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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

November 9, 2001
TXR 0050210

MEMORANDUM

SUBJECT: D277274: Propanil (028201)
Toxicology Chapter for the reregistration eligibility decision (RED)

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: Generate the toxicology disciplinary chapter for the reregistration eligibility decision (RED) document for propanil.

CONCLUSIONS: The Toxicology Chapter for propanil (028201) is attached.

PROPANIL

PC Code: 028201

Toxicology Disciplinary Chapter for the Reregistration Eligibility Decision Document

TXR 0050210

Date completed:
October 30, 2001

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Arlington, VA 22202

Prepared by:

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Susan L Makris Date 10/30/01

Reviewed by:

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Alberto Protzel Date 10/31/01

EPA Reviewer: Susan L. Makris, M.S. _____, Date 10/30/01
Toxicology Branch (7509C)
EPA Secondary Reviewer: Alberto Protzel, Ph.D. _____, Date 10/31/01
Toxicology Branch (7509C)

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1.0 HAZARD CHARACTERIZATION

The toxicological database for propanil is considered minimally adequate for hazard characterization. The studies submitted to support guideline requirements are supplemented by relevant open literature publications.

The data base for acute toxicity for the purpose of product labeling and preliminary toxicity assessment is considered complete. No additional screening acute toxicity studies are required at this time. As evaluated in the standard acute screening study battery, propanil has low acute toxicity, with toxicity categories of III (oral) and IV (dermal, inhalation, and primary skin irritation); no dermal sensitization was observed, however, primary eye irritation was observed in rabbits (toxicity category II).

The acute oral systemic toxicity of propanil has not been adequately characterized. The HIARC has recommended that a study be conducted to examine the onset of methemoglobinemia following oral administration of propanil in the rat; this study would include blood measures on day 1 after initiation of treatment and could provide information for use in acute risk assessment scenarios.

For non-acute exposures, administration of propanil to different species for varying lengths of time leads characteristically to the development of methemoglobinemia. The resulting methemoglobinemia causes the development of hemolytic anemia, which is characterized by decreases in some or all of the following parameters: hemoglobin, RBC count and packed cell volume. Hematological and histopathological evaluations also revealed Heinz bodies in RBCs and hemosiderin deposits in the spleen and kidneys.

Subchronic dietary administration of propanil in rodents and dogs resulted in findings consistent with methemoglobinemia and hemolytic anemia. In rats, this included decreased hemoglobin and increased spleen weight at doses of 1000 mg/kg/day and higher. In the mouse, cyanosis of the ears and skin, decreased erythrocyte counts, increased liver and spleen weights, and histopathological lesions of the liver and spleen were observed. In the liver, these histopathological findings included incidences of hepatic pleomorphism, multifocal necrosis, nuclear variation, and pigmented Kupffer cells at higher doses, and treatment-related incidences of hepatocytic pleomorphism and/or hepatocytic multifocal necrosis at the LOAEL of 30 mg/kg/day. In the spleen, there was an increase in the severity of the grade of lesions (hemosiderin and extramedullary hematopoiesis) observed at higher doses. Following 21 days of consecutive dermal applications in New Zealand white rabbits, decreased body weight gain and food consumption were observed at 500 mg/kg/day; however, there were no observed treatment-related alterations in hematological or organ parameters that were consistent with methemoglobinemia. The HIARC recommended that several studies be conducted to further characterize the toxicity of propanil following short or intermediate-term exposures. These include a 28-day inhalation study and a 30-day oral study in rats that includes methemoglobin measurements at days 1, 5, 7, 14, 21, and 30. Additionally, due to evidence in the published

literature suggesting that propanil is a potential immunotoxic chemical, the HIARC recommended that the Registrant conduct a guideline immunotoxicity study or submit a literature search to better characterize its immunotoxic potential.

Other than slightly decreased fetal body weights (with or without accompanying delays in skeletal ossification), there was no apparent effect of *in utero* propanil exposure on the morphological development of the fetuses in the prenatal developmental toxicity studies in rats and rabbits. In the two-generation reproduction study in rats, delayed vaginal perforation and balanopreputial separation was observed in F1 adolescents, and decreased mean testicular sperm count and production rate was noted in F1 adult males. These findings are highly suggestive of neuroendocrine disruption, although hormonal measurements in the two-generation reproduction study did not identify specific alterations in testosterone, luteinizing hormone (LH), or estradiol levels in F0 males at study termination. Nevertheless, the delays in sexual development are supported by a number of other considerations, including: the presence of treatment-related testicular interstitial cell tumors in the rat chronic/oncogenicity study with propanil (often related to neuroendocrine disruptions), and the similarities between the reproductive toxicity profile of propanil to linuron and flutamide, two structurally-related chemicals with a demonstrated neuroendocrine mode of action affecting the hypothalamic-pituitary-testicular (HPT) axis. The HIARC judged that the evidence consistent with neuroendocrine disruption in the 2-generation reproduction study was indicative of qualitative susceptibility of the offspring.

