Image4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

November 9, 2001
TXR 0050209

MEMORANDUM

SUBJECT: D278575: Propanil (028201)
Review of 1) prenatal developmental toxicity studies in rats, 2) prenatal developmental toxicity study in rabbits, and 3) two-generation reproduction study in rats

TO: George T. Myers
Chemical Review Manager
Special Review and Reregistration Division (7508C)

FROM: Susan L. Makris 11/9/01
Toxicology Branch
Health Effects Division (7509C)

THRU: Alberto Protzel, Branch Senior Scientist 11/28/01
Toxicology Branch 3
Health Effects Division (7509C)

CC: Richard Griffin (7509C)

ACTION REQUESTED: Review the following toxicology studies in support of the reregistration eligibility decision for propanil (028201):

1. Prenatal developmental toxicity study in rats
2. Prenatal developmental toxicity study in rabbits
3. Two-generation reproduction study in rats

CONCLUSIONS:

1. Prenatal developmental toxicity study in rats (replaces TXR 000425)

Citation: Kam, C., Stevens, K.R. and Gallo, M.A. Teratologic Evaluation of Stam Technical in the Albino Rat. Booz, Allen and Hamilton, Inc., Foster D. Snell

Division, Florham Park, NJ. Snell Project No. 10065-008. February 29, 1980. MRID 00058588 and 45518802 (legible copy of 00058588). Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. **The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.**

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. **The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.**

This developmental toxicity study in the rat is classified **Acceptable/guideline** and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

2. Prenatal developmental toxicity study in rabbits (replaces TXR 000425)

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits. Argus Research Laboratories, Inc. (Parkside, PA). Rohm and Haas Company Study Number 80P-113 (Argus Project Number 018-001), December 17, 1980. MRID 00058589. Unpublished study.

Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits, Analytical Report. Rohm and Haas Company, Philadelphia, PA. Rohm and Haas Report No. 81RC-015B, April 30, 1981. MRID 45518801. Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). **The maternal toxicity LOAEL is 100 mg/kg/day, based on mortality, clinical signs of toxicity and weight loss during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.**

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. **The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.**

This developmental toxicity study in the rabbit is classified **Acceptable/guideline** and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

3. Two-generation reproduction study in rats

Citation: Stump, D.G. (1998) A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats. WIL Research Laboratories, Inc., 1407 George Rd. Ashland, Ohio 448505-9281. WIL Study Identification No. 141013. July 1, 1998. MRID 44604301 Unpublished.

Executive Summary: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and

during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. **The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).**

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. **The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).**

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. **The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual**

maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

This study is classified as **Acceptable/guideline** and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

Cover Memo Summary

Draft

TXR: 0050209 **Division:** HED **CM Authors:** Susan Makris **Signoff Date:** 11/09/2001

PC Codes

028201 Propanamide, N-(3,4-dichlorophenyl)-

Registration Number / Product Name

000707-00075 STAM F-34 HERBICIDE

DER Information

Grp.	C / S	R / S	Related TXR
01	N	R	-
02	N	R	-
03	-	R	-
04	-	S	0050209
05	-	S	0050209

Citation Information

MRID	C / S	Citation Help
00058588	N	Kam, C.; Stevens, K.R.; Gallo, M.A. (1980) Teratologic Evaluation of
00058589	N	Florek, M.C.; Christian, M.S.; Christian, G.D.; et al. (1980) Stam Te
44604301	-	No Citation Listed for 44604301
45518801	-	No Citation Listed for 45518801
45518802	-	No Citation Listed for 45518802

Cover Memo Conclusions:

1. Prenatal developmental toxicity study in rats (replaces TXR 000425)

Citation: Kam, C., Stevens, K.R. and Gallo, M.A. Teratologic Evaluation of Stam Technical in the Albino Rat. Booz, Allen and Hamilton, Inc., Foster D. Snell Division, Florham Park, NJ. Snell Project No. 10065-008. February 29, 1980. MRID 00058588 and 45518802 (legible copy of 00058588). Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

2. Prenatal developmental toxicity study in rabbits (replaces TXR 000425)

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits. Argus Research Laboratories, Inc. (Parkside, PA). Rohm and Haas Company Study Number 80P-113 (Argus Project Number 018-001), December 17, 1980. MRID 00058589. Unpublished study.

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits, Analytical Report. Rohm and Haas Company, Philadelphia, PA. Rohm and Haas Report No. 81RC-015B, April 30, 1981. MRID 45518801. Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was

administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). The maternal toxicity LOAEL is 100 mg/kg/day, based on mortality, clinical signs of toxicity and weight loss during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rabbit is classified Acceptable/guideline and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

3. Two-generation reproduction study in rats

Citation: Stump, D.G. (1998) A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats. WIL Research Laboratories, Inc., 1407 George Rd. Ashland, Ohio 448505-9281. WIL Study Identification No. 141013. July 1, 1998. MRID 44604301 Unpublished.

Executive Summary: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

This study is classified as Acceptable/guideline and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

File

Attachment(s):   

44604301.DER.w 00058589.DER.w 00058588.DER.w

Updated By: Alberto Protzel **on:** 11/16/2001 03:11 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

Cover Memo Summary

Draft

TXR: [redacted] Division: HED CM Authors: Susan Makris Signoff Date: 11/09/2001

PC Codes

028201 Propanamide, N-(3,4-dichlorophenyl)-

Registration Number / Product Name

000707-00075 STAM F-34 HERBICIDE

Sometimes this happens.

DER Information

Grp.	C / S	R / S	Related TXR
01	N	R	-
02	-	R	-
03	-	R	-
04	-	S	[redacted]
05	-	S	[redacted]

Citation Information

MRID	C / S	Citation Help
00058588	N	Kam, C.; Stevens, K.R.; Gallo, M.A. (1980) Teratologic Evaluation of
00058589	-	Florek, M.C.; Christian, M.S.; Christian, G.D.; et al. (1980) Stam Te
44604301	-	No Citation Listed for 44604301
45518801	-	No Citation Listed for 45518801
45518802	-	No Citation Listed for 45518802

Cover Memo Conclusions:

1. Prenatal developmental toxicity study in rats (replaces TXR 000425)

Citation: Kam, C., Stevens, K.R. and Gallo, M.A. Teratologic Evaluation of Stam Technical in the Albino Rat. Booz, Allen and Hamilton, Inc., Foster D. Snell Division, Florham Park, NJ. Snell Project No. 10065-008. February 29, 1980. MRID 00058588 and 45518802 (legible copy of 00058588). Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

2. Prenatal developmental toxicity study in rabbits (replaces TXR 000425)

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits. Argus Research Laboratories, Inc. (Parkside, PA). Rohm and Haas Company Study Number 80P-113 (Argus Project Number 018-001), December 17, 1980. MRID 00058589. Unpublished study.

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits, Analytical Report. Rohm and Haas Company, Philadelphia, PA. Rohm and Haas Report No. 81RC-015B, April 30, 1981. MRID 45518801. Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was

administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). The maternal toxicity LOAEL is 100 mg/kg/day, based on mortality, clinical signs of toxicity and weight loss during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rabbit is classified Acceptable/guideline and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

3. Two-generation reproduction study in rats

Citation: Stump, D.G. (1998) A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats. WIL Research Laboratories, Inc., 1407 George Rd. Ashland, Ohio 448505-9281. WIL Study Identification No. 141013. July 1, 1998. MRID 44604301 Unpublished.

Executive Summary: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

This study is classified as Acceptable/guideline and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

File

Attachment(s):   

44604301.DER.w 00058589.DER.w 00058588.DER.w

Updated By: Alberto Protzel **on:** 11/16/2001 03:11 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

Cover Memo Summary

Draft

TXR: 0050209 **Division:** HED **CM Authors:** Susan Makris **Signoff Date:** 11/09/2001

PC Codes

028201 Propanamide, N-(3,4-dichlorophenyl)-

Registration Number / Product Name

000707-00075 STAM F-34 HERBICIDE

DER Information

Grp.	C / S	R / S	Related TXR
01	-	R	-
02	-	R	-
03	-	R	-
04	-	S	0050209
05	-	S	0050209

Citation Information

MRID	C / S	Citation Help
00058588	-	Kam, C.; Stevens, K.R.; Gallo, M.A. (1980) Teratologic Evaluation of
00058589	-	Florek, M.C.; Christian, M.S.; Christian, G.D.; et al. (1980) Stam Te
44604301	-	No Citation Listed for 44604301 Study Cat — See #3
45518801	-	No Citation Listed for 45518801 — See #2
45518802	-	No Citation Listed for 45518802 — legible copy of 00050209

Cover Memo Conclusions:

1. Prenatal developmental toxicity study in rats (replaces TXR 000425)

Citation: Kam, C., Stevens, K.R. and Gallo, M.A. Teratologic Evaluation of Stam Technical in the Albino Rat. Booz, Allen and Hamilton, Inc., Foster D. Snell Division, Florham Park, NJ. Snell Project No. 10065-008. February 29, 1980. MRID 00058588 and 45518802 (legible copy of 00058588). Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

2. Prenatal developmental toxicity study in rabbits (replaces TXR 000425)

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits. Argus Research Laboratories, Inc. (Parkside, PA). Rohm and Haas Company Study Number 80P-113 (Argus Project Number 018-001), December 17, 1980. MRID 00058589. Unpublished study.

Citation: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits, Analytical Report. Rohm and Haas Company, Philadelphia, PA. Rohm and Haas Report No. 81RC-015B, April 30, 1981. MRID 45518801. Unpublished study.

Executive Summary: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). The maternal toxicity LOAEL is 100 mg/kg/day, based on mortality, clinical signs of toxicity and weight loss during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rabbit is classified Acceptable/guideline and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

3. Two-generation reproduction study in rats

Citation: Stump, D.G. (1998) A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats. WIL Research Laboratories, Inc., 1407 George Rd. Ashland, Ohio 448505-9281. WIL Study Identification No. 141013. July 1, 1998. MRID 44604301 Unpublished.

Executive Summary: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

This study is classified as Acceptable/guideline and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

File Attachment(s):



44604301.DER.w 00058589.DER.w 00058588.DER.w

Updated By: Susan Makris **on:** 11/09/2001 12:32 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

[Propanil] **Developmental Study OPPTS 870.3700 (§83-3(a))**

EPA Reviewer: Linnea Hansen, Ph.D. Linnea L. Hansen, Date 10/31/01
Toxicology Branch (7509C)
EPA Secondary Reviewer: Susan L Makris, M.S. Susan L Makris, Date 10/31/01
Toxicology Branch (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - rat; OPPTS 870.3700 [§83-3(a)]

DP BARCODE: D277274, D278575 SUBMISSION CODE: S601797
P.C. CODE: 028201 TXR NO.: 0050209

TEST MATERIAL, PURITY: Stam technical, 85.4% a.i.

SYNONYMS: Propanil; N–(3,4-dichlorophenyl)propanamide

CITATION: Kam, C., Stevens, K.R. and Gallo, M.A. Teratologic Evaluation of Stam Technical in the Albino Rat. Booz, Allen and Hamilton, Inc., Foster D. Snell Division, Florham Park, NJ. Snell Project No. 10065-008. February 29, 1980. MRID 00058588 and 45518802 (legible copy of 00058588). Unpublished study.

SPONSOR: Rohm and Haas Company Research Laboratories, Spring House, PA.

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. **The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.**

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or

or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. **The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.**

This developmental toxicity study in the rat is classified **Acceptable/guideline** and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

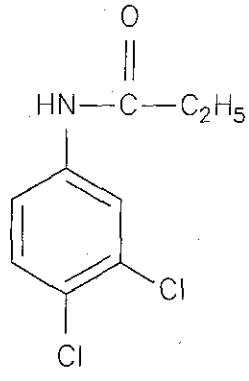
COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were not provided. The study protocol, appended to the study report, stated that the study would be "submitted to and reviewed by the United States Environmental Protection Agency (EPA) and is subject to their Regulation for the Enforcement of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and to their Quality Assurance Standards. Therefore, strict adherence to the protocol will be maintained and generally recognized good laboratory practices will be followed..."

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Stam (propanil)
   Description: technical, black lumpy solid. Stored at room temperature.
   Lot/Batch #: 9287
   Purity: 85.4% a.i.
   CAS #: 709-98-8

   PROPANIL



2. Vehicle: Mazola® corn oil
   Description: none given
   Lot/Batch #: Not provided
   Purity: None given

3. Test animals: Species: Rat
   Strain: BLU:(SD)BR

Age at mating: about 13 weeks of age
Weight at mating: about 250 g, average (no individual animal data provided for pretreatment body weights)
Source: Animals were delivered already pregnant to Booz, Allen and Hamilton Inc. FDS Life Sciences Laboratory by Taconic Farms, Inc., Germantown, NY. Matings were managed by Blue Spruce Farms, Inc., Altamont, NY
Housing: individual wire-mesh cages except during mating
Diet: Ralston Purina Laboratory Chow (formulation not indicated), *ad libitum*
Water: local tap water, *ad libitum*
Environmental conditions:
Temperature: target of 22°±1°C target (actual range not given in report)
Humidity: target of 40% to 60% (actual range not given in report)
Air changes: Not indicated in report
Photoperiod: 12 hrs dark/12 hrs light
Acclimation period: Not indicated

B. PROCEDURES AND STUDY DESIGN

1. In-life dates: Start: December 17, 1979 (start of insemination). End: January 6, 1980 (end of terminal sacrifice).

2. Mating: Rats were pre-mated by the supplier prior to shipment to the testing laboratory. Sexually mature females were placed in a cage with sexually males of the same strain (3:1 per cage). Pregnancies were identified by the presence of a vaginal sperm plug on the day after each mating period, and this was identified as gestation day (GD) 0. Matings were done for 3 consecutive days (December 17, 18 and 19, 1979) to yield a total of 125 pregnant dams that were delivered to the testing laboratory. Pregnant females were received by the testing laboratory on December 21.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. Assignment was random.

TABLE 1 Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	25
Low (LDT)	0.8	25
Mid 1 (MDT 1)	4.0	25
Mid 2 (MDT 2)	20	25
High (HDT)	100	25

4. Dose selection rationale: The study report did not provide a rationale for the doses selected in this study, nor indicate whether a range-finding study was performed.

5. Dosage preparation and analysis: According to the study protocol, the test substance formulations were prepared daily by suspending appropriate amounts of test substance with corn oil, although frequency of preparation was not mentioned in the text of the study report itself. Test material was added to give the stated dosing levels as active ingredient (i.e., were adjusted for purity). The study report did not provide any analysis data for stability, homogeneity or concentration. Information provided by the registrant (from V.J. Piccirillo, consultant to the Propanil Task Force) in a letter to the Agency, dated July 18, 2001, confirms that concentration analyses of dose suspensions were not performed for this study. Stability analyses of dose suspensions were not performed since doses were mixed daily. The study protocol, appended to the study report, stated that witnessed records showing the amounts of compound used in preparing each dosing solution were retained. These calculations were provided in the study report. Analytical chemistry data (MRID 45518801) for the developmental toxicity study in rabbits (MRID 00058589) indicate that similar mixing procedures to those used in the developmental rat study resulted in dose suspension concentrations which were only 2-3% above nominal; the test substance appeared to be readily suspended in corn oil (which was used as the vehicle in the rat study as well). In consideration of all relevant information, it appears likely that dose suspensions could have been prepared adequately for this study. On that basis, it is judged that the lack of analytical data should not jeopardize the acceptability of this study.

