13	213.6 ± 20.40	203.4 ± 14.66**(↓7)	210.5-248.0
Females					
Day of vaginal patency	37.0 ± 2.34	37.9 ± 2.68	38.8 ± 3.38*(↑5)	40.0 ± 3.17**(↑8)	31.9-38.8
BW on day of vaginal patency	119.8 ± 14.11	125.4 ± 12.78	130.2 ± 18.52	128.3 ± 18.05	102.8-119.5

a Data obtained from Tables 51 and 53 on pages 241 and 245 in the study report.
b Historical control data were obtained from Appendix E on page 3141 of the study report.
BP Balanopreputial

4. Offspring postmortem results:

a) Organ weights: Absolute and relative (to body) weights of the brain, spleen and thymus were comparable to controls in the F_1 pups. In the F_2 females, absolute and relative thymus weights were decreased at ≥20 ppm (↓12-28%; $p \leq 0.05$). There were no other changes in organ weights in the F_2 males or females that could be unequivocally attributed to treatment. Absolute spleen weight was noted at ≥20 ppm in the females and at 50 ppm in the males, and decreased absolute thymus weights were noted in the ≥20 ppm males. However, the relative (to body) weights of these organs were comparable to controls. Thus, these differences are likely related to the decreased ($p \leq 0.05$) terminal body weights in these animals.

TABLE 11. Selected mean (±SD) absolute (g) and relative to body (%) thymus weights in the F_2 female pups [a]

Organ	Concentration (ppm)			
	Control	5	20	50
Final body weight (g)	43 ± 5.2	41 ± 5.8	36 ± 5.6** (↓16)	35 ± 4.3** (↓19)
Thymus				
absolute (g)	0.203 ± 0.057	0.176 ± 0.035	0.153 ± 0.041** (↓25)	0.146 ± 0.034** (↓28)
relative (%)	0.472 ± 0.092	0.436 ± 0.069	0.417 ± 0.074* (↓12)	0.413 ± 0.067* (↓13)

a Data obtained from Tables 101 and 102 on pages 394 and 396 in the study report; n=23-25. Percent difference from controls, calculated by reviewers, is included in parentheses.

** Significantly different from control at $p \leq 0.01$

b) Pathology

1) Macroscopic examination: No treatment-related gross pathological findings were noted in the F_1 or F_2 pups sacrificed on schedule. Among the pups that were found dead, there was an increase in the number of pups with no milk in the stomach at 50 ppm in both generations (23-37 treated vs 8-9 controls).

2) Microscopic examination: Microscopic examinations were not performed.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that the LOAEL for parental toxicity was 20 ppm based on decreased food consumption and increased absolute and relative thymus weights. The LOAEL for offspring toxicity was 20 ppm based on decreases in body weights, body weight gains, live litter size, number born, post-natal survival, thymus weights, and body weight on the day of balanopreputial separation and on increased time to vaginal patency. The LOAEL for reproductive toxicity was 50 ppm based on increased number of primordial follicles and decreased numbers of corpora lutea and implantation sites.

B. REVIEWER COMMENTS

1. PARENTAL ANIMALS: The majority of the effects noted in parental animals occurred at the 50 ppm concentration level. Indications of toxicity at this concentration consisted of decreases in body weight/body weight gain, changes in organ weights (adrenal glands, testis, epidydimis, cauda epididymis, testis, brain, kidneys, and thymus) as well as gross pathology and histopathology findings (liver and respiratory tract). Although some changes in the absolute and/or relative weights of the adrenal glands, the thymus, and the testis were observed at the 20 ppm concentration level, these changes were not corroborated by histopathology and were only seen in one generation making their toxicological relevance equivocal. Similarly, the toxicological relevance of the decreases in body weight/body weight change noted in males was also equivocal since they were seen sporadically. As a result, it was concluded that the effects

seen at 20 ppm were not appropriate as the basis of an LOAEL and were thus considered NOAELs. In the case of the respiratory tract, degeneration of the olfactory epithelium ranging in severity from mild to minimal at various levels of the nasal passages was noted at 50 ppm.

Under the conditions of this study, the parental NOAEL is set at 20 ppm and the LOAEL is established at 50 ppm based on decreases in body weight, body weight gain, changes in organ weights (adrenal glands, testis, cauda epidymis, epidydimis, and thymus) as well as gross pathology and histopathology findings. The port of entry NOAEL is 20 ppm and the LOAEL is 50 ppm based on subacute lung inflammation and minimal-mild degeneration of the olfactory epithelium.