In the most recent, acceptable chronic toxicity assessments with propanil, long-term dietary exposure resulted in evidence of treatment-related methemoglobinemia in rats and dogs; NOAELs were not identified in either species. In the chronic toxicity/carcinogenicity study in Sprague-Dawley rats, this evidence consisted of increased methemoglobin levels, decreased packed cell volume and red blood cells, and enlarged spleens at the lowest dose tested; additional hematological findings, with increased severity, were observed at higher dose levels. Histopathological findings (brown pigment in hepatic Kupffer cells and in the proximal convoluted tubules of the kidney) were also presumed to be related to the methemoglobinemia. Evidence of hepatic toxicity included centrilobular liver cell enlargement and hepatic granulomatous inflammation. Kidney toxicity was demonstrated by increases in blood urea nitrogen (BUN). Unrelated to the methemoglobinemia in this study, toxicity to the reproductive system included hypoplastic prostate and seminal vesicle, epididymal aspermia, and interstitial cell adenomas of the testes in males, and endometrial polyps, mammary galactocoeles, dilated uteri, and cystic ovaries in females. These findings are consistent with the neuroendocrine etiology described above. Other observed toxicity to the nervous system consisted of axonal degeneration of the sciatic nerve at the highest dose tested. In beagle dogs, macrocytic, regenerative methemoglobinemia was observed as decreased levels of RBCs, hemoglobin, hematocrit, and MCHC and increased levels of MCV, methemoglobin, and reticulocytes. Hemosiderin deposition was observed in the bone marrow, kidney, and liver. Kidney toxicity was evidenced by increases in BUN, creatinine, and potassium, and hepatic toxicity was evidenced by increased absolute and relative liver weights.

A developmental neurotoxicity study is required for propanil, based upon evidence of neurotoxicity in the data base, consisting of neuropathological lesions (axonal degeneration of the sciatic nerve) in the rat chronic/carcinogenicity study and evidence consistent with neuroendocrine disruption in the two-generation reproduction study (delayed sexual maturation) rat chronic/carcinogenicity study (Leydig cell tumors).

In a battery of acceptable mutagenicity assays, propanil was not found to be genotoxic. Propanil was not mutagenic in bacteria or in cultured mammalian cells. There was also no indication of a clastogenic effect up to toxic doses *in vivo*. Propanil did, however, cause DNA damage in a DNA repair-deficient strain of *B. subtilis* but not in the pol A^- strain of *E. coli.* The relevance, therefore, of this positive result in *B. subtilis* is unclear, since DNA damage was not manifested as point mutations in microbial systems or mammalian cells, mitotic recombinations in yeast, DNA damage in mammalian cells or chromosomal aberrations in whole animals.

In an evaluation of the carcinogenic potential of propanil, an increased incidence of testicular interstitial (Leydig) cell adenomas was observed in Sprague-Dawley rats following 2 years of exposure and was attributed to treatment. Hepatocellular adenomas in female Sprague-Dawley rats in the same study were attributed to excessive toxicity, and were not considered to be relevant to the evaluation of the carcinogenic potential of propanil. Additionally, evidence of a treatment-related increase in commonly-occurring malignant lymphomas in female CD-1 mice following 18 months of propanil exposure was considered to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil. Based upon these findings and the lack of genotoxicity in a battery of assays, propanil was classified into the category of "Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential."

In a metabolism study in rats, the majority of propanil and its metabolites were excreted in the urine within 24 hours, with only 2-13% excreted in the feces and minimal retention in the carcass or internal organs. Of the total of 13 metabolites identified, three major metabolites accounted for 17-44% of the radioactivity and resulted from hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3, 4-dichloroaniline, and its N-hydroxy and 6-hydroxy derivatives which have been associated with methemoglobin formation in open literature studies.

Propanil also has been reported to be contaminated with the cytochrome P450 enzyme inducers 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), which are structural analogs of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and produce typical dioxin-like effects, although with 2 to 6 times less potency than dioxin.