6. Dosage administration: All doses were administered once daily by gavage, on presumed GD 6 through 15 (inclusive), in a volume of 10 ml corn oil/kg of body weight/day. Control group animals received only the vehicle at the same volume. According to the study protocol that was included in the report, dosing for each individual animal was based on its GD 6 weight for the entire dosing period, although this was not specifically stated in the study report itself.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The dams were checked daily for clinical signs of toxicity, signs of abortion or mortality. Body weights were measured on GD 0, 6, 10, 15 and 20. Food consumption was recorded as the amounts of food consumed (g/animal/day) in the intervals between GD 6-10, 10-15 and 15-20. Dams were sacrificed on day 20 of gestation by CO_2 inhalation. Examinations at sacrifice consisted of gross examination of the uterine contents and genital tracts. The following cesarean parameters were recorded: number of corpora lutea/ovary, no. implantation sites, no. early/late resorption sites, no. live/dead fetuses, body weight of live fetuses and the sex of live fetuses. In addition, any grossly visible condition observed in the urogenital tract or any other organ was noted. For any dam that died

on study, uterine examinations were conducted but were not included in the data analysis.

2. Fetal Evaluations - The fetuses were examined in the following manner: at the time of cesarean examination, all fetuses were examined visually for external variations and were weighed. Of the fetuses collected, about 1/3 were preserved in Bouin's fluid for visceral examination using the Wilson free-hand slicing technique. The remaining 2/3 were stained with Alizarin red-S dye for skeletal examination.

D. DATA ANALYSIS

1. Statistical analyses: Noncontinuous or incidence data were analyzed using confidence belts for proportions of computation of exact probabilities. Statistical significance was identified at $p<0.01$. Continuous data such as body weight data were analyzed using ANOVA. When significant differences were observed, pairwise comparison of the treated groups with the control group were analyzed by the Least Significant Difference Test. Statistical significance was identified at $p<0.05$.

2. Indices: Formulas for calculations of cesarean parameters were not provided in the study report. However, based on the summary tables of the report, calculations of corpora lutea/dam, implantations/dam, live or dead fetuses/dam and resorptions/dam were determined by dividing the total number of these findings in all litters examined by the number of litters examined. The pregnancy rate was determined by dividing the total number of females that were identified as pregnant in the cesarean evaluation by the total number of females that were mated. In addition the following indices were calculated by the reviewer:

$$\text{Preimplantation loss (\%)} = \frac{\text{Total \# corpora lutea - Total \# implantations}}{\text{Total \# corpora lutea}}$$

$$\text{Postimplantation loss (\%)} = \frac{\text{Total \# implantations - Total \# live fetuses}}{\text{Total \# implantations}}$$

3. Historical control data: Historical control data were not provided.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: One female at 100 mg/kg/day died on GD 11 (#5119). This female was not pregnant. Because only 1 female died and there was evidence of possible gavage injury (red stomach lining, red fluid in intestines), the reviewer agreed with the study authors that it was probably not treatment-related.

There did not appear to be treatment-related clinical signs of toxicity during this study. Incidences of alopecia, red nasal discharge, rales and diarrhea were sporadic.

2. Body Weight - Mean body weight and body weight gain data (not adjusted for gravid uterine weights) are summarized in Table 2 and mean terminal body weight and adjusted body weight data are summarized in Table 3, below:

TABLE 2: Maternal Body Weight and Weight Gain, Unadjusted (g)[a]

Interval	Dose in mg/kg/day (N)				
	0 (25)	0.8 (25)	4.0 (25)	20 (25)	100 (25)
Body weights (g)					
Gestation day 0	NA	NA	NA	NA	NA
6	255.05±5.23	249.81±5.59	247.34±4.00	246.06±5.90	262.43±5.39
10	258.65±3.91	254.95±5.60	253.23±3.97	245.21±6.10	259.89±5.50
15	285.37±4.84	282.60±7.25	284.60±4.87	271.31±7.23	282.40±6.26 (24)
20	340.04±9.06	336.58±12.45	339.36±8.61	324.34±10.87	354.22±8.83 (24)
Body weight gains (g) [b]					
Pretreatment: Days 0 - 6	NA	NA	NA	NA	NA
Treatment:					
Days 6 - 10	3.60	5.14	5.89	-0.85	-2.54
10 - 15	26.72	27.65	31.37	26.10	22.51 (24)
6 - 15	30.32	32.79	37.26	25.25	19.97 (24)
Posttreatment: Days 15 - 20	54.67	53.98	54.76	53.03	71.82 (24)
Cumulative:					
Days 6 - 20	84.99	86.77	92.02	78.28	91.79 (24)
0 - 20	NA	NA	NA	NA	NA

a Data extracted from Table 2, MRID 00058588. N = 25 except where noted in parentheses next to weight values.

b All body weight gain values calculated by the reviewer (not analyzed statistically).

NA Data not available because GD 0 body weight data were not included in the study report.

There were no significant differences in mean body weight observed at any dose level. However, mean body weight gain at 100 mg/kg/day was reduced during treatment. A weight loss of -2.54 g (vs. gain of 3.60 g, controls) was observed between GD 6-10. Between GD 10-15, mean gain was slightly decreased (-16 % less than controls) resulting in a reduction of mean body weight gain of -34% below controls for the entire treatment period (GD 6-15). When gains were calculated as percentage of initial body weights, in high dose animals during the treatment period it represented a

gain of 7.6% of the GD 6 body weight, vs. 11.9% in controls (-4.3%). The lack of differences in mean body weight was due to the 100 mg/kg/day group having a higher mean body weight than controls at GD 6. The decreased gain observed was not accompanied by decreased food consumption. By day 20, body weight gain at 100 mg/kg/day was slightly greater than controls due to greater gain in the posttreatment phase (GD 15-20). At 20 mg/kg/day, weight gain was also slightly reduced compared to controls, but because some variation in weight gain occurred among the lower dose groups and because as a percent of initial body weight, the decrease was very small (gain during treatment was -1.6% less than controls), it was not considered to be treatment-related. Terminal body weights with and without adjustment for the gravid uterine weights were similar. The study authors did not discuss weight gain data, but did not consider there to be any treatment-related changes in maternal body weights. The decrease at HDT is considered to be a mild treatment-related effect. It is noted that for the control group, the values provided in the study report for mean adjusted terminal body weight (mean and S.E.; Table 5 of report) was incorrect; the corrected value, recalculated from the individual study data, is presented in Table 3 below.

TABLE 3: GD 20 Maternal Body Weight and Adjusted Maternal Body Weight ± S.E. (g)[a]

	Dose in mg/kg/day (N)				
	0 (20)	0.8 (23)	4 (22)	20 (21)	100 (22)
Termination body weight	356.10±7.44	346.63±10.94	344.19±7.72	342.30±8.10	360.66±6.69
Gravid uterine weight	69.83±3.24	66.46±4.86	68.70±3.22	61.12±4.06	67.87±3.03
Body weight minus gravid uterine weight	286.25±6.02	280.16±7.70 [b]	279.23±5.61[c]	281.18±6.65	292.79±4.80

a Data extracted from Tables 5 and 6, MRID 00058588.
b N = 22
c N = 21

3. Food Consumption - There were no treatment-related effects on food consumption. Between GD 6-10 and 10-15, slight but not statistically significant decreases in the mean food consumption of the treated dams were observed. However, these were not considered treatment-related because the decreases were mild and/or a dose-response was not observed (GD 6-10; maximum -10% at 20 mg/kg/day; GD 10-15; maximum -11% below controls at 100 mg/kg/day).

4. Gross Pathology - No treatment-related gross abnormalities were reported at necropsy.

5. Cesarean Section Data - Data are summarized in Table 4, below:

TABLE 4: Cesarean Section Observations[a]

Observation	Dose (mg/kg/day)				
	0	0.8	4.0	20	100
# Animals Assigned (Mated)	25	25	25	25	25
# Animals Pregnant	20	23	23	21	22
Pregnancy Rate (%)	80	92	92	84	88
# Nonpregnant	5	2	2	4	3
Maternal Wastage					
# Died	0	0	0	0	1
# Died Pregnant	0	0	0	0	0
# Died Nonpregnant	0	0	0	0	0
# Aborted	0	0	0	0	0
# Premature Delivery	0	0	1	0	0
Total # Corpora Lutea	294	329	280	262	333
Corpora Lutea/Dam	14.70	14.30	12.72	13.10	15.14
Total # Implantations	239	266	255	213	273
Implantations/Dam	11.95	11.57	11.59	10.38**	12.41
Total # Litters	20	23	22	21	22
Total # Live Fetuses	229	255	248	203	254
Live Fetuses/Dam	11.45	11.09	11.27	9.67	11.55
Total # Dead Fetuses	0	0	0	0	0
Dead Fetuses/Dam	0	0	0	0	0
Total # Resorptions	10	11	7	10	19
Early	10	11	7	10	19
Late	0	0	0	0	0
Resorptions/Dam	0.50	0.48	0.32	0.48	0.86
Early	0.50	0.48	0.32	0.48	0.86
Late	0	0	0	0	0
Litters with Total Resorptions	0	0	0	0	0
Mean Fetal Weight (g) Day 1	3.31	3.38	3.44	3.70	2.88
Day 2	4.63	4.53	4.47	4.38	4.29
Day 3	3.95	3.58	3.85	3.36	3.64
Overall	4.00	3.80	3.89	3.92	3.63
Sex Ratio (% Male)	44.5	49.0	51.2	47.8	49.2
Preimplantation Loss (%)	18.7	19.1	6.3	18.7	18.0
Postimplantation Loss (%)	4.2	4.1	2.7	4.7	7.0

a Data extracted from Table 6, MRID 00058588. Early and late resorption values were calculated by the reviewer from the individual animal data in Appendix III. Pre- and postimplantation loss also calculated by the reviewer.

There were no treatment-related effects on fetal viability or sex ratio. At 100 mg/kg/day, mean fetal weight was slightly reduced (-9.3% less than controls). The reviewer agreed with the study authors that this was probably a treatment-related effect. A slight increase in resorptions/dam (early) was also observed but the rate at this dose was still low (0.86) and not statistically significant, and was not considered treatment-related. In Table 4, it is noted that (1) the number of total corpora lutea provided in the study report Table 6 for the 4.0 mg/kg/day group (250) was incorrect; the value in this DER (280) was calculated from the individual animal data and (2) animal #5098 of the 20 mg/kg/day group was missed in the corpora lutea counts.

B. DEVELOPMENTAL TOXICITY

1. External Examination - There were no treatment-related external abnormalities or malformations reported. The only gross observations reported at necropsy were blood around 2 control fetuses from 1 litter, fusion of placenta of 2 fetuses (1 litter) at 4.0 mg/kg/day and of 2 fetuses (observed in 2 litters) at 100 mg/kg/day.

2. Visceral Examination - There were no treatment-related soft-tissue abnormalities or malformations reported. The findings reported in this study are summarized below in Table 4a. The incidence of slightly dilated brain ventricles was increased at 100 mg/kg/day, although statistical significance was not achieved and a consistent dose-response in either fetal or litter incidence was not established. The number of fetuses (litters) affected at each dose was 5(2), 13(4), 7(2), 2(1), and 20(3), for the control through high-dose groups, respectively. Based upon the lack of statistical significance and dose response, the finding of slightly dilated brain ventricles was judged not to be treatment-related.

TABLE 5a. Fetal Visceral Examinations[a]

Observations	Dose (mg/kg/day)				
	0	0.8	4.0	20	100
#Fetuses(litters) examined	73 (20)	88 (22) [b]	88 (22)	65 (19) [b]	88 (22)
Observations , fetal (litter) % incidence [c]					
Dilated brain ventricles, slight	6.8 (10.0)	14.8 (18.2)	8.0 (9.1)	3.1 (5.0)	22.7 (13.6)
Hydroureter	45.2 (90.0)	26.1 (63.6)	26.1 (54.5)	44.6 (70.0)	33 (72.7)
Hydronephrosis	8.2 (25)	8.0 (22.7)	4.5 (18.2)	4.6 (15.0)	5.7 (13.6)

a Data extracted from Table 8 of MRID 00058588.
b One litter had no fetuses assigned to visceral examination.
c Fetal (litter) incidence = percentage of fetuses (litters) affected.

3. Skeletal Examination - Fetal skeletal findings are shown below in Table 4b. At 100 mg/kg/day, a few bones showed slightly increased fetal and litter incidences in delayed ossification, or lack of ossification, when compared to controls. These included: incomplete ossification of the manubrium, the 4th sternebrae and the cervical vertebrae, and unossified 5th sternebrae and xiphoid process (no statistical significance identified). The reviewer agreed with the study authors that these were possibly treatment-related increases.

TABLE 5b. Fetal Skeletal Examinations[a]

Observations	Dose (mg/kg/day)				
	0	0.8	4.0	20	100
#Fetuses(litters) examined	156 (20)	167 (23)	163 (22)	133 (21)	168 (22)
Observations, fetal (litter) % incidence [b]					
Skull, incompletely ossified	14.1 (20)	7.8 (21.7)	4.3 (13.6)	6.8 (14.3)	10.1 (27.3)
Manubrium, incompletely ossified unossified	9.6 (25) 0	15.6 (30.4) 1.8 (13)	8.0 (31.8) 0	13.5 (28.6) 0	20.8 (50) 0.6 (4.5)
Sternebra 2, incompletely ossified unossified	48.7 (75) 7.8 (15)	46.7 (73.9) 6 (21.7)	60.7 (95.5) 1.2 (11)	57.1 (90.5) 0	58.3 (90.9) 11.9 (22.7)
Sternebra 3, incompletely ossified unossified	10.9 (35) 3.8 (10)	15 (52.2) 1.8 (8.7)	12.3 (31.8) 0	5.3 (23.8) 0	27.4 (59.1) 1.2 (11)
Sternebra 4, incompletely ossified unossified	33.3 (70) 6.4 (10)	35.3 (70) 3.6 (13)	42.3 (72.7) 0	45.1 (81.0) 0	53.0 (95.5) 3.0 (13.6)
Sternebra 5, incompletely ossified unossified	60.9 (39.1) 39.1 (25)	61.1 (73.9) 38.9 (73.9)	58.9 (86.4) 0	53.4 (86.4) 44.6 (85.7)	41.1 (81.8) 58.9 (90.9)
Xiphoid, incompletely ossified unossified	19.9 (50) 13.5 (25)	24.6 (52.2) 14.4 (34.8)	20.2 (45.5) 9.8 (27.3)	22.6 (47.6) 9.8 (23.8)	12.5 (45.5) 27.4 (45.5)
Ribs, >13	6.4 (25)	6.6 (13)	6.7 (22.7)	8.3 (28.6)	6.0 (22.7)
Incompletely ossified cervical vertebrae	9.6 (10)	9.6 (13)	1.8 (4.5)	3.0 (9.5)	14.3 (22.7)
Incompletely ossified thoracic vertebrae	3.2 (15)	0	2.5 (18.2)	2.3 (14.3)	5.4 (22.7)
Incompletely or unossified pubis	5.8 (10)	3.0 (13)	0	0	6.0 (13.6)

a Data extracted from Table 9, MRID 00058588.
b Fetal (litter) incidence: percentage of fetuses (litters) affected.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study authors determined that no maternal toxicity was observed at any of the doses tested. The only fetal findings considered to be related to treatment were the reduction in mean fetal weight and the slight increase in the fetal/litter incidence of delayed ossification and/or unossification of some bones at 100 mg/kg/day. No other developmental variations or teratogenic findings were observed.