2. **OFFSPRING:** At 50 ppm, decreases were observed in the number of pups born alive, PND 0-1 survival, and viability index for PND 0-4 in both generations. Additionally, decreases were observed in the live birth index and PND 1-4 survival in the F_1 pups; and decreased number born were observed in the F_2 pups. Among the pups that were found dead, there was an increase in the number of pups with no milk in the stomach at 50 ppm in both generations.

In the F_2 generation, pup body weights were decreased beginning on PND 7 in the 50 ppm males and beginning on PND 14 at ≥20 ppm in both sexes. Body weight gains were decreased in both sexes at ≥20 ppm beginning on PND 4. In the F_2 females, absolute and relative thymus weights were decreased at ≥20 ppm.

Under the conditions of this study, the offspring NOAEL is 5 ppm and the LOAEL is 20 ppm based on decreases in body weight, body weight gain, as well as lower absolute and relative thymus weights.

Reproductive parameters such as sperm count, motility, and morphology as well as balanopreputial separation and estrous cyclicity were unaffected by treatment with the test article. Attainment of vaginal patency, however, was delayed at 20 ppm (2 days) and 50 ppm (3 days). Also noted at the 50 ppm concentration was a 19% increase in the number of primordial follicles with a concomitant 20% decrease in the number of corpora lutea.

The LOAEL for reproductive toxicity is 20 ppm based on delays in attainment of vaginal patency. The NOAEL is 5 ppm.

C. **STUDY DEFICIENCIES:** No deficiencies were noted.

DATA FOR ENTRY INTO ISIS

Reproductive Study - rats (870.3800)

PC code	MRID #	Study type	Species	Duration	Route	Concentration method	Concentration range ppm	Concentrations tested ppm	NOAEL ppm	LOAEL ppm	Target organ(s)	Comments
000011	45710301	reproductive	rats	2 generat	inhalation	whole body	5-50	0, 5, 20, 50	5	20	decr BWG decr FC, organ wts., portal of entry effects	Parental/ systemic
000011	45710301	reproductive	rats	2 generat	inhalation	whole body	5-50	0, 5, 20, 50	5	20	decr BW decr BWG, decr thymus wts.	Offspring
000011	45710301	reproductive	rats	2 generat	inhalation	whole body	5-50	0, 5, 20, 50	20	50	delay in vaginal patency	Reproductive

3

EPA Reviewer: Elizabeth Méndez, PhD **Signature:**
Reregistration Branch I/ Health Effects Division (7509C) **Date** 9/29/04
EPA Secondary Reviewer: Whang Phang, PhD **Signature:**
Reregistration Branch I/ Health Effects Division (7509C) **Date** 9/29/04

Template version 11/01

TXR#: 0052771

Note: This robust summary describes the findings reported at the one-year interim sacrifice. A full DER may be prepared upon submission of the final study report.

DATA EVALUATION RECORD

STUDY TYPE: Combined chronic toxicity/carcinogenicity *via* Inhalation -RAT; OPPTS 870.4300 [§83-5]; OECD 453.

PC CODE: 000011 **DP BARCODE:** DP304187

TEST MATERIAL (PURITY): Iodomethane (99.7% a.i.)

SYNONYMS: Methyl iodide

CITATION: Kirkpatrick, D.T. (2003) A 24-month inhalation combined chronic toxicity/carcinogenicity study of iodomethane in rats. Wil Research Laboratories, Inc., Ashland OH. Study Number Wil-418019, December 2, 2003. MRID 46203707. Unpublished.

SPONSOR: Arvesta Corporation

EXECUTIVE SUMMARY:

In a combined chronic toxicity/carcinogenicity study in rats (MRID 46203707),iodomethane (99.7% a.i., Batch No. 02/Lot # 007403) was administered to Crl:CD®(SD)IGS BR rats *via* whole body inhalation at concentrations of 0, 5, 20, or 60 ppm for 6 hours/day 5 days/week. Sixty animals/sex/concentration were exposed to 0, 5, or 20 ppm iodomethane while 70/sex were exposed at the 60 ppm level. Animals were observed for moribundity and mortality twice daily and clinical observations once daily. Once a week a detailed physical examination was conducted including but not limited to evaluations of changes in appearance, autonomic activity (*e.g.* lacrimation, piloerection, pupil size, breathing patterns), gait, posture, response to handling, stereotypic and/or bizarre behavior. In addition, evaluations of clinical chemistry, hematology, urinalysis, gross pathology and histopathology parameters were conducted. This robust summary describes the findings reported in the One-Year Interim Report for this study.