2.0 REQUIREMENTS

The requirements (CFR 158.340) for Food Use for Propanil are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes 1	yes 2
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	90-Day Inhalation	yes 3	no
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	no	---
870.6200b	90 Day Neuro. Screening Battery (rat)	no	---
870.6300	Developmental Neurotoxicity	yes 4	no
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	---
870.7800	Immunotoxicity	yes 5	no

1 To further characterize the acute and short-term toxicity of propanil, the Agency requires a 30-day oral study in rats, with methemoglobin measurements at days 1, 5, 7, 14, 21, and 30.

2 This data requirement is satisfied by a chronic toxicity study in dogs.

3 A 90-day inhalation study is not a guideline requirement for propanil. However, a 28-day inhalation study has been required by the Agency due to use patterns that indicate a high potential for inhalation exposure.

4 The developmental neurotoxicity study is required by the Agency, based upon a weight-of-evidence evaluation of the toxicology data base.

5 Due to information in the published literature that indicates that propanil is a potential immunotoxic chemical, the Agency requires a guideline immunototoxicity study, or a literature study to better characterize the immunotoxic potential of propanil.

3.0 DATA GAP(S)

The HIARC determined that a 28-day inhalation study is required to address the concern for inhalation exposure potential based on the use pattern. The Registrant can follow the 90-day inhalation study protocol but cease exposure at 28 days. The HIARC also determined that a developmental neurotoxicity study is required. In addition, the HIARC recommended a 30-day oral study in rats with methemoglobin measurements at days 1, 5, 7, 14, 21, and 30 for potential hazard identification. There is evidence in the published literature suggesting that propanil is a potential immunotoxic compound. Therefore, the HIARC recommended that the Registrant conduct a guideline immunotoxicity study (OPPTS 870.7800) or submit a literature search to better characterize its immunotoxic potential.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The data base for acute toxicity for the purpose of product labeling is considered complete. No additional screening acute toxicity studies are required at this time.

As evaluated in the standard acute screening study battery, propanil has low acute toxicity, with toxicity categories of III (oral) and IV (dermal, inhalation, and primary skin irritation); no dermal sensitization was observed, however, primary eye irritation was observed in rabbits (toxicity category II). The acute toxicity screening data on Propanil Technical are summarized below in Table 2.

The acute oral systemic toxicity of propanil has not been adequately characterized. The HIARC has recommended that a 30-day oral study be conducted to examine the onset and course of methemoglobinemia following oral administration of propanil in the rat (see Section 3.0 Data Gaps). This study would include blood measures on day 1 after initiation of treatment and could provide information for use in acute risk assessment scenarios.

Table 2. Acute Toxicity Data on Propanil

Guideline No./ Study Type	MRID No. HED Doc. No.	Results	Toxicity Category
870.1100 Acute oral toxicity	41360801 008722	LD_{50} = 1080 mg/kg (M&F)	III
870.1200 Acute dermal toxicity	41360901 008722	LD_{50} >2000 mg/kg	III
870.1300 Acute inhalation toxicity	41415501 008423	LC_{50} >6.1 mg/L	IV
870.2400 Acute eye irritation	41360501 008430	Iritis, conjunctivitis present in all rabbits, cleared by day 14; corneal opacity cleared by 4 days	II
870.2500 Acute dermal irritation	41360601 008430	Slightly irritating P.I. = 0.2/4.0	IV
870.2600 Skin sensitization	41360401 008430	Nonsensitizer	N/A

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The data base for subchronic toxicity is considered complete with respect to the guideline requirements for a food-use pesticide. However, the HIARC has recommended the submission of a 28-day inhalation study (i.e., using the 90-day inhalation study protocol but ceasing exposure at 28 days) to address the concern for inhalation exposure potential based on the use pattern. In addition, the HIARC recommended a 30-day oral study in rats with methemoglobin measurements at days 1, 5, 7, 14, 21, and 30 for potential hazard identification.

In rodents, subchronic dietary administration of propanil resulted in findings consistent with methemoglobinemia and hemolytic anemia. This included decreased hemoglobin and increased spleen weight at doses of 1000 mg/kg/day and higher in the rat study. In the mouse, cyanosis of the ears and skin, decreased erythrocyte counts, increased liver and spleen weights, and histopathological lesions of the liver and spleen were observed. In the liver, these histopathological findings included incidences of hepatic pleomorphism, multifocal necrosis, nuclear variation, and pigmented Kupffer cells at higher doses, and treatment-related incidences of hepatocytic pleomorphism and/or hepatocytic multifocal necrosis at the LOAEL of 30 mg/kg/day. In the spleen, there was an increase in the severity of the grade of lesions