B. REVIEWER'S DISCUSSION

The reviewer agreed with the study authors' conclusions, with the exceptions as noted below. The study is classified as **Acceptable/guideline** and satisfies the requirements for a prenatal developmental toxicity study in rodents (OPPTS 870.3700).

1. MATERNAL TOXICITY: Although there were no treatment-related differences observed in mean maternal body weight, at 100 mg/kg/day weight loss was observed between GD 6-10. Mean body weight gain during the treatment period of GD 6-15 was decreased by -34% (-4.3%, when gain was calculated as a percentage of initial body weight and compared to controls). This decrease was considered to be an effect of treatment. This determination is supported by the observation of increased maternal body weight gain following the cessation of treatment (commonly described as a rebound effect). Weight loss at 100 mg/kg/day was also observed during the first week of treatment in the rabbit developmental toxicity study on propanil (MRID 00058589). The maternal toxicity LOAEL and NOAEL are 100 mg/kg/day and 20 mg/kg/day, respectively.

2. DEVELOPMENTAL TOXICITY:
   a. Deaths/Resorptions: *In utero* exposure to propanil did not increase the rate of fetal resorptions or abortions, nor decrease overall fetal viability. Fetal sex ratios were not affected.
   b. Altered Growth: At 100 mg/kg/day, mean fetal weight was decreased (-9.3% below controls). Although this decrease was not statistically significant, it was considered to be treatment-related. Slightly decreased fetal weight was also observed at 100 mg/kg/day in the rabbit developmental toxicity study on propanil (MRID 00058589).
   c. Developmental Variations: There were no treatment-related increases in the incidence of external variations observed in this study. A non-significant increase in the high-dose incidence of slightly dilated brain ventricles in the visceral examination was not judged to be related to treatment, due to the lack of a clear dose-response pattern. It is noted that evaluation of the rabbit developmental toxicity study with propanil (MRID 00058589) does not further elucidate this issue, since internal brain structure of rabbit fetuses was not evaluated in that study. In the skeletal examination, some incidences of delayed ossification or lack of ossification were slightly greater at 100 mg/kg/day than in controls or lower dose groups (sternebrae 4 and 5, manubrium, xiphoid

process, and cervical vertebrae). The reviewer agreed with the study author that these skeletal delays were probably related to treatment, and were likely associated with the fetal growth retardation observed at that dose level.

d. Malformations: No treatment-related malformations were observed in this study.

Based on the findings of this study, propanil resulted in slight toxicity to the developing fetuses at 100 mg/kg/day in the form of decreased fetal weight (not statistically significant) and an increased incidence of delayed ossification/unossification of some sternebral and vertebral sites. At the same dose level, toxicity was observed in the pregnant dams (decreased weight gain during treatment). There was no evidence of treatment-related effects on fetal viability or teratogenicity at the dose levels tested. The developmental toxicity NOAEL and LOAEL are 100 mg/kg/day and 20 mg/kg/day, respectively. The study is classified as **Acceptable/guideline** and satisfies the requirements for a prenatal developmental toxicity study in rodents (OPPTS 870.3700).

C. STUDY DEFICIENCIES: (1) Analytical data on the concentration and homogeneity of the dosing solutions were not provided, although evaluation of the analytical data for the prenatal developmental toxicity study in rabbits resulted in the conclusion that it appears likely that dose suspensions could have been prepared adequately for this study; and (2) GD 0 body weight and food consumption data were not included in the study report because animals were supplied premated (day of delivery, GD 6 and to GD 20 sacrifice were provided). These deficiencies were not judged to compromise the overall interpretation of the study data.

Root Data Evaluation Summary

Draft

TXR: 0050209 **Division:** HED **Reviewers:** Linnea Hansen **Signoff Date:** 11/09/2001

MRID	PC Code	Chemical Name
00058588	028201	Propanamide, N-(3,4-dichlorophenyl)-

Guideline Indicator: Yes
Study Status: Acceptable/Guideline
Source of Review: US
Guideline: 83-3 Teratogenicity -- 2 Species
Primary Guideline: 83-3 Teratogenicity -- 2 Species
Toxicity Category:

Study Type: Developmental, Oral, 10 Gestation Days. GD 6-15; C-section on GD 20

Executive Summary:

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

OneLiner Summary:

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 00058588), Stam (propanil technical, 85.4% a.i.) was administered to 25 presumed pregnant BLU:(SD)BR rats/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 0.8, 4.0, 20 or 100 mg/kg/day from presumed gestation days (GD) 6 through 15, inclusive. Cesarean sections were performed on surviving dams on GD 20. Dosing for each animal throughout the treatment period was based on its body weight on GD 6.

At 100 mg/kg/day, although no significant changes in mean body weight were observed, mean maternal body weight loss (-2.54 g, vs. gain of 3.60 g, controls) was observed between GD 6-12 (first week of treatment) and mean body weight gain between GD 6-15 (treatment) was reduced by 34% below controls (when gain was expressed as a

percentage of the GD 6 mean body weight, the decrease was –4.3%). A rebound in body weight was observed following the cessation of treatment. There were no treatment-related clinical signs of toxicity nor effects observed on food consumption (g/animal/day) or cesarean parameters and no effects were reported at 4.0 or 20 mg/kg/day. The maternal toxicity LOAEL is 100 mg/kg/day, based on decreased body weight gain during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, decreased mean fetal weight (-9.3% below controls; not statistically significant) and slight increases in the incidence of delayed ossification or unossification of some bones (sternebrae 4 and 5, manubrium, xiphoid process, cervical vertebrae; not statistically significant) were observed. There were no treatment-related effects on fetal survival, sex ratio, or developmental malformations observed at any dose tested. No effects were observed at 4.0 or 20 mg/kg/day. The developmental toxicity LOAEL is 100 mg/kg/day, based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae. The developmental toxicity NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rat is classified Acceptable/guideline and satisfies the guideline requirement for a rodent developmental toxicity study [OPPTS 870.3700; §83-3(a)].

File Attachment(s):

00058588.DER.w

Updated By: Susan Makris **on:** 11/20/2001 05:10 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

Study Citation Summary

Draft

TXR Number: 0050209

MRID	PC Code	Chemical Name
00058588	028201	Propanamide, N-(3,4-dichlorophenyl)-

PC Code	CAS Number
028201	709-98-8

Reregistration Case:
Chemical Category: Amide
Chemical Classification: Herbicide
Test Material: Technical
Batch/Lot No: 9287
Study Ingredient: 85.4% ai
Formulation Type: Emulsifiable Concentrate
Registration Number: 000707-00075 STAM F-34 HERBICIDE
Submitter:
Citation: Kam, C.; Stevens, K.R.; Gallo, M.A. (1980) Teratologic Evaluation of Stam Technical in the Albino Rat: Snell Project # 10065-008. (Unpublished study received Feb 11, 1981 under 707-75; prepared by Booz, Allen & Hamilton, Inc., submitted by Rohm & Haas Co., Philadelphia, Pa.; CDL:224328-A; 244329; 244330; 244331)
Journal: No
Guideline: 83-3 Teratogenicity -- 2 Species
Project Number: 10065/008
Testing Lab: 959849 FOSTER D. SNELL INC.
Study Completion Date: 02/29/80
Data Owner's Name:
Species/Strain: Rat : BLU:(SD)

Updated By: Susan Makris **on:** 11/20/2001 05:16 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

EPA Reviewer: Linnea Hansen, Ph.D. Linnea T. Hansen, Date 10/31/01
Toxicology Branch (7509C)
EPA Secondary Reviewer: Susan L. Makris, M.S. Susan L Makris, Date 10/31/01
Toxicology Branch (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Prenatal Developmental Study - rabbit; OPPTS 870.3700 [§83-3(b)]

DP BARCODE: D277274, D278575 SUBMISSION CODE: S601797
P.C. CODE: 028201 TXR NO.: 0050209

TEST MATERIAL, PURITY: Stam technical, 85.4% a.i.

SYNONYMS: Propanil; N–(3,4-dichlorophenyl)propanamide

CITATION: Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits. Argus Research Laboratories, Inc. (Parkside, PA). Rohm and Haas Company Study Number 80P-113 (Argus Project Number 018-001), December 17, 1980. MRID 00058589. Unpublished study.

Florek, M.C., Christian, M.S., Christian, G.D. and Johnson, E.M. (1980) STAM Technical Teratogenicity Study in Rabbits, Analytical Report. Rohm and Haas Company, Philadelphia, PA. Rohm and Haas Report No. 81RC-015B, April 30, 1981. MRID 45518801. Unpublished study.

SPONSOR: Rohm and Haas Company Research Laboratories, Spring House, PA.

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). **The maternal toxicity LOAEL is 100 mg/kg/day,**

maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. **The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.**

This developmental toxicity study in the rabbit is classified **Acceptable/guideline** and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

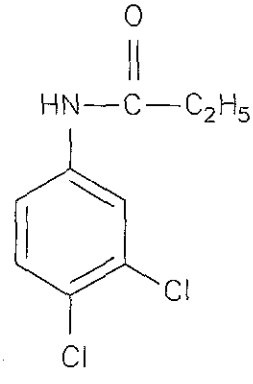
COMPLIANCE: A signed Quality Assurance Statement was provided stating that the study was conducted according to FDA GLP Regulations for Non-Clinical Studies and that two inspections were conducted by the Argus Research Laboratories Quality Assurance Unit. Data Confidentiality and Flagging statements were not provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Stam (propanil)
   Description: technical, black lumpy solid
   Lot/Batch #: 9287
   Purity: 85.4% a.i.
   CAS #: 709-98-8

PROPANIL



2. Vehicle: corn oil
   Description: none given
   Lot/Batch #: XAUG 80A5E (Mazola®)

Purity: None given

3. Test animals: Species: Rabbit
Strain: New Zealand White (DLI:NZW)
Age at mating: 193 to 208 days
Weight at mating: about 2.76 to 5.83 kg
Source: Dutchland Laboratories, Inc., Swampbridge Rd., Denver, PA
Housing: individual stainless steel cages
Diet: Ralston Purina Certified Rabbit Chow #5322, 160 g/animal/day
Water: local tap water, *ad libitum*
Environmental conditions:
Temperature: 62 to 70°F target (actual 58 to 78°F due to lower temperatures on 4 study days and higher temperatures on 6 days)
Humidity: 35% to 65%
Air changes: 12 to 15 changes/hr of 100% fresh air, HEPA-filtered
Photoperiod: 12 hrs dark/12 hrs light
Acclimation period: approximately 1 month

B. PROCEDURES AND STUDY DESIGN

1. In life dates: start: April 27, 1980 (start of insemination). End: May 30, 1980 (end of terminal sacrifice).

2. Mating: Female rabbits were divided into 4 groups (A through D) of 5 animals/dose group. One group/day was artificially inseminated over a period of 4 days (April 27-April 30, 1980). Sperm was collected from 4 male New Zealand White rabbits (a different male used on each day of insemination) obtained from the same source as the females and previously demonstrated as breeders. Group D females (Day 4) were reinseminated, about 3 hrs following the first insemination, with sperm from the male used on day 1 due to low sperm motility (80%) in the male selected for day 4.

3. Animal Assignment: Animals were assigned to dose groups as indicated in Table 1. Assignment was random.

TABLE 1 Animal Assignment

Test Group	Dose (mg/kg/day)	Number of Females
Control	0	20
Low (LDT)	4.0	20
Mid (MDT)	20	20
High (HDT)	100	20

4. Dose selection rationale:

The study report stated that doses were selected on the basis of available LD50 data (not provided). The report did not indicate whether a range-finding study was performed.

5. Dosage preparation and analysis

Test substance formulations were prepared daily as a suspension by mixing appropriate amounts of test substance with corn oil and were used immediately. Analytical chemistry data were submitted to the Agency in a supplemental report (MRID 45518801). From the data provided, it appeared that the formulations had been adjusted for purity of the active ingredient; nominal formulations were listed as 4.7, 23.4, and 117.1 mg/ml for the 4, 20, and 100 mg/kg/day dose groups. Dosing suspensions prepared on dosing days 1, 2, 3, 4, 5, 8, 12, and 16 were analyzed for propanil concentration. Average analytical values (±S.D.) were 4.8 ± 0.6, 24.1 ± 1.52, and 119.0 ± 14.0 mg/ml. These values are 102, 103, and 102% of nominal, respectively, and demonstrate acceptable formulation procedures. Data for homogeneity of dosing suspensions were not provided.

6. Dosage administration: All doses were administered once daily by gavage, on presumed gestation days 6 through 18 (inclusive), in a volume of 10 ml corn oil/kg of body weight/day. Control animals received only the vehicle at the same volume. Dosing was based on the body weight of each individual animal on GD day 6 for the entire treatment period.

C. OBSERVATIONS

1. Maternal Observations and Evaluations - The animals were checked several times during the prestudy interval and on day 0 of presumed gestation for mortality and clinical signs. During the treatment period, animals were observed several times daily. Post-treatment, animals were observed for general health and signs of abortion. Body weights were measured pretreatment, on GD 0 and daily between GD 6 to 30 (treatment and post-treatment periods). The study report stated that does received 160 g food/day, but actual food consumption was not reported. Dams were sacrificed on day 30 of gestation by CO_2 inhalation and their uteri were examined for pregnancy. Gravid uterine weights were not recorded. In pregnant does, the number and placement of implantations, early or late resorptions and live or dead fetuses was determined. The number of corpora lutea were also determined. Does were also evaluated for any grossly visible abnormalities at necropsy. Uteri, ovaries and any abnormal gross findings were preserved in 10% formalin.

2. Fetal Evaluations - At the scheduled GD 30 cesarean examination, the fetuses were

examined in the following manner: all fetuses, pups and late resorptions were weighed, tagged and examined externally for abnormalities. Live pups and fetuses were sacrificed by CO_2 inhalation and cavitated organs were examined grossly for abnormalities. The fetal brains were not examined. Skeletal variations were evaluated after Alizarin red-S staining. (It is noted that the study report provides only minimal details on the methods used for fetal preparation and evaluation.) In addition, pups that were delivered on GD 28 or later but prior to the scheduled termination date were examined for external, soft tissue and skeletal examinations, unless they were cannibalized or autolyzed. Cesarean data for these litters were provided in the individual animal data tables but were not included in the calculations for cesarean parameters. The findings from these litters were, however, included with those of the fetuses examined at scheduled termination.