The majority of the treatment-related findings were limited to animals in the 60 ppm group. An

increase in mortality was reported at the 60 ppm concentration in males (8/70 *vs* 5/60 in control) and females (13/70 *vs* 1/60). Of these deaths, 14 (6 ♂ and 8 ♀) were attributed by the study authors to a malfunction of the inhalation chamber that lead to an overexposure of the animals to the test article.[1] Histopathological evaluation of tissues from decedents revealed a high incidence of salivary gland squamous cell metaplasia (7/8 ♂ and 9/11 ♀ *vs* 0 control), lymphoid depletion in the spleen (5/8 ♂ and 7/13 ♀ *vs* 0 control), lymphoid hystiocytosis of various organs, degeneration of the olfactory epithelium at Nasal Levels III-VI (6-7/8 ♂ and 4-13/13 ♀ *vs* 0 control), ultimobranchial cysts of the thyroid (2/8 ♂ and 5/13 ♀), and follicular cell hyperplasia (2/8 ♂ and 6/13 ♀ *vs* 0 in control group).

Clinical observations and physical examinations revealed a higher incidence of hypoactivity (4/70♂ and 3/70♀ *vs* 0 control), hyper-reactivity to touch (8/70 ♂ *vs* 2/60 control), and thinness (6/70 ♀ *vs* 0 control) at the 60 ppm exposure level. Also noted at this exposure level was a decrease in body weight of males (↓11-23%) and females (↓10-15%) beginning during the fourth week of exposure. Similarly, overall body weight gains were reduced by 24-26% in both sexes at 60 ppm. These decreases in body weight and body weight gain are accompanied by decreases in food consumption in males (↓7-21%) and females (↓5-20%). In general, hematology parameters were unaffected by treatment with the test article. The few changes noted were of minimal magnitude and sporadic rendering their toxicological relevance equivocal. During the week 26 clinical chemistry evaluations, increases in alkaline phosphatase (↑48% and 28% in males and females, respectively) and cholesterol (↑81% ♂ and ↑40% ♀) were noted at 60 ppm. Alterations of thyroid hormone levels and TSH were also observed at this exposure level [see Table 1]. Cholesterol levels were also elevated in females at the 20 ppm exposure level (↑33%). By the week 52 evaluation, however, alkaline phosphatase and cholesterol levels were comparable across treatment groups. Urinalysis parameters were unaffected by treatment with the test article except for a 45% decrease in urine volume noted at the 60 ppm concentration level during the week 52 assessment.

Gross pathology examination of animals sacrificed on schedule (*i.e.* week 52) revealed a 25% incidence of enlarged thyroids in males treated at the 60 ppm exposure level. This observation is consistent with the increased absolute and relative weight of the thyroid/parathyroid (↑83% and 120%, respectively) seen at this concentration level. Also noted at 60 ppm were absolute weight changes in the brain (↓11%♂ and 5%♀), kidneys (↓22%♂ and 16%♀), spleen (↓19%♂), heart (↓14%♂), and adrenal glands (↓17%♂). Organ weights relative to body weight and brain weights were generally comparable across test groups or higher than control suggesting that the decreases noted in the absolute weights were a function of overall decreased body weight rather than organ-specific toxicity. One year exposure to 60 ppm iodomethane elicited various histopathological changes primarily confined to the respiratory tract, thyroid, and salivary glands. Increased incidences of salivary gland squamous cell metaplasia, atrophy of salivary glands, ultimobranchial thyroid cysts, follicular cell hyperplasia, follicular cell adenomas, thyroid cytoplasmic vacuolation, as well as olfactory epithelium degeneration and cysts were reported at the highest concentration tested (60 ppm) [see Table 2]. An increase in the incidence

[1] Symbols: ♂ = male, ♀ = female

of salivary gland squamous cell metaplasia was also seen at the 20 ppm exposure concentration..

Under the conditions of this study, the interim NOAEL is 5 ppm; the LOAEL is established at 20 ppm based on increased incidence of salivary gland squamous cell metaplasia. The NOAEL for port of entry effects (respiratory tract) is 20 ppm and the LOAEL is 60 ppm based on degeneration of the olfactory epithelium.