(hemosiderin and extramedullary hematopoiesis) observed at higher doses. Following 21 days of consecutive dermal applications in New Zealand white rabbits, decreased body weight gain and food consumption were observed at 500 mg/kg/day; however, there were no observed treatment-related alterations in hematological or organ parameters that were consistent with methemoglobinemia

870.3100 90-Day Oral Toxicity - Rat

In a subchronic toxicity study (MRID 00015459, 00046259), Wistar rats (10/sex/dose) were administered concentrations of 0, 0.01, 0.033, 0.10, 0.33, 1.0, and 5.0 percent of propanil (97%) in the diet for three months. (These dose levels are equivalent to 0, 100, 330, 1000, 10000, or 50000 ppm in the diet, or as calculated by standard formula, approximately equivalent to 0, 10, 33, 100, 1000, or 5000 mg/kg/day.) Body weights were recorded weekly; food consumption was measured over a 3-day period during week 13 of study. Terminal studies (at week 13) included hematology, urinalysis, gross necropsy, selected organ weights, and histopathology.

All rats at the 5.0 percent dietary level died. Decreased body weight and food consumption were observed at the 0.33 and 1.0 percent levels in females and at the 1.0 percent level in males. At all dietary levels in females and at the 0.10 and 1.0 percent levels in males, there were increases in neutrophils. Hemoglobin was decreased at 0.33 and 1.0 percent in females and at 0.10, 0.33, and 1.0 percent in males. Increased relative spleen weight was observed in females at 0.10, 0.33, and 1.0 percent levels and in males at 0.33 and 1.0 percent dietary level. There were no treatment-related histopathological findings. The NOAEL is 0.033 percent (33 mg/kg/day). The LOAEL is 0.10 percent (100 mg/kg/day) based upon increased relative spleen weight in females and decreased hemoglobin in males.

This study was classified **Core-Supplementary**, since individual data were not provided, and it does not meet the guideline requirement for a subchronic toxicity study **(870.3100)** in rodents.

870.3100 90-Day Oral Toxicity - Mouse

Propanil (98.0%) was administered to COBS-CD1 mice (10/sex/dose) at dietary levels of 0, 25, 200, 1600, or 12800 ppm (0, 6.6, 49, 442, or 5325 mg/kg/day for males and 0, 9.6, 78, 566, or 6467 mg/kg/day for females) for 13 weeks (MRID 40402901). Clinical observations, body weights, and food consumption were measured weekly. Clinical chemistry, hematology, and urinalysis data were recorded during week 13 of study. Following termination, all mice were necropsied, selected organs were weighed (brains, gonads, hearts, livers, kidneys, and spleens), liver fractions were assayed for p-nitroanisole-O-demethylase (MFO) activity and histopathological examination of tissues was performed.

There were no treatment-related mortalities during the study. At 12,800 ppm, findings in both sexes included cyanosis (bluish-gray discoloration of the ears and skin; also observed in males at 1600 ppm), significantly increased food consumption, and significantly reduced body weight.

There were no effects on clinical chemistry or urinalysis parameters; however, erythrocyte counts were significantly decreased in both sexes at 12,800 ppm. MFO activity was significantly increased in both sexes at 1600 and 12,800 ppm. Gross necropsy revealed darkened blood, spleen, liver, heart, lungs, and kidneys in both sexes at 1600 and 12,800 ppm; absolute and relative spleen weights were significantly increased for males and females at both doses. At 12,800 ppm, relative liver weight was significantly increased for males; for females, significant organ weight changes included increased absolute and relative liver weight, increased relative heart and brain weight, and decreased relative ovarian weight. Treatment-related histopathological lesions of the liver and spleen were noted in males and females at 1600 and 12,800 ppm. In the liver, these findings included incidences of hepatic pleomorphism, multifocal necrosis, nuclear variation, and pigmented Kupffer cells; in the spleen, there was an increase in the severity of the grade of lesions (hemosiderin and extramedullary hematopoiesis) observed. Additionally, at 200 ppm, there were treatment-related incidences of hepatocytic pleomorphism (1/10 in females and 3/10 in males) and of hepatocytic multifocal necrosis (1/10 in males). The NOAEL is 25 ppm (6.6 mg/kg/day); the LOAEL is 200 ppm (49 mg/kg/day), based upon histopathological findings in the liver (hepatocytic pleomorphism and hepatocytic multifocal necrosis.)

The study was classified **Core-Minimum** and satisfied the guideline requirement for a subchronic toxicity study **(870.3100)** in rodents.

870.3150 90-Day Oral