D. DATA ANALYSIS

1. Statistical analyses: Maternal body weight data were analyzed using Bartlett's test, an ANOVA and an ANCOVA. Caesarean-sectioning data were analyzed using the Kruskal-Wallis test, Fisher's Exact test, the normal approximation to the binomial distribution and the variance test for homogeneity of the binomial distribution. Fetal body weights and ossification site values were analyzed using Bartlett's test and ANOVA. Fetal anomaly data were analyzed by the Fisher's Exact test, the normal approximation to the binomial distribution and the variance test for homogeneity of the binomial distribution.

2. Indices: No formulas for calculations of cesarean findings were provided in the study report. However, based on the summary tables of the report, calculations of corpora lutea/doe, implantations/doe, live or dead fetuses/doe and resorptions/doe were determined by dividing the total number of these findings in all does by the number of litters examined. The pregnancy rate was determined by dividing the total number of females that were identified as pregnant in the cesarean evaluation by the total number of females that were mated. In addition the following indices were calculated by the reviewer:

$$\text{Preimplantation loss (\%)} = \frac{\text{Total \# corpora lutea - Total \# implantations}}{\text{Total \# corpora lutea}}$$

$$\text{Postimplantation loss (\%)} = \frac{\text{Total \# implantations - Total \# live fetuses}}{\text{Total \# implantations}}$$

3. Historical control data: Historical control data on external malformations only were provided for DLI:NZW rabbits. The data were collected from 150,246 litters born at the breeding facility (Dutchland Laboratories) between 1974-1980. The historical data did not include any findings that were observed in the concurrent study, and therefore were not useful in the interpretation of the data from this study.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and Clinical Observations: The following observations were reported: Five high dose females died prior to scheduled sacrifice. Deaths occurred on GD 13 (#5238), 15 (#5237), 16 (#5232), 19 (#5239) and 20 (#5233). All of these females were pregnant; of these, #5237 and #5238 were resorbing their implantations. Clinical signs reported before the death of these animals included loss of righting reflex, decreased motor activity and diarrhea once in #5233; lacrimation (2 days) and blood in cage pan (day 7), #5233; and blood in cage pan, #5238 (days 7, 8, 13). Because no mortality was reported in the lower-dose groups, the deaths were considered treatment-related. No treatment-related clinical signs of toxicity were observed in the animals that survived to the scheduled caesarean section.

2. Body Weight - Mean body weight and weight gain data are summarized in Table 2, below:

TABLE 2 Maternal Body Weight and Weight Gain (kg)[a]

Interval		Dose in mg/kg/day (N) 0 (20)	4 (20)	20 (20)	100 (20)
Body weights					
Gestation day	0	4.68±0.56	4.74±0.56	4.59±0.41	4.56±0.50
	6	4.73±0.60	4.78±0.54	4.65±0.40	4.61±0.46
	12	4.72±0.58	4.80±0.54	4.65±0.36	4.42±0.42
	18	4.64±0.58	4.79±0.52	4.61±0.36	4.31±0.50 (12)
	30	4.69±0.55 (17)[b]	4.70±0.50	4.66±0.41	4.52±0.65 (7)
Body weight gains					
Pretreatment: Days 0 - 6[c]		0.05	0.04	0.06	0.05
Treatment: Days 6 - 12		-0.01	0.02	-0.04	-0.19**
6 - 18		-0.09	0.01	0.04	-0.24 (12)
Posttreatment: Days 18 - 30[c]		0.08 (17)	-0.08 (14)	0.06 (14)	0.15 (7)
Cumulative: Days 6 - 30		-0.02 (17)	0.04 (14)	0.04 (14)	0.09 (7)
0 - 30		0.03 (17)	0.09 (14)	0.10 (14)	0.18 (7)

** Statistically significant, p<0.01.
a Data extracted from Tables 4 and 5, MRID 00058589 (GD 18-30 weight gain values calculated using individual animal data from Table 5 for those animals sacrificed on day 30).
b Numbers in parentheses next to body weight or weight gain values indicate number of animals evaluated when N was reduced by maternal mortality, lack of pregnancy or abortion.
c Values calculated by reviewer. Not analyzed statistically.

At 100 mg/kg/day, a transient but statistically significant mean weight loss was observed between GD 6-12 (-0.19, vs. -0.01, concurrent controls). Weight loss was observed in the does that were removed from the study due to death or abortion, as well as those that survived. Increased weight loss was observed during the entire treatment period (-0.24 kg vs. -0.09 kg, controls). At GD 12 and GD 18, mean gestational body weight was -6.4% and -7.1% below controls, respectively (not statistically significant); however, some of this decrease reflected the lower GD 6 body weight of the HDT animals. Post-treatment, no significant decreases in body weight or weight gain were observed. This reviewer agreed with the study authors that the decrease in body weight and body weight gain during the period of administration at the HDT was related to treatment.

3. Food Consumption - No food consumption data were provided in the study report. Does were administered a fixed amount of diet each day (160 g/day).

4. Gross Pathology - At necropsy, no treatment-related findings were reported. Erosion of the pyloric mucosa in 2 low and 1 high dose animal did not show a dose-response..

5. Cesarean Section Data - Data are summarized in Table 3, below:

No treatment-related changes in abortions, premature delivery, fetal death, early/late resorptions, sex ratio or pre/post-implantation loss were observed. Pregnancy rate, corpora lutea and implantations did not show significant differences among dose. However, as noted previously, maternal survival was affected by treatment at the high dose of 100 mg/kg/day (25% mortality). Due to a combination of maternal death, abortion, premature delivery and nonpregnancy, a low number of litters were available for evaluation at 100 mg/kg/day (7 litters for cesarean evaluation instead of the guideline-recommendation of 12).

Among the fetal parameters evaluated at cesarean section, the only finding was a slight (not statistically significant) decrease in mean fetal body weight (-6.1% less than concurrent controls; similar in male and female fetuses when evaluated separately). This finding is considered to be treatment-related and possibly related to maternal body weight loss during the first week of treatment. The incidences of late resorptions/dam and postimplantation loss were higher at 20 and 100 mg/kg/day than in controls or lower dose groups, but because a dose-response was not observed and statistical significance was not achieved, these findings were not considered treatment-related.

TABLE 3 Cesarean Section Observations[a]

Observation	Dose (mg/kg/day)			
	0	4 (LDT)	20 (MDT)	100 (HDT)
# Animals Assigned (Mated)	20	20	20	20
# Animals Pregnant	18	19	15	17
Pregnancy Rate (%)	90	95	75	85
# Nonpregnant	2	1	5	3
Maternal Wastage				
# Died	0	0	0	5***
# Died Pregnant	0	0	0	5
# Died Nonpregnant	0	0	0	0
# Aborted	1	3	0	4
# Premature Delivery	0	2	1	1
Total # Corpora Lutea	189	156	136	74
Corpora Lutea/Doe	11.1	11.1	9.7	10.6
Total # Implantations	128	98	77	51
Implantations/Doe	7.5	7.0	5.5	7.3
Total # Litters	17	14	14	7
Total # Live Fetuses	113	91	56	41
Live Fetuses/Doe	6.6	6.5	4.0	5.9
Total # Dead Fetuses	0	0	0	0
Dead Fetuses/Doe	0	0	0	0
Total # Resorptions	6	8	22	10
Early	5	6	20	10
Late	1	2	2	0
Resorptions/Doe	0.9	0.5	1.5	1.4
Early	0.8	0.4	1.4	1.4
Late	0.1	0.1	0.1	0.0
Litters with Total Resorptions	1	0	1	0
Mean Fetal Weight (g)	47.3	48.0	50.1	44.4
Males	47.8	48.6	49.2	44.5
Females	46.3	45.1	49.3	44.3
Sex Ratio (% Male)	51.3	62.6	50.0	41.5
Preimplantation Loss (%)[b]	32.3	35.9	43.4	31.1
Postimplantation Loss (%)[b]	11.7	7.1	27.3	19.6

a Data extracted from Tables 6 through 9, MRID 00058589. See Data Analysis section, above for calculation of parameters.

b Calculated by reviewer. Data not analyzed statistically.

*** Statistically significant, $p<0.005$.

B. DEVELOPMENTAL TOXICITY

The external,visceral and skeletal data include pups from any premature litters that were born on or after GD 28 and that were not autolyzed or cannibalized (2 litters at 4 mg/kg/day and 1 at 100 mg/kg/day).

1. External Examination - There were no treatment-related external abnormalities or malformations reported. All findings reported in this study are summarized below in Table 4a.

2. Visceral Examination - There were no treatment-related soft-tissue abnormalities or malformations reported. The findings reported in this study are summarized below in Table 4b.

3. Skeletal Examination - No treatment-related skeletal abnormalities or malformations were reported. Selected findings observed in the HDT (and lower dose groups) are shown below in Table 4c. Most findings were fused vertebrae or ribs and delays in ossification that did not show a relationship to treatment.

TABLE 4a. External Examinations[a]

Observations	Dose (mg/kg/day)			
	0	4	20	100
#Fetuses(litters) examined	114 (16)	108 (16)	67 (14)	49 (8)
Total # Fetuses(litters) w/external findings	1 (1)	4(4)	0	0
Observations , fetal (litter) % incidence				
Small body size	0.9 (6.2)[b]	0	0	0
Head and neck edema	0	0.9 (6.2)	0	0
Disarthrosis, right forelimb	0	0.9 (6.2)	0	0
Short tail	0	0.9 (6.2)	0	0
Lived less than 5 minutes	0	0.9 (6.2)	0	0

a Data extracted from Table 12, MRID 00058589.
b Fetal (litter) incidence

TABLE 4b. Visceral Examinations[a]

Observations	Dose (mg/kg/day)			
	0	4	20	100
#Fetuses(litters) examined	113 (16)	106 (16)	65 (14)	49 (8)
Total # Fetuses(litters) w/visceral findings	0	1(1)	1(1)	0
Observations , fetal (litter) % incidence				
Fetal edema	0	0.9 (6.2)[b]	0	0
Diaphragmatic hernia	0	0	1.5 (7.1)	0

a Data extracted from Table 13, MRID 00058589.
b Fetal (litter) incidence

TABLE 4c. Skeletal Examinations[a]

Observations	Dose (mg/kg/day)			
	0	4	20	100
#Fetuses(litters) examined	114 (16)	108 (16)	67 (14)	49 (8)
#Fetuses(litters) with skeletal findings	22 (12)	30 (13)	14 (6)	7 (4)
Observations, fetal (litter) % incidence				
Asymmetric sternebrae (1 or more)	4.4 (25.0)[b]	0.9 (6.2)	3.0 (14.3)	4.1 (25.0)
Incompletely ossified sternebrae (1)	7.9 (37.5)	15.7 (56.2)	7.5 (21.4)	4.1 (12.5)
Incompletely or unossified xiphoid	4.4 (18.8)	7.4 (31.2)	7.5 (7.1)	6.1 (37.5)

a Data extracted from Table 14, MRID 00058589.
b Fetal (litter) incidence

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study authors determined that maternal toxicity was observed at 100 mg/kg/day (HDT), based on mortality (25%) and weight loss between GD 6-12. The clinical signs observed in some does, including those that died, were not considered treatment-related because they were single incidences or were not dose-dependent. No developmental toxicity including teratogenicity or increased fetal mortality was observed at any dose tested.

B. REVIEWER'S DISCUSSION

The reviewer agreed with the study authors' conclusions, with the exceptions noted below:

1. MATERNAL TOXICITY: The reviewer agreed with the study authors that maternal toxicity was observed only at 100 mg/kg/day. Five does died between GD13-20, whereas there were no deaths in any of the other test groups. The study authors did not consider the clinical signs observed before death to be treatment-related; however, the reviewer considered them to be possibly treatment-related. A mean weight loss of -0.19 kg vs -0.01 kg in controls (statistically significant compared to controls) between GD 6-12 was also noted. By scheduled termination on GD 30, body weight gain of the surviving does was comparable to the controls. No treatment-related changes were observed in maternal animals at cesarean section for any dose tested.

2. DEVELOPMENTAL TOXICITY:
   a. Deaths/Resorptions: *In utero* exposure to propanil did not increase resorptions, abortions or affect fetal survival. The rate of fetal postimplantation loss was increased at 20 and 100 mg/kg/day, but was not statistically significant and did not show a dose-response and was therefore not considered treatment-related.
   b. Altered Growth: At 100 mg/kg/day, mean fetal weight was decreased, but the decrease was not statistically significant (-6.1% below controls, combined male and female weights). This was considered to be a slight treatment-related effect and possibly secondary to maternal weight loss during the first week of treatment.
   c. Developmental Variations: There were no treatment-related external, visceral or skeletal variations observed in this study.
   d. Malformations: No treatment-related malformations were observed in this study.

Based on the findings of this study, propanil resulted in mild toxicity to the developing fetuses in the form of decreased fetal weight (not statistically significant) at a dose level that caused significant toxicity to the pregnant does (mortality, weight loss during the first week of treatment). There was no evidence of treatment-related effects on fetal survival, incidence of fetal anatomical variations or teratogenicity at the dose levels tested. A LOAEL of 100 mg/kg/day and NOAEL of 20 mg/kg/day for both maternal and developmental toxicity were identified.

C. STUDY DEFICIENCIES: (1) The number of litters available for fetal examination at the high dose (100 mg/kg/day) was below the guideline recommendation (7 were examined for cesarean parameters and 8 for fetal findings, instead of the 12 recommended in the guideline used at the time that this study was conducted); (2) in accordance with procedures common at the time this study was conducted, the fetal brain was not examined; therefore, internal anomalies such as minimal hydrocephaly or dilation of the lateral ventricles would not have been detectable in this study; (3) the does were

41

maintained on a restricted diet of 160 g/day, but food consumption data were not provided. It could not be determined whether the decreased mean body weight in high dose females was associated with a decrease in food consumption; (4) the methodologies used in preparation and evaluation of fetuses were not described in detail.

The number of litters available for examination were significantly reduced at the HDT due to maternal mortality (5), infertility (3), spontaneous abortion (4) and premature delivery (1). However, a NOAEL and LOAEL for both maternal and developmental toxicity could be determined and significant maternal mortality (25%) was observed at the HDT. There were adequate litters and fetuses available for examination at the NOAEL (MDT). No fetal death or malformations were reported in the rat study on propanil as well (MRID 00058588). In the absence of food consumption data suggesting otherwise, the reductions in body weight gain observed at the HDT are considered treatment-related. In summary, none of the listed deficiencies compromise the validity of the reported data or the interpretation of the study; therefore, this study is classified as **Acceptable/guideline**.

Root Data Evaluation Summary

Draft

TXR: 0050209 **Division:** HED **Reviewers:** Linnea Hansen **Signoff Date:** 11/09/2001

MRID	PC Code	Chemical Name
00058589	028201	Propanamide, N-(3,4-dichlorophenyl)-

Guideline Indicator: Yes
Study Status: Acceptable/Guideline
Source of Review: US
Guideline: 83-3 Teratogenicity -- 2 Species
Primary Guideline: 83-3 Teratogenicity -- 2 Species
Toxicity Category:

Study Type: Developmental, Oral, 13 Gestation Days. GD 6-18; C-section on GD 30

Executive Summary:

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). The maternal toxicity LOAEL is 100 mg/kg/day, based on mortality, clinical signs of toxicity and weight loss during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rabbit is classified Acceptable/guideline and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

OneLiner Summary:

EXECUTIVE SUMMARY: In an oral developmental toxicity study (MRID 00058589, 45518801), Stam (propanil technical, 85.4% a.i.) was administered to 20 presumed pregnant (artificially inseminated) New Zealand white rabbits/dose group by gavage in corn oil vehicle (10 ml/kg body weight) at dose levels of 0, 4, 20 or 100 mg/kg/day from gestation days (GD) 6 through 18, inclusive. Cesarean sections were performed on GD 30 for surviving does. Dosing for each doe was based on its body weight on GD 6.