This combined chronic toxicity/carcinogenicity study is **acceptable/non-guideline** and **does not** satisfy the guideline requirement for a in rats [OPPTS 870.4300); OECD 453].

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

Table 1. Serum Hormone Analysis

Observations		Exposure Concentration (ppm)			
		0	5	20	60
Males					
Total T3 (ng/dL)	Week 26	57.50 ± 5.80	51.40 ± 18.63	57.12 ± 21.19	38.08 ± 16.27 (↓34%)
	Week 52	43.23 ± 11.36	38.95 ± 15.64	51.34 ± 40.35	38.29 ± 11.37 (↓11%)
Total T4 (µg/dL)	Week 26	3.87 ± 0.99	3.38 ± 0.44	3.24 ± 0.47	1.71 ± 1.41** (↓56%)
	Week 52	2.56 ± 0.82	2.45 ± 0.85	3.44 ± 0.69	3.42 ± 0.81* (↑34%)
TSH (ng/mL)	Week 26	2.46 ± 1.23	3.78 ± 1.86	4.92 ± 3.87	30.53 ± 13.69** (↑12.4x)
	Week 52	2.25 ± 0.90	2.26 ± 0.64	3.60 ± 2.79	9.11 ± 11.38 (↑4x)
rT3 (ng/mL)	Week 26	0.13 ± 0.05	0.12 ± 0.05	0.11 ± 0.05	0.15 ± 0.03
	Week 52	0.09 ± 0.03	0.09 ± 0.05	0.09 ± 0.04	0.19 ± 0.05* (↑2x)
Females					
Total T3 (ng/dL)	Week 26	67.54 ± 28.27	55.38 ± 17.05	80.12 ± 21.93	49.44 ± 19.65 (↓27%)
	Week 52	81.78 ± 33.13	78.70 ± 20.46	60.10 ± 9.84	72.55 ± 15.68 (↓11%)
Total T4 (µg/dL)	Week 26	2.03 ± 0.59	1.68 ± 0.57	1.93 ± 0.51	1.78 ± 0.65 (↓12%)
	Week 52	2.02 ± 0.27	2.16 ± 0.45	1.74 ± 0.3 (↓14%)	2.23 ± 0.60 (↑10%)
TSH (ng/mL)	Week 26	1.76 ± 0.62	1.76 ± 0.54	2.09 ± 0.66	12.92 ± 13.36** (↑7x)
	Week 52	2.61 ± 0.70	3.33 ± 1.91	2.87 ± 1.31	5.49 ± 6.37 (↑2x)
rT3 (ng/mL)	Week 26	0.10 ± 0.05	0.11 ± 0.03	0.15 ± 0.05	0.19 ± 0.09
	Week 52	0.12 ± 0.04	0.14 ± 0.06	0.09 ± 0.02	0.33 ± 0.16** (↑3x)

* Statistically different from control at 0.05
** Statistically different from control at 0.01

Table 1. Select Histopathological Findings at Week 52 Interim Sacrifice

Observations		Exposure Concentration (ppm)			
		0	5	20	60
Males					
Salivary Gland Squamous Cell Metaplasia		0	0	3/10	16/20
Salivary Gland Atrophy		0	0	0	8/20
Ultimobranchial Thyroid Cysts		2/10	2/10	4/10	11/20
Follicular Cell Hyperplasia		0	1/10	1/10	8/20
Thyroid Cytoplasmic Vacuolation		0	1/10	0	7/10
Follicular Cell Adenomas		0	0	0	3/20
Degeneration Olfactory Epithelium	Nasal Level III	0	0	0	13/20
	Nasal Level IV	0	0	0	15/20
	Nasal Level V	0	0	1/10	18/20
	Nasal Level VI	0	0	0	16/20
Olfactory Epithelium Cysts	Nasal Level III	0	0	0	11/20
	Nasal Level IV	0	0	0	11/20
	Nasal Level V	0	0	0	14/20
	Nasal Level VI	0	0	0	5/20
Females					
Salivary Gland Squamous Cell Metaplasia		0	0	3/10	18/20
Salivary Gland Atrophy		0	0	0	1/20
Ultimobranchial Thyroid Cysts		6/10	4/10	3/10	10/20
Follicular Cell Hyperplasia		0	0	0	2/20
Follicular Cell Adenomas		0	0	0	1/20
Degeneration Olfactory Epithelium	Nasal Level III	0	0	0	1/20
	Nasal Level IV	0	1/10	0	6/20
	Nasal Level V	0	0	0	15/20
	Nasal Level VI	0	0	0	8/20