At 100 mg/kg/day, 5 does died between GD 6-20 (25% mortality rate). Transient weight loss between GD 6-12 (-0.19 kg vs. -0.01 kg, controls; $p<0.01$) was observed, resulting in increased weight loss compared to controls for the treatment period (-0.25 kg vs. -0.09 kg, controls) and decreased mean body weight (at GD 18, -7.1% less than controls, due in part to lower initial mean body weights; not sustained post-treatment). Clinical signs of toxicity in some does before death included loss of the righting reflex, decreased motor activity and blood in cage pans, which were possibly related to treatment. No effects were observed at the cesarean examination and no treatment-related

findings were observed at 4 or 20 mg/kg/day. Food consumption was not measured (animals given 160 g/animal/day). The maternal toxicity LOAEL is 100 mg/kg/day, based on mortality, clinical signs of toxicity and weight loss during treatment. The maternal toxicity NOAEL is 20 mg/kg/day.

At 100 mg/kg/day, a slight decrease in mean fetal weight was observed (-6.1% below controls; not statistically significant). There were no treatment-related developmental abnormalities or malformations observed at any dose tested and fetal survival was not affected. The developmental toxicity LOAEL is 100 mg/kg/day, based on slightly decreased mean fetal weight. The developmental NOAEL is 20 mg/kg/day.

This developmental toxicity study in the rabbit is classified Acceptable/guideline and satisfies the guideline requirement for a prenatal developmental toxicity study in rabbits [OPPTS 870.3700; §83-3(b)].

File Attachment(s):

00058589.DER.w

Updated By: Susan Makris **on:** 11/20/2001 04:42 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

Study Citation Summary

Draft

TXR Number: 0050209

MRID	PC Code	Chemical Name
00058589	028201	Propanamide, N-(3,4-dichlorophenyl)-

PC Code	CAS Number
028201	709-98-8

Reregistration Case:

Chemical Category: Amide

Chemical Classification: Herbicide

Test Material: Technical

Batch/Lot No: 9287

Study Ingredient: 85.4% a.i.

Formulation Type: Emulsifiable Concentrate

Registration Number: 000707-00075 STAM F-34 HERBICIDE

Submitter:

Citation: Florek, M.C.; Christian, M.S.; Christian, G.D.; et al. (1980) Stam Technical Teratogenicity Study in Rabbits: Argus Project 018- 001; Rohm and Haas Company Study 80P-113. (Unpublished study received Feb 12, 1981 under 707-75; prepared by Argus Research Laboratories, Inc., submitted by Rohm & Haas Co., Philadelphia, Pa.; CDL:244332-A)

Journal: No

Guideline: 83-3 Teratogenicity -- 2 Species

Project Number: 018/001
80P/113

Testing Lab: 959822 ARGUS RESEARCH LABORATORIES

Study Completion Date: 12/17/80

Data Owner's Name:

Species/Strain: Rabbit : DLI:NZW

Updated By: Susan Makris **on:** 11/20/2001 04:46 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

D

Propanil **Reproduction Study (OPPTS 870.3800; 83-4)**

Reviewer: Laurence D. Chitlik, D.A.B.T. Date 10/31/01
Toxicology Branch (7509C)
Secondary Reviewer: Susan L. Makris, M.S. Date 10/31/01
Toxicology Branch (7509C)

DATA EVALUATION RECORD

STUDY TYPE: Multigeneration Reproduction - Rat OPPTS 870.3800 [§83-4]

DP BARCODE: D277274, D278575 SUBMISSION CODE: S601797
P.C. CODE: 028201 TXR NO.: 0050209

TEST MATERIAL (PURITY): Propanil (98%)

CITATION: Stump, D.G. (1998) A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats. WIL Research Laboratories, Inc., 1407 George Rd. Ashland, Ohio 448505-9281. WIL Study Identification No. 141013. July 1, 1998. MRID 44604301 Unpublished.

SPONSOR: Propanil Task Force, c/o Edward Ruckert McDermott, Will and Emory, 1850 K St., NW, Suite 500, Washington, DC 2006

EXECUTIVE SUMMARY: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. **The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food**

46

consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. **The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).**

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. **The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).**

This study is classified as **Acceptable/guideline** and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

COMPLIANCE: Signed and dated GLP, FIFRA and Health Effects Test Guidelines Compliance Statements, Statement of No Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

47

A. MATERIALS

1. Test material: Propanil, received as 5 aliquots #s 6-10,
Description: Brownish gray crystalline powder
Batch No.: #02, WIL Log No. 2825A
Purity: Results of purity analyses for aliquots # 6 and 7, which were used in this study: 98.3% and 98.4% (mean purity = 98.4%), but considered to be 100% pure for concentration calculations.
Stability of compound: The test article was determined to be stable for 10 days when stored at room temperature protected from light.

2. Vehicle

PMI Feeds, Inc., Certified Rodent LabDiet 5002.

3. Test animals

Species: rat
Strain: Sprague Dawley CRL:CD®(SD)BR
Age and weight: Animals were 31 days of age when received. At the time of randomization, male weights ranged from 153 to 235 grams and female weights ranged from 125 to 170 grams.
Source: Charles River Laboratories, Portage, Michigan (animals received 11/30/95)
Housing: Animals were housed in groups of 3 per cage in suspended wire-mesh cages for 3 days to adapt to the automatic watering system. After this, animals were housed individually except during mating. Following evidence of mating, animals were transferred to plastic maternity cages with nesting material (Bed-O'-Cobs). Animals were housed in these cages until weaning on lactation day 21). Animals were uniquely identified with Monel metal eartags.
Diet: PMI Feeds, Inc., Certified Rodent LabDiet 5002, *ad libitum*
Water: Tap water was available *ad libitum.*
Environmental conditions:
Temperature: 71 - 74°F
Humidity: F0 16-59%, F1 40-68%
Air Changes: 10/hour
Photoperiod: 12 hour light/dark
Acclimation period: 12 days

4. Diet preparation and analysis

Fresh diets were prepared weekly and were stored at room temperature. Micronized propanil was weighed for each test group into tared weighing

containers. This was added to 5 kg of rodent diet in a Hobart blender. The preparation was mixed for ten minutes. This premix was transferred to a V-twin shell blender and mixed for 15 minutes "with enough rodent meal to obtain a sufficient batch of homogeneous diet of the appropriate concentration for each test group." An intensifier bar was used during the first and last five minutes of blending. The test diets were then placed in labeled storage bags.

Each week, 100 gram aliquots of each concentration were taken from the middle of each formulation and stored frozen at WIL. These samples were retained for possible future analyses. Other samples were analyzed at weeks 0, 1, 2, 3, and at monthly intervals thereafter.

Prior to initiation of dosing, representative batches of diet were prepared for analyses and 100 gram samples were collected from the top, middle and bottom of the preparations for each dose level and control. One set of samples was analyzed for homogeneity and the second set was combined and stored under lab conditions for 10 days and then analyzed for stability. Since there was a change of dose levels at the two high dose levels (150 and 600 ppm) these levels were not analyzed prior to initiation of the study although analyses were completed at comparable levels (180 and 540 ppm) which had been previously specified for these two dose levels.

Results – Analytical results were presented in Appendix B (beginning on page 2368) of the report. They indicated that the diet preparations were stable for 10 days at room temperature, were homogeneous, and contained the specified amounts of test article at each dose level (generally within 10% of target).

B. STUDY DESIGN

1. In life dates

Start: Treatment of F0 animals began on December 12, 1995 and F1 parental animals were necropsied by September 10, 1996.

2. Animal assignment

Animals judged to be in good health and meeting "acceptable body weight requirements" were selected for use in the computer randomization procedure. Using the WIL Toxicology Data Management System, a printout was generated containing the animal numbers, corresponding body weights and individual group assignment based on body weight stratification randomized in a block design. Animals were approximately six weeks old at the initiation of treatment. F0 male body weights ranged from 152 to 222 grams and F0 female

weights ranged from 125 to 178 grams. The F0 and F1 parental animals were assigned to groups as shown below in Table 1:

TABLE 1: Animal Assignment

Dose group	Propanil in diet[a] (ppm)	No. of parental animals per group			
		F0 Generation		F1 Generation	
		Male	Female	Male	Female
0 (Control)	0	30	30	30	30
1 (Low)	60	30	30	30	30
2 (Mid)	150	30	30	30	30
4 (High)	600	30	30	30	30

Data taken from page 30 of the test report.

Thirty male and female F1 pups from each group were randomly selected (using a computer randomization procedure) prior to lactation day 21 to comprise the F1 generation. A minimum of one male and female per litter (when possible) were selected and offered test diet beginning on postpartum day 22.

F1 and F2 litters were reduced to 8 pups per litter, 4 per sex when possible, on PND day 4. The remaining offspring were weighed, euthanized and discarded on PND 4.

3. Dose selection rationale

The report stated (page 27) that dose levels were selected based on the results of a range-finding study conducted at WIL. Although a copy of this report was not provided for review, it was reported that parental toxicity was noted at 600, 1200, and 1800 ppm based on changes in the clinical condition of the animals and inhibition of body weight gain and/or food consumption throughout the study. Reduced mean pup weights, live litter size and viability indices on PND 1 and 4 (before litter standardization) were reported at the 1200 and 1800 ppm dose levels. At 600 ppm, a reduced viability index on PND 4 (before litter standardization) was also reported.

C. METHODS

1. Mating procedure and schedule

Vaginal smears were prepared daily to determine the stage of estrus for each female beginning 21 days prior to pairing and continuing until evidence of

50

mating was observed. If no evidence of mating was observed, smearing continued until termination of the mating period. Vaginal smears were also performed on the day of necropsy to determine the state of estrus.

Animals were paired on a 1:1 basis within each treatment group. They were paired for mating in the home cage of the male. Positive evidence of mating was confirmed by the presence of a copulatory plug or the presence of sperm in a vaginal smear. The day when evidence of mating was noted was termed day 0 of gestation. After evidence of mating was observed, males were housed in suspended wire-mesh cages until necropsy of the parental generations and females were transferred to plastic maternity cages with nesting materials until weaning of their litters on lactation day 21. Each generation was mated once to produce one litter per generation. Prior to mating of the F0 (study week 10), the animals were approximately 17 weeks old and prior to mating of the F1, animals were 14 to 16 weeks old. All females were allowed to deliver naturally.

Each dam and litter remained together until weaning on lactation day 21. If maternal females showed no evidence of mating after 10 days of pairing, they were placed with another male from the same treatment group for an additional 5 days. If mating was not evident after a total of 15 days, the female was placed in a plastic maternity cage with nesting material.

2. Observation schedule

a. Parental animals

Detailed exams were performed at least once weekly throughout the study, the rats were subjected to detailed clinical observations. Animals were observed twice daily, for appearance, behavior, pharmacotoxic signs, morbidity, mortality and evidence of dystocia, prolonged labor, delayed labor or other adverse signs during expected parturition.

Body weights of the F0 and F1 males were recorded weekly throughout the study. Females were weighed weekly until evidence of copulation was observed and then on days 0, 4, 7, 11, 14, 17 and 20 of gestation and days 1, 4, 7, 11, 14, 17 and 21 of lactation. After weaning, weekly body weights were recorded.

Individual food consumption for the F0 and F1 adults was measured weekly until mating. Food consumption was not measured during the mating period. Female food consumption was recorded on gestation days 0, 4, 7, 11, 14, 17, and 20 and on lactation days 1, 4, 7, 11, 14, 17, and 21. Male food consumption was measured weekly after mating until necropsy. Food consumption was calculated and reported as g/kg/day. Compound

consumption and food efficiency were calculated from mean food consumption and the concentration of propanil in the diet.

b. Reproductive performance

Mating pairs were examined daily. During the expected period of parturition, females were observed twice daily for initiation and completion of parturition and for signs of dystocia. Gestation lengths were determined using the date that delivery was initiated. The following mating and fertility indices were listed in the report:

Male Fertility Index (%) = (# of males siring a litter/Total # of males used for mating) X 100

Female Fertility Index (%) = (# of females with confirmed pregnancy/ Total # of females used for mating) X 100

Male/Female Mating Index (%) = [# of males (females) with evidence of mating/ Total # of males (females) used for mating] X 100

c. Litter observations

All females were allowed to litter normally and rear their young to weaning. On the day of parturition, pups were sexed and examined for gross malformations and the numbers of stillborn and live pups were recorded. Each litter was examined twice daily for survival and all deaths were recorded. All pups were identified by application of tattoo markings. A daily record of litter size was maintained. Intact offspring that died were necropsied using the method of Stuckhardt and Poppe. The report also stated that, "Pups with external abnormalities which would warrant further skeletal examination were cleared and stained as described by Dawson for skeletal evaluation." Findings were described as either developmental variations or malformations. A detailed gross exam was performed on any pup dying after postnatal day 4 and prior to weaning.

Each male pup was observed for balanopreputial separation beginning on PND 40. The day on which it was first observed was recorded for each pup. Examination of pups continued daily until balanopreputial separation was present. Each female pup was observed for vaginal perforation on PND 30. The day on which the vaginal lumen was first observed to open was recorded for each pup. Examination of the females was continued daily until vaginal perforation was present.

The following litter size and survival indices were calculated in this study:

Live Litter Size	= # of viable pups on PND 0/ # of litters with viable pups on PND 0
Viability Index (%) between PND 0 and PND 4 (Pre-culling)	= (# Viable Pups per litter on PND1 or PND 4/ # of pups viable on day 0) X 100
Viability Index (%) (after culling)	= (# viable pups on PND (N)/ # viable on PND 4 post-cull) X 100 (Where N = 7, 14, or 21)

3. Postmortem studies

a. Sacrifice

F0 adults were sacrificed after selection of the F1 generation and detailed clinical examinations had been performed. Surviving F1 adults were sacrificed following weaning of the F2 pups. As previously described, selected F1 and F2 pups were killed at the time of litter standardization (PND 4) or at weaning (PND 21).

b. Necropsy

1) Parental animals - Necropsies were to be conducted on all F0 and F1 parental animals dying spontaneously or at termination. All animals were sacrificed by carbon dioxide inhalation.

2) Offspring - One F1 weanling per sex/litter was selected for a complete necropsy. Apparently no F2 weanlings received a gross necropsy. The necropsy included examination of the external surface, all orifices, the cranial cavity, the external surfaces of the brain and spinal cord, and the thoracic, abdominal and pelvic cavities including viscera. All surviving non-selected F1 and F2 weanlings were euthanized and partially necropsied on postnatal day 21 with a focus on developmental and reproductive system morphology.

c. Hormonal Evaluation of F0 Males

The study report states (page 41) that, "The structure of Propanil is similar to the nonsteroidal antiandrogens, flutamide and linuron. The compounds affect the regulation of the hypothalamic-pituitary-testicular axis by competitively blocking the binding of testosterone to the androgen receptor. This results in elevated levels of serum luteinizing hormone (LH), estradiol and testosterone (flutamide only). Therefore, a quantitative assessment of hormone levels was performed on all F0 males following euthanization. Blood samples (approximately 6 ml) were collected from

53

the vena cava of each F0 male at the scheduled euthanization. Serum was isolated from the samples, divided into two aliquots of approximately 0.5 ml and 1.5 ml and frozen. The 0.5 ml aliquots from 20 randomly selected F0 males in the control and high dose groups were shipped frozen to AniLytics, Inc. (Gaithersburg, MD), where levels of the following hormones were measured by radioimmunoassay:"

Estradiol
Luteinizing hormone (LH)
Testosterone

d. Spermatogenic Endpoint Evaluations

Following sacrifice, the reproductive tract of each F0 and F1 male was exposed via a ventral mid-line incision. The right testis and epididymis were then removed and weighed. In the distal region of the right cauda epididymis, an incision was made and the entire epididymis was then placed in 40 ml of Dulbecco's phosphate buffered saline with 10 mg/ml bovine serum albumin for 10 minutes then preserved with the right testis for histopathology. After a ten minute incubation period, a sample was placed in a 100 um cannula for determination of sperm motility. Motility measurements were performed under constant temperature (approximately 37°C) using the Hamilton-Thorne HTM-IVOS version 10 computer-assisted sperm analysis system. A minimum of 200 sperm/animal were analyzed in all dose groups.

A second sample of sperm was obtained from the same 40 ml suspension and smears of epididymal sperm were prepared in duplicate on microscope slides. The slides were allowed to air dry and were stained with Weigert's iron hematoxylin, counterstained with 1% eosin-phloxine and cover slipped. Using a microscope, abnormal forms of sperm from a differential count of 200 spermatozoa per animal, if possible, were examined.

The left testis and epididymis from all F0 and F1 males of all groups were stored frozen, homogenized and then evaluated for homogenization-resistant spermatid count and sperm production rate using the method of Blazak and the Hamilton-Thorne computer assisted sperm analysis (CASA) system. Samples were thawed and homogenized and a sample retained for subsequent analysis. Samples were added to DNA-specific flourescent dye. Each sample was mixed and an aliquot examined via illumination from a xenon lamp within the HTM-IVOS analyzer. A minimum of 200 cells, or 20 fields were counted for each sample.

e. Necropsy observations

All F0 and F1 parental animals (and one randomly selected F1 weanling per sex per litter) were subjected to gross necropsy consisting of external and internal examinations. The following tissues (X) were preserved in 10% neutral buffered formalin and weighed (XX).

X	Adrenals (2)*	X	Lymph node
X	Aorta	XX	Ovaries and oviducts (2)*
X	Bone with marrow	X	Pancreas
X	Brain*	X	Peripheral nerve (Sciatic)
X	Cervix	XX	Pituitary
X	Coagulating gland	XX	Prostate
X	Eyes with optic nerve	X	Salivary gland(submax)
X	Gastrointestinal tract	XX	Seminal vesicles (2)
X	Esophagus	X	Skeletal Muscle
X	Stomach	X	Skin with mammary gland
X	Duodenum	X	Spinal cord
X	Jejunum	XX	Spleen*
X	Ileum	XX	Testes with epididymides ** and vas deferens
X	Cecum		
X	Colon	XX	Thymus*
X	Rectum	X	Thyroids with parathyroids
X	Heart	X	trachea
X	Kidneys (2)*	X	Urinary bladder
X	Liver (two lobes)*	XX	Uterus with vagina
X	Lungs		All gross lesions

* These organs were also weighed in selected F1 weanlings.
** The right testis and epididymis was fixed in Bouin's solution. Transverse sections were made for the testis, and longitudinal sections for the epididymis.

f. Histopathological Examination

Histopathologic examinations were conducted on the following tissues from all F0 and F1 parental animals from the control and high dose groups and for all dead and moribund adults. In addition, spleens from all F0 and F1 animals in all groups were examined from all parental animals dying spontaneously or euthanized *in extremis* and from one F1 pup/sex/litter in the control and high dose groups:

Adrenal glands+
Brain
Epididymis (right) caput, corpus, and cauda
Cervix
Coagulating gland
Kidneys+
Liver+
Ovaries+**
Oviducts
Prostate
Seminal vesicles
Spleen+
Testis (right)+*
Thymus+
Uterus
Vagina
Vas deferens
All gross (internal) lesions+

55

Pituitary

+ These organs from the selected F1 weanlings were examined microscopically; the left and right testes were examined.
* PAS and hematoxylin staining were used for the right testis and epididymis.
** The ovaries from each F0 and F1 parental female (control and high dose groups) were serially sectioned and 10 sections per ovary were selected for evaluation of follicle counts and follicular maturation.

4. Historical control data - Historical control data for the Sprague-Dawley Crl:CD BR rat, from studies conducted at WIL Laboratories, were provided in Appendices G (page 2534) and H (page 2569) of the test report. These data included reproductive performance and spermatogenic endpoints, respectively.

D. STATISTICAL ANALYSES

All tests except those specifically designated were conducted using two tailed tests for a minimum significance level of 5% with comparisons to the controls. Means were presented with standard deviations and the N used to calculate them. Nongravid animals were excluded from the assessment. Statistical analyses were also not performed, "when weekly food or body weight data for one or more animals were not available because the animals remained in the lactation phase." The following statistical tests were utilized in this study:

1. Chi-square test with Yates correction was used for parental mating and fertility indices, pup sex ratios, numbers of stillborn and dead, viability indices and live birth index.

2. One-way ANOVA with Dunnett's test was utilized for parental weekly body weights and weight changes, gestation and lactation body weights and body weight changes, parental food consumption, mean gestation length, pre-coital interval, pup body weights, absolute and relative organ weights, live litter size, sperm production rate, sperm numbers, and age of balanopreputial separation.

3. Kruskal-Wallis test with Mann-Whitney U test was used to assess sperm motility and sperm morphology.

4. Kolmogorov-Smirnov test (one-tailed test) was used to assess histopathological findings.

II. RESULTS

A. SYSTEMIC TOXICITY/PARENTAL TOXICITY

1. Mortality and clinical signs

With the exception of control male # 45376, all F0 parental animals survived to the scheduled sacrifice. There were no dose- or treatment-related clinical signs of toxicity in the parental F0 males and females.

One F1 female died in the 150 ppm group (on PND 27) and one in the 600 ppm group (on PND 31). The investigators also noted that no deaths were observed in a previous range-finding study at higher doses of 1200 and 1800 ppm; therefore, it was concluded that these deaths were not associated with administration of the test material. No treatment related clinical signs were noted at any dose level.

2. Body weight and food consumption

a. Premating

F0 mean body weight data for the premating period were presented in Tables 4 and 5 of the test report. At 600 ppm, statistically significant reductions in mean weights were noted in F0 males during weeks 4, 7, 8, 10 and 15-18 ($p \leq 0.05$). In addition, mean weekly body weights in this group were slightly lower than the control values beginning at week 1 and continuing throughout the F0 generation. Mean body weights were 5.9% lower than control at week 19. In F0 females, mean body weights in the 600 ppm group were lower than the controls beginning at week 2 and continuing throughout the pre-mating period (weeks 3-10) and also during the post-weaning period (weeks 18 and 19) $p \leq 0.01$ or $p \leq 0.05$). Mean female weights were 7.9% lower than the control group. Consistent effects upon body weight and body weight gain were not observed in F0 animals at lower dose levels.

Food consumption was not measured during the breeding period (weeks 11-13). Statistically significantly increased food intake values (g/kg/day) in all groups was noted throughout the F0 generation ($p<0.01$ and $p<0.05$) and decreased g/animal/day in the 600 ppm group females during weeks 7-8 and 18-19.

Mean body weight gains in F1 males were statistically significantly reduced at the 600 ppm level ($p<0.01$ or $p<0.05$) during the first week of the F1 post-weaning period through weeks 24-25 with a cumulative

reported reduction relative to control of 13.9% (weeks 18-25). Mean body weight gains were generally similar to controls during the rest of the study (except during week 29-30 and 35-36). Mean body weights of 600 ppm F1 males were statistically significantly lower than controls throughout the F1 generation (weeks 18-38).

In F1 females, mean body weight gains at the 600 ppm level were statistically significantly reduced from weeks 18 to 26 with a cumulative reduction of 14.1%. Mean body weights in the 600 ppm F1 females were statistically reduced beginning week 19 and continuing through both the pre-mating and the post-weaning period. By week 38, the mean body weights were reduced 11.5%.

Consistent treatment-related effects on premating body weight, body weight gain, or food consumption were not observed at either the 60 ppm or 150 ppm dose levels.

b. Gestation and lactation

Data presented in Tables 6 to 9 of the report supported the contention that mean body weights of F0 females remained statistically significantly lower at the 600 ppm level throughout gestation and lactation ($p<0.01$ or $p<0.05$) although mean weight gain during this period was not affected. At the 150 ppm level, body weights were slightly lower during gestation, but findings were not statistically significant. The only statistically significant difference was an increased ($p<0.01$) mean body weight gain in the 150 ppm group for the total lactation period, days 1-21.

Food consumption (grams/animal /day) was slightly reduced in F0 females at the 600 ppm level throughout the gestation period and reached statistical significance for days 4-7, 14-17, 17-20 and 0-20 ($p<0.01$ or $p<0.05$)

During lactation of F0 females, the only statistically significant differences from the control group was increased g/kg/day values in the 150 and 600 ppm groups during days 1-4 and 1-21 of lactation ($p<0.01$ or $p<0.05$). Increases (grams/animal/day or g/kg/day) were also noted in the 150 ppm group throughout the remainder of lactation on days 4-7, 7-11, 11-14, 14-17 and 17-21.

During gestation, F1 body weights in the 600 ppm females were statistically significantly lower ($p<0.01$) throughout the gestation period. Generally, mean body weight gains at the high dose level were similar to control values throughout gestation.

58

Mean body weights of 150 ppm F1 females were statistically significantly lower during much of the gestation period (days 0, 4, 7, and 11). These differences represented a 5 to 8% reduction in mean weights. Mean body weight gain was not affected at this dose level. No reductions in mean body weight were apparent at the low dose level.

F1 body weights were statistically significantly reduced in 600 ppm females throughout the lactation period. However, mean body weight gains at the 600 ppm level were increased during days 1-21 of the lactation period. Mean body weight and mean body weight gains were not affected at the high dose level.

Food consumption (g/animal/day) was reduced throughout the pre-mating and post-mating periods in the 600 ppm F1 males. Throughout the balance of the study, food consumption (g/kg/day) was slightly increased in the high dose group males. In F1 females, food consumption at the high dose level (g/animal/day) was often statistically significantly reduced throughout the pre-mating period. On a g/kg/day basis, food consumption was not generally affected at the high dose level. Food consumption was not generally affected at the 60 and 150 ppm level in F1 males and females. Some slight increases in consumption were noted from weeks 24 to 34 in either the 60 or 150 ppm levels, but these findings were often not observed in a dose related manner.

3. Test Substance Intake

The following table presents compound consumption data for parental animals in this study.

TABLE 2: Average Test Substance Intake (mg/kg/day)

Study Interval	Sex	Concentration in diet		
		60 ppm	150 ppm	600 ppm
F0 Generation				
Premating	Males	4	11	43
	Females	5	13	51
Gestation	Females	4	10	38
Lactation	Females	10	26	101

TABLE 2: Average Test Substance Intake (mg/kg/day)				
F1 Generation				
Premating	Males	5	13	53
	Females	6	16	61
Gestation	Females	4	10	41
Lactation	Females	10	25	103

Data extracted from Tables 16-18 and 58-60 of the test report.

4. Hormonal Evaluation (F0 Males)

F0 male estradiol, luteinizing hormone (LH), and testosterone levels are summarized in Table 3 below. There were no apparent treatment-related differences between control and high-dose data.

TABLE 3: Mean (±SD) Hormone Values				
	0 ppm	60 ppm	150 ppm	600 ppm
Estradiol	81.70±6.755	N/A	N/A	81.60±7.482
Luteinizing Hormone	0.92±0.324	N/A	N/A	1.05±0.538
Testosterone	1.44±1.360	N/A	N/A	1.56±1.288
Data were extracted from Table 18A, page 146. N = 20				

5. Postmortem Results

a. Organ weights

Treatment-related increases in mean absolute and/or relative spleen weight were observed in the F0 and F1 parental males and females (Table 4). Other significant changes noted in mean organ weight values (i.e., decreased absolute kidney and liver weights) were attributed to terminal body weight deficits, as demonstrated by a lack of significance following calculation of relative weight values.

TABLE 4a: Mean (+SD) Spleen Weight Data - F0 Parental Animals				
Parameter	0 ppm	60 ppm	150 ppm	600 ppm
	Males			
Final body wt (g)	594±54.4	591±55	596±58.7	559±58.3
Absolute wt (g)	0.86±0.101	0.88±0.130	0.84±0.124	0.90±0.131
Relative to body wt	0.146±0.0184	0.149±0.0214	0.141±0.0191	0.161±0.0214*
	Females			
Final body wt (g)	315±19.2	315±19.8	313±25.4	294±17.9**
Absolute wt (g)	0.59±0.112	0.58±0.109	0.59±0.089	0.73±0.068**
Relative to body wt	0.186±0.0308	0.184±0.0317	0.190±0.0300	0.249±0.0215**

Data extracted from Tables 27 and 28, pages 159-169.
* Statistically significant, $p<0.05$, using Dunnett's test.
** Statistically significant, $p<0.01$, using Dunnett's test.

TABLE 4b: Mean (+SD) Spleen Weight Data - F1 Parental Animals				
Parameter	0 ppm	60 ppm	150 ppm	600 ppm
	Males			
Final body wt (g)	640±57.9	626±63.9	639±68.6	558±47.8**
Absolute wt (g)	0.94±0.139	0.88±0.128	0.95±0.151	0.92±0.114
Relative to body wt	0.147±0.0171	0.140±0.0162	0.149±0.0199	0.166±0.0196**
	Females			
Final body wt (g)	340±27.7	332±35.8	322±25.2	295±30.0**
Absolute wt (g)	0.59±0.066	0.59±0.091	0.60±0.084	0.77±0.110**
Relative to body wt	0.175±0.0212	0.179±0.0214	0.186±0.0243	0.262±0.0322**

Data extracted from Tables 75 and 76, pages 312-322.
** Statistically significant, $p<0.01$, using Dunnett's test.

61

b. Pathology

1) Gross pathology - No dose- or treatment-related gross abnormalities were observed in the F0 or F1 males and females.

Control male number 45376 died during week 5 of the study. Necropsy findings included dark red contents in the stomach and ileum, dilated renal pelves and white areas in the kidneys, distended urinary bladder with calculi and ureters, calculi in the urethra and enlarged renal and iliac lymph nodes. All other animals survived to the scheduled necropsy.

2) Microscopic pathology
The cause of death for control male 45376 was determined to be kidney failure. Microscopic examination revealed changes not associated with administration of the test material (as this was a control animal).