Observations		Exposure Concentration (ppm)			
		0	5	20	60
Olfactory Epithelium Cysts	Nasal Level III	0	0	0	3/20
	Nasal Level IV	0	0	1/10	10/20
	Nasal Level V	0	0	0	15/20
	Nasal Level VI	0	0	0	8/20

n = 10 at 0, 5, and 20 ppm exposure levels; n = 20 at 60 ppm exposure levels

Table 2. Serum Hormone Analysis

Observations		Exposure Concentration (ppm)			
		0	5	20	60
Males					
Total T3 (ng/dL)	Week 26	57.50 ± 5.80	51.40 ± 18.63	57.12 ± 21.19	38.08 ± 16.27 (↓34%)
	Week 52	43.23 ± 11.36	38.95 ± 15.64	51.34 ± 40.35	38.29 ± 11.37 (↓11%)
Total T4 (µg/dL)	Week 26	3.87 ± 0.99	3.38 ± 0.44	3.24 ± 0.47	1.71 ± 1.41** (↓56%)
	Week 52	2.56 ± 0.82	2.45 ± 0.85	3.44 ± 0.69	3.42 ± 0.81* (↑34%)
TSH (ng/mL)	Week 26	2.46 ± 1.23	3.78 ± 1.86	4.92 ± 3.87	30.53 ± 13.69** (↑12.4x)
	Week 52	2.25 ± 0.90	2.26 ± 0.64	3.60 ± 2.79	9.11 ± 11.38 (↑4x)
rT3 (ng/mL)	Week 26	0.13 ± 0.05	0.12 ± 0.05	0.11 ± 0.05	0.15 ± 0.03
	Week 52	0.09 ± 0.03	0.09 ± 0.05	0.09 ± 0.04	0.19 ± 0.05* (↑2x)
Females					
Total T3 (ng/dL)	Week 26	67.54 ± 28.27	55.38 ± 17.05	80.12 ± 21.93	49.44 ± 19.65 (↓27%)
	Week 52	81.78 ± 33.13	78.70 ± 20.46	60.10 ± 9.84	72.55 ± 15.68 (↓11%)
Total T4 (µg/dL)	Week 26	2.03 ± 0.59	1.68 ± 0.57	1.93 ± 0.51	1.78 ± 0.65 (↓12%)
	Week 52	2.02 ± 0.27	2.16 ± 0.45	1.74 ± 0.3 (↓14%)	2.23 ± 0.60 (↑10%)
TSH (ng/mL)	Week 26	1.76 ± 0.62	1.76 ± 0.54	2.09 ± 0.66	12.92 ± 13.36** (↑7x)
	Week 52	2.61 ± 0.70	3.33 ± 1.91	2.87 ± 1.31	5.49 ± 6.37 (↑2x)
rT3 (ng/mL)	Week 26	0.10 ± 0.05	0.11 ± 0.03	0.15 ± 0.05	0.19 ± 0.09
	Week 52	0.12 ± 0.04	0.14 ± 0.06	0.09 ± 0.02	0.33 ± 0.16** (↑3x)

DATA FOR ENTRY INTO ISIS

Chronic/Carcinogenicity Study - rodents (870.4300)

PC code	MRID	Study	Species	Duration	Route	Admin	Exposure range ppm	Exposure Concentration ppm	NOAEL ppm	LOAEL ppm	Target organ	Comments
000011	46203707	chronic/onc	rat	52 weeks	inhalation	whole body	5-60	0, 5, 20, 60	5	20	salivary gland squamous cell metaplasia	Toxicity, tumors
000011	46203707	chronic/onc	rat	52 weeks	inhalation	whole body	5-60	0, 5, 20, 60	20	60	portal of entry effects (degeneration of olfactory epithelium)	Toxicity

13544

R103100

Chemical:	**Methane, iodo-**
PC Code:	**000011**
HED File Code	**13000 Tox Reviews**
Memo Date:	**09/28/2004**
File ID:	**TX0052771**
Accession Number:	**412-05-5000**

HED Records Reference Center
10/26/2004