In the spleen, increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in F0 and F1 males and females at all dose groups and correlated with the increase in absolute and/or relative spleen weights in the 600 ppm group animals (Tables 5a and 5b). The severity of the finding increased with increasing dose level. The severity in the 60 and 150 ppm groups were primarily mild, while those at the 600 ppm dose level were moderate. The HIARC, at a meeting of July 19, 2001, determined that the pigmented macrophages in the spleen observed at 60 and 150 ppm are not considered adverse effects, due to a lack of dose response relationship and since pronounced effects were observed only at the HDT of 600 ppm.

The investigators also reported minimal findings in the control group raising the possibility of some control diet contamination. In response to this finding, the investigators noted that, "the normal function of the spleen is to remove effete red blood cells from the circulation," and therefore, minimal-to-mild pigmenting of macrophages in the spleen of control animals is not unexpected. However, the investigators did not present historical control data to support their contention that this was a normal background finding. In addition, the pathologist reading the slides noted the findings as "remarkable" and apparently did not consider this finding as a normal and unremarkable. In order to resolve this issue, it would be necessary to have historical control data from other WIL studies

and/or another facility conducted during the same time frame. No other treatment related histopathology was apparent.

TABLE 5a: Histopathology Findings in the Spleen of F0 Parental Animals				
Dose level	Control	60 ppm	150 ppm	600 ppm
Males				
Total examined	29	30	30	30
Unremarkable	3	3	7	0
Macrophages, pigmented	26	27*	23	30*
Minimal	14	5	4	1
Mild	9	19	16	3
Moderate	3	3	3	26
Females				
Total Examined	30	30	30	30
Unremarkable	3	1	0	0
Macrophages, pigmented	27	29	30*	30*
Minimal	18	11	2	0
Mild	9	17	23	0
Moderate	0	1	5	30

Data extracted from Table 30 of the test report.

* Significantly different from the control group, $p<0.05$, using the Kolmogorov-Smirnov one-tailed test.

TABLE 5b: Histopathology Findings in the Spleen of F1 Parental Animals				
Dose level	Control	60 ppm	150 ppm	600 ppm
Males				
Total examined	30	30	30	30
Unremarkable	3	2	0	0
Macrophages, pigmented	27	28	30*	30*
Minimal	20	20	9	0
Mild	7	8	21	2
Moderate	0	0	0	28
Females				
Total Examined	30	30	29	29
Unremarkable	3	1	0	0
Macrophages, pigmented	27	29	29*	29*
Minimal	17	12	8	0
Mild	8	15	19	1
Moderate	2	2	2	28

Data extracted from Table 78 of the test report.

* Significantly different from the control group, $p<0.05$, using the Kolmogorov-Smirnov one-tailed test.

Microscopic ovarian follicle counts revealed no biological or statistical differences between control and 600 ppm F0 or F1 females (Table 6). There was no indication of a treatment-related depletion of primordial or growing follicles.

TABLE 6: Mean (±SD) Ovarian Follicle Counts				
Generation/Dose	F0		F1	
	0 ppm	600 ppm	0 ppm	600 ppm
Primordial follicles	58.6±35.95	59.3±29.03	67.2±28.83	57.1±27.96
Growing follicles	33.0±13.92	35.0±16.13	32.5±15.61	36.8±20.68
Corpora lutea	115.2±44.83	121.9±39.17	156.4±66.20	136.7±39.47

Data extracted from Tables 30A and 78A, pages 190 and 341.

64

3) Sperm Evaluations

Spermatogenic endpoint evaluations are summarized in Table 7. For F0 males, no adverse effects were apparent for mean testicular and epididymal sperm numbers, sperm production rate and sperm motility and morphology. Although a statistically significant decrease in mean epididymal sperm number was observed at the high dose level for F0 males as compared to the control, the WIL historical control range (compiled from 115 males in 6 studies) was 412.0 to 521.3 x 10^6 sperm/gram of tissue (report Appendix H, pages 2569-2574). Therefore, the concurrent F0 control value (641.2 x 10^6) is considerably outside the historical range, and if the 600 ppm level results are compared to the historical control range, there would be no statistical difference noted. In addition, no effects on epididymal sperm numbers were observed in the F1 generation, and the F1 control value (467.1 x 10^6) is within the range of historical control. It was therefore concluded that the statistical significance noted for F0 epididymal sperm count was not associated with administration of the test material.

In the F1 males, a statistically significant decrease in mean testicular sperm number and sperm production rate were noted in the high dose group. The investigators stated that these findings were within the ranges of values in the WIL historical control data, and could be dismissed. Examination of the historical data (from 115 males in 6 studies) revealed testicular sperm numbers with a mean of 90.0$\pm$9.94 and a range of 76.2-106.7 sperm in millions/gram of tissue. From these same historical studies, mean testicular sperm production rate was reported as 14.8$\pm$1.63 with a range of 12.5-17.5 sperm in millions/gram of tissue/day. While the mean testicular sperm count and production rate for F1 males are within the historical range, they are in fact lower than the mean historical values. Therefore, it is considered more important to rely on the concurrent control data for interpretation of effects noted in treated animals, and the reductions in testicular sperm number and sperm production rate for F1 males at 600 ppm are judged to be treatment-related. However, no effects were seen in epididymal sperm count, motility, or morphology for F1 males.

Table 7: Spermatogenic Endpoint Evaluations

	F0 Males				F1 Males			
Finding	0 ppm	60 ppm	150 ppm	600 ppm	0 ppm	60 ppm	150 ppm	600 ppm
Sperm number a								
Testis	100.9	N/A	N/A	94.8	104.6	N/A	N/A	85.1*
Epididymis	641.2	N/A	N/A	502.3**	467.1	N/A	N/A	454.3
Sperm production rate b								
Testis	16.5	N/A	N/A	15.6	17.1	N/A	N/A	14.0*
Motility (% motile)	78	75	78	73	91.6	90.3	90.9	91.2
Morphology								
Normal sperm (%)	99	N/A	N/A	98.9	98.6	N/A	N/A	99.1
Misshapen head with normal flagellum (%)	0.2	N/A	N/A	0.4	0	N/A	N/A	0

Data extracted from Tables 20-24 (F0 males) and Tables 67 -71 (F1 males).
a Number of sperm in millions/gram of tissue
b Number of sperm in millions/gram of tissue/day
* Significantly different from control group, $p<0.05$, using Dunnett's Test.
** Significantly different from control group, $p<0.01$, using Dunnett's Test.

B. REPRODUCTIVE PERFORMANCE

Selected F0 reproductive performance data are summarized in Table 8. There was no observed effect of treatment at any dose level. Fertility indices, male and female mating indices, the mean numbers of days between pairing and coitus, mean length of gestation, and the regularity and duration of estrus were not affected by treatment.

TABLE 8: F0 Generation Reproductive Performance (F1 litters)				
Observation	Dose level			
	0 ppm	60 ppm	150 ppm	600 ppm
Males				
Number paired	30	30	30	30
Females				
Number paired	30	30	30	30
Number with evidence of mating (males)	29 (100%)	28 (93.3%)	30 (100%)	30 (100%)
Number with evidence of mating (females)	30 (100%)	29 (96.7%)	30 (100%)	30(100%)
Number delivering	28	29	30	27
Mean number of live pups/dam	13.7	13.5	13.8	13.1
Mean number of stillbirths/litter	0.11	0.28	0.13	0.30
Indices (%)				
Female mating index	100	96.7	100	100
Female fertility index	93.3	96.7	100	90
Mean pre-coital interval	2.8	2.9	2.2	2.50
Mean gestation length (days)	21.9	21.9	21.9	21.90

Data extracted from Tables 2 and 19 of the test report

As shown in Table 9, reproductive performance was also unaffected by test diet administration during the F1 mating to produce F2 litters:

TABLE 9: F1 Generation Reproductive Performance (F2 litters)

Observation	Dose level			
	0 ppm	60 ppm	150 ppm	600 ppm
Males				
Number paired	30	30	30	30
Females				
Number paired	30	30	30	30
Number with evidence of mating (males)	23 (76.7%)	28 (93.3%)	27 (93.1%)	26 (89.7%)
Number with evidence of mating (females)	27 (90%)	28 (93.3%)	28 (96.6%)	27 (93.1%)
Number pregnant	25 (83.3%)	27 (90%)	26 (89.7%)	28 (96.6%)
Number delivering	24 (96%)	27 (100%)	26 (100%)	28 (100%)
Mean number of live pups/dam	13.0	13.2	12.7	13.2
Mean number of stillbirths/litter	0.25	0.22	0.00	0.39
Indices (%)				
Female mating index	90	93.3	96.6	93.1
Female fertility index	83.3	90	86.7	96.6
Mean pre-coital interval	4.1	3.0	3.6	3.00
Mean gestation length (days)	22	21.8	21.8	21.80

Data extracted from Tables 44 and 61 of the test report.

C. OFFSPRING TOXICITY

1. Viability and clinical signs

The numbers of stillborn per litter, live litter size, and gestation survival indices were not affected for F1 offspring. No statistically significant differences in F1 pup survival were noted at the 60, 150, and 600 ppm dose levels through weaning. F1 pup sex ratios were not adversely affected at any dose level. There were 6, 12, 8, and 10 pups found dead during lactation in the control, 60, 150, and 600 ppm dose groups, respectively. In addition, 3, 2, 3, and 3 pups were missing and presumed cannibalized in these same groups, respectively. No dose related effects associated

68

with clinical signs or physical condition were apparent in the F1 pups. One pup in the 60 ppm group was noted to have multiple malformations including mandibular micrognathia, absent nares, a great vessel anomaly, anopthalmia (right), microphthalmia (left), maxillary micrognathia (bilateral) and astomia. Another pup in the same litter had the same great vessel anomaly.

Relative to F2 litters, live litter size, live birth index, sex ratio, gestation survival index, viability on lactation days 1-4 before and after selection, and viability on days 7, 14, and 21 of lactation were comparable to the control values.

Pups found dead throughout lactation numbered 10, 10, 11, and 18 in the control, 60, 150, and 600 ppm dose groups, respectively. In addition, 5, 4, 3, and 10 pups were missing, respectively, in the same groups. Physical condition was similar in all dose groups, and no dose response relationships were apparent.

2. Body weight

Slight but statistically significant effects on F1 pup body weights were apparent at a number of intervals at the 600 ppm level during lactation as shown in Table 10a. Effects on body weight were not apparent on PND 1, but were evident by days 4, 7, 14, and 21. Statistically significant effects were not apparent at lower dose levels.

TABLE 10a: Mean F1 Pup Body Weights (g)				
Day of lactation	0 ppm	60 ppm	150 ppm	600 ppm
Combined sexes				
Day 1	6.8	6.7	6.8	6.6
Day 4 (postcull)	9.8	9.9	9.7	9.3
Day 7	16.3	16.3	16.0	15.3*
Day 14	32.3	32.2	32.7	30.9
Day 21	50.2	50.5	50.9	47.3*
Males				
Day 1	7.0	6.9	7.0	6.8
Day 14	33.9	32.9	33.6	31.5
Day 21	51.3	51.6	52.3	48.5
Females				
Day 1	6.6	6.6	6.6	6.4
Day 14	31.5	31.5	31.9	30.2
Day 21	48.8	49.3	49.4	45.9*

Data extracted from Tables 34 and 35, pages 195-197.
*Significantly different from controls, $p<0.05$, using Dunnett's test.

Statistically significant reductions in F2 pup weights were apparent from postnatal day 1 through the entire lactation period at the 600 ppm dose level (Table 10b). Slight non-significant reductions were also consistently noted at the 150 ppm dose level.

TABLE 10b: Mean F2 Pup Body Weights (g)				
Day of lactation	0 ppm	60 ppm	150 ppm	600 ppm
Combined sexes				
Day 1	7.0	6.8	6.7	6.5**
Day 4 (postcull)	10.2	9.9	9.8	9.2**
Day 7	16.6	16.2	15.8	15.0**
Day 14	33.4	32.8	31.6	30.6*
Day 21	53.4	51.3	49.9	47.8**
Males				
Day 1	7.2	7.0	7.0	6.7*
Day 4 (postcull)	10.4	10.3	10.1	9.5**
Day 14	33.6	33.6	32.2	31.4
Day 21	54.6	52.7	51.2	49.4**
Females				
Day 1	6.9	6.6	6.5	6.3**
Day 4 (postcull)	9.9	9.6	9.6	8.9**
Day 7	16.2	15.6	15.5	14.6**
Day 14	33.0	32.0	31.0	29.8**
Day 21	52.2	49.9	49.5	46.2**

Data extracted from Table 66 of the test report, pages 297-299.
* Significantly different from control, $p<0.05$, using Dunnett's test.
** Significantly different from control, $p<0.01$, using Dunnett's test.

3. Developmental Landmarks (F1)

A. Balanopreputial Separation

There was a statistically significant dose- and treatment-related increase in the mean age at which balanopreputial separation occurred at the 600 ppm dose level (Table 11). The age at which all male pups had achieved this maturational endpoint was delayed by 8 days at the 600 ppm dose compared to controls. Both the 60 ppm and the 150 ppm level also showed some dose related delay, but these were not reported

71

as statistically significant. Corollary body weight data (i.e., body weights on the day of achievement) were apparently not recorded; therefore no conclusion can be drawn regarding the influence of body weight on the delayed sexual maturation of these F1 males.

TABLE 11: Balanopreputial Separation in F1 Males

	0 ppm	60 ppm	150 ppm	600 ppm
Day of 100% achievement	45	48	48	53
Mean day of achievement (±SD)	42.9±1.35	43.3±2.05	43.9±1.99	45.9±2.38**

Data extracted from Tables 41 and 41A, pages 217-219.
** Significantly different from control, $p<0.01$, using Dunnett's test.

B. Vaginal opening

Vaginal perforation was achieved in 100% of the F1 females at postnatal days 36, 36, 40, and 43 for the control, 60 ppm, 150 ppm, and 600 ppm groups, respectively (report Table 42). Although this represents a 7 day delay in this endpoint at the HDT as compared to controls, and appears to be treatment-related at that dose level, the study report did not include an analysis of mean day of achievement, and the study author did not consider this difference to be treatment-related. As with the F1 males, lack of corrollary body weight data confounds the interpretation of this finding.

4. Necropsy findings of pups

No dose related findings which could be attributed to the test material were identified in the F1 pups based on postmortem examination of surplus and selected pups. Dilated renal pelves were observed in 2 and 5 pups respectively from the control and 60 ppm dose levels of those pups not selected for mating at 21 days. Of those selected at 21 days, dilated renal pelves were noted in one male in the 600 pm level and in 2, 3, 2 and 1 female pups in the control, 60, 150, 600 ppm groups, respectively. Other findings included one male control weanling with enlarged iliac lymph nodes, reddened cervical lymph nodes in a control female pup and one female in the 60 ppm group with distended ureter.

No treatment related gross findings were noted at any dose level in the F2 pups. Background incidences of dilated renal pelves were observed in 8, 0, 4, and 1 pups of the control, 60, 150 and 600 ppm dose levels, respectively. One F1 female in each of the 150 and 600 ppm dose groups was found dead on PND 27 and PND 31, respectively.

5. Weanling Organ Weights

Mean absolute and relative organ weights in F1 males and female weanlings were not affected by administration of the test material at any dose level. Although some statistically significant relative weights were noted (Table 12), no mean absolute weights or organ-to-brain-weight ratios were affected. Therefore, a clear relationship with treatment was not apparent for any of these relative organ weight findings.

Table 12: F1 Weanling Mean Organ Weights (g)

Group	0 ppm	60 ppm	150 ppm	600 ppm
Male terminal wt	50	51	52	49
Female terminal wt	49	50	50	46
Female Mean Brain Wt	1.4480	1.4573	1.4544	1.4408
Female Relative Brain Wt	3.003	2.957	2.912	3.162
Male Mean Brain Wt	1.4963	1.4736	1.4973	1.5001
Relative Male Brain Wt	3.016	2.915	2.878	3.074
Male Mean Testis wt	0.2303	0.2403	0.2406	0.2366
Male Relative Testis Wt	0.455	0.467	0.459	0.482*
Female Mean Liver Wt	1.99	2.0900	2.1266	2.0034
Female Relative Liver Wt	4.087	4.192	4.240	4.372*
Female Mean Adrenal Wt	0.0165	0.0182	0.0191	0.0188
Female Relative Adrenal Wt	0.034	0.037	0.038	0.041**

Data extracted from Tables 38, 39 and 39A, pages 198-204.
* Significantly different from control, $p<0.05$, using Dunnett's test.
** Significantly different from control, $p<0.01$, using Dunnett's test.

Mean spleen weights (absolute, relative to body weight and brain weight) were increased 30 to 50% ($p<0.01$) in 600 ppm female F2 pups (see Table 13). In addition, statistically significant decreases in mean liver, kidney and/or pituitary gland weights (absolute and/or relative to brain weight) were noted at the high dose level. These organ weight changes are considered to be treatment-related. Other differences in relative organ weights were noted at the high dose level in males and females, but these findings were not noted in absolute organ weights and were considered related to decreases in body weights.

Table 13: F2 Weanling Mean Organ Weights (g) (Absolute [relative to brain] g/100g)

Group	0 ppm	60 ppm	150 ppm	600 ppm
Female, terminal body wt	340	332	322	295**
Female, brain	2.02(0.596)	1.98 (0.602)	2.00 (0.624)	2.02 (0.690**)
Female, liver	13.34 (661.876)	13.39 (678.244)	13.01(650.654)	12.14* (599.763*)
Female, kidney	2.61 (129.356)	2.59 (130.876)	2.52 (125.857)	2.36**(116.58**)
Female, spleen mean wt	0.59 (29.501)	0.59 (29.943)	0.60 (29.993)	0.77** (38.232**)
Female, adrenal glands	0.0748(3.716)	0.0768 (3.883)	0.0778 (3.894)	0.0752 (3.720)
Female pituitary	0.0187 (0.928)	0.0182(0.920)	0.0188 (0.943)	0.0167 (0.824*)
Ovaries (relative to terminal body wt only)	0.045	0.047	0.048	0.054**
Male, Liver	24.86 (1124.253)	(23.80 1089.931)	24.62 (1113.876)	22.08 ** (1018.458*)
Male, kidneys	4.36	4.39	4.51	4.05*
Male, spleen	0.94	0.88	0.95	0.92

Data extracted from Tables 146, 147 and 147A, pages 2289-2360.
* Significantly different from control, $p<0.05$, using Dunnett's test.
** Significantly different from control, $p<0.01$, using Dunnett's test.

6. Histopathologic examination of pups

Only selected F1 pups (1/sex/litter) were examined from the 600 ppm dose and controls. No treatment related findings were apparent from data presented in the study report (Tables 40 and Table 111). However, this was a very limited screen of organs (i.e., adrenal glands, kidneys, liver, spleen, thymus, ovaries, and testes) in a very limited sample size. No F2 pups received a histopathological examination.

III. DISCUSSION

Male and female Crl:CD®(SD)BR rats were fed 0, 50, 150, and 600 ppm propanil in the diet for two generations. One litter was produced in each generation. The following findings were noted:

1. PARENTAL TOXICITY

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material.

Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups and correlated with the increase in absolute and relative spleen weights in the 600 ppm group animals. The investigators claimed that the severity in the 60 and 150 ppm groups was typically mild, while it was reported as moderate at the high dose level. The HIARC, at a meeting of July 19, 2001, determined that the pigmented macrophages in the spleen observed at 60 and 150 ppm are not considered adverse effects, due to a lack of dose response relationship and since pronounced effects were observed only at the HDT of 600 ppm.

The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

The investigators also reported minimal findings of pigmented macrophages in the spleen in the control group raising the possibility of some control diet contamination. In response to this finding, the investigators noted that, "the normal function of the spleen is to remove effete red blood cells from the circulation," concluding that therefore, minimal-to-mild pigmenting of macrophages in the spleen of control animals is not unexpected. However, the investigators did not present historical control data to support their contention that this was a normal background finding. In addition, the pathologist reading the slides noted the findings as "remarkable" and apparently did not consider this finding as a normal and unremarkable. It is noted that in a chronic/carcinogenicity study conducted in Sprague-Dawley rats (MRID 43303201) with propanil, evidence of treatment-related hemosiderosis was observed in splenic tissue of both sexes at interim and terminal sacrifice (52 and 104 weeks of study, respectively), as summarized in the following table.

Incidence of Hemosiderosis of the Spleen in a Combined Chronic Toxicity/ Carcinogenicity Study in Rats																
	Treatment level															
ppm	0		200		600		1800		0		200		600		1800	
mg/kg/day	0		9.0		27.7		88		0		11.5		38.3		145	
	Males - 52 weeks								Females - 52 weeks							
# examined	19		19		20		20		20		19		20		20	
Trace	8		11		8		7		4		2		4		0	
Minimal	6		4		9		8		13		15		14		12	
Moderate	0		0		0		3		3		2		2		8	
	Males - 104 weeks								Females - 104 weeks							
	DoS	TK	DoS	TK	DoS	TK	DoS	TK	DoS	TK	DoS	TK	DoS	TK	DoS	TK
# examined	35	15	33	17	27	23	19	31	31	19	32	18	30	20	17	33
Trace	2	2	1	6	0	6	1	3	2	4	1	0	2	1	3	7
Minimal	2	2	6	5	9	7	5	13	16	11	15	1	13	3	5	17
Moderate	2	0	4	1	7	5	4	11	9	3	12	2	12	1	5	9
Marked	1	0	0	0	0	0	3	2	2	1	0	0	1	1	0	0

From MRID 43303201; DoS = Died on Study, TK = Terminal Kill

The chronic/carcinogenicity study and the two-generation reproduction study were conducted at two different laboratories (i.e., Huntingdon Research Center in the UK vs. WIL Research Laboratories, respectively). The source of the rats used in both studies was Charles River Laboratories in Portage Michigan, although the studies were conducted years apart (the chronic study was reported in July, 1994, suggesting in-life dates circa 1991, while the reproduction study animals were received from the breeder in November, 1995). It is important to note that, in spite of the differences in study disposition and conduct described above, the presence of hemosiderin in splenic tissue was observed in the control groups of both studies, generally at "trace" or "minimal" severity, but moving towards increased gradings as the animals aged. This information leads the Agency reviewer to view the presence of hemosiderosis in control animals with somewhat less concern than would be assumed if contamination of control feed with test substance was indicated. It is also noted that concentration analyses data (study report pages 2384-2396) demonstrate no detection of test substance in control formulations for this study. Nevertheless, in order to resolve this issue with greater certainty, it would be necessary to have adequate historical control data from other WIL studies and/or another studies conducted at another facility during the same time frame which support the investigator's statements.

2. REPRODUCTIVE TOXICITY

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male.

There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. While group mean body weight data from early post-weaning F1 males and females indicates significant reductions at 600 ppm as compared to control, suggesting that the delays in sexual maturation may be related to affected growth, these data do not precisely corollate with each other (since pups are at different ages when they are placed into the second generation).

The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

3. OFFSPRING TOXICITY

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were delayed in F1 offspring. F2 male and female weanling spleen weights were significantly increased, and liver, kidney, and pituitary weights were significantly decreased at 600 ppm. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups.

The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

4. STUDY DEFICIENCIES - The following deficiencies were not considered to compromise the evaluation of the study.

   Historical data were not presented to support the registrant position that control incidences of pigmented macrophages in the spleen are within historical control limits.

   Vaginal perforation data were not statistically analyzed.

5. CLASSIFICATION

   This study is classified as **Acceptable/guideline** and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

Root Data Evaluation Summary

Draft

TXR: 0050209 **Division:** HED **Reviewers:** Larry Chitlik **Signoff Date:** 11/09/2001

MRID	PC Code	Chemical Name
44604301	028201	Propanil; N-(3,4-

Guideline Indicator: Yes
Study Status: Acceptable/Guideline
Source of Review: US
Guideline: NonGuideline } 83-4 2 gen repro.
Primary Guideline: NonGuideline }
Toxicity Category:

Study Type: Reproduction, Oral, 2 Generations. Dietary

Executive Summary:

EXECUTIVE SUMMARY: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial

separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

This study is classified as Acceptable/guideline and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

OneLiner Summary:

EXECUTIVE SUMMARY: Propanil (98.4% a.i; Batch No. #02, WIL Log No. 2825A) was administered to groups of 30 male and 30 female Crl:CD® (SD)BR rats in the diet at concentrations of 0, 60, 150, and 600 ppm for two generations (MRID 44604301). Premating doses for the F0 males were estimated to be 0, 4, 11, and 43 mg/kg/day, respectively and for the F0 females were 0, 5, 13, and 51 mg/kg/day, respectively. Premating doses for the F1 males were estimated to be 0, 5, 13, and 53 mg/kg/day, respectively, and for the F1 females were 0, 6, 16, and 61 mg/kg/day, respectively. Animals were given test or control diet for at least 70 days then mated within the same dose group. All animals were exposed to test material in the diet and during lactation until sacrifice.

Mean body weight, body weight gain, and food consumption (g/animal/day) were reduced in 600 ppm parental animals during the pre-mating, gestation and/or lactation periods. Necropsies did not reveal any findings associated with treatment with the test material. Mean spleen weights at the high dose level were statistically significantly increased in both the F0 and F1 animals. Increases in the severity of pigmented macrophages (described as brown, granular, intracytoplasmic pigment, morphologically consistent with hemosiderin) were observed in spleens of F0 and F1 males and females in all dose groups; at the 600 ppm dose level, these findings were moderate in severity and were correlated with the increase in absolute and relative spleen weights. The parental/systemic LOAEL is 600 ppm (43 mg/kg/day in males and 51 mg/kg/day in females), based on decreased body weight, body weight gain, and food consumption, increased absolute and/or relative spleen weights, and increased incidence and severity of pigmented macrophages in the spleen. The parental/systemic NOAEL is 150 ppm (11 mg/kg/day in males and 13 mg/kg/day in females).

Reproductive performance of the F0 and F1 parental animals was not affected by treatment with propanil. No statistically significant treatment related effects on ovarian follicle counts were noted at the 600 ppm level in either generation. Mean estradiol, luteinizing hormone and testosterone levels were unaffected by treatment at any dose level in F1 males. However, sperm evaluations, conducted at the time of necropsy revealed significant decreases in mean testicular sperm count and production rate for F1 males at 600 ppm. Postmortem studies (gross pathology, organ weights, and histopathological evaluation) did not identify any treatment-related findings in the male reproductive organs, although a malformed left testis was noted in one F1 male. There was a significant increase in mean age to balanopreputial separation for F1 males at the 600 ppm dose level; the day of 100% achievement of balanopreputial separation and vaginal perforation was also delayed at 600 ppm. The relationship of these findings to general maturational status was compromised by the lack of corollary body weight data from the day of endpoint achievement. The LOAEL for reproductive toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females), based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and on decreased mean testicular sperm count and production rate in F1 adult males. The reproductive toxicity NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

Mean pup weights were lower in the 600 ppm dose group throughout most of the F1 and F2 lactation periods. Sex ratios, live litter size, gestation and postnatal survival indices were not affected by treatment. Balanopreputial separation and vaginal opening were significantly delayed in F1 offspring. In F2 weanlings at 600 ppm, female weanling spleen weights were significantly increased, female pituitary weights were significantly decreased, and liver and kidney weights were significantly decreased in both sexes. No gross or microscopic findings were noted

in F1 or F2 pups, but only a limited histopathological examination of 1 pup/sex/litter was conducted on high dose and control F1 weanlings and no histopathology examination was conducted on any F2 pups. The LOAEL for offspring toxicity is 600 ppm (43 mg/kg/day for males and 51 mg/kg/day for females) based on reduced F1 and F2 pup weights, delayed sexual maturation in F1 males and females, and organ weight alterations in F2 weanlings (increased absolute and relative spleen weights and decreased relative pituitary weights in females, decreased absolute and/or relative liver and kidney weights in both sexes). The offspring NOAEL is 150 ppm (11 mg/kg/day for males and 13 mg/kg/day for females).

This study is classified as Acceptable/guideline and satisfies the guideline for a reproduction and fertility effects study (OPPTS 870.3800) in rats.

File Attachment(s):

44604301.DER.w

Updated By: Susan Makris **on:** 11/20/2001 05:29 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

Study Citation Summary

Draft

TXR Number: 0050209

MRID	PC Code	Chemical Name
44604301	~~028201~~	~~Propyzamide~~

PC Code	CAS Number
028201	709-98-8

Reregistration Case:
Chemical Category:
Chemical Classification:
Test Material: Technical
Batch/Lot No: #02, WIL Log No. 2825A
Study Ingredient: 98.4% a.i.
Formulation Type:
Registration Number:
Submitter: Propanil Task Force
Citation: ~~No Citation Listed for 44604301~~ The citation is on the DER.
Journal: No
Guideline: ~~NonGuideline~~ 83-4
Project Number: 141013
Testing Lab: WIL Laboratories
Study Completion Date: 07/01/98
Data Owner's Name: Propanil Task Force
Species/Strain: Rat : CrL:CD(SD)BR Sprague-Dawley

Updated By: Susan Makris **on:** 11/20/2001 05:33 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM

Study Citation Summary

Draft

TXR Number: 0050209

MRID	PC Code	Chemical Name
44604301		

PC Code **CAS Number**

Reregistration Case:
Chemical Category:
Chemical Classification:
Test Material: Technical
Batch/Lot No: #02, WIL Log No. 2825A
Study Ingredient: 98.4% a.i.
Formulation Type:
Registration Number:
Submitter:
Citation: No Citation Listed for 44604301
Journal: No
Guideline: NonGuideline
Project Number:
Testing Lab:
Study Completion Date: 07/01/98
Data Owner's Name:
Species/Strain: Rat : CrL:CD(SD)BR Sprague-Dawley

BR=(the original breeding lab which I can't remember)
SD= Sprague-Dawley
CD = Cesarean derived
Crl = Charles River Laboratories

I noticed that the species/strain selection has a huge number of repetitive categories for the typical Charles River Sprague-Dawley rat. They need to be consolidated.

Updated By: Susan Makris **on:** 11/20/2001 05:33 PM
Created By: Marion Copley **on:** 10/19/2001 08:42 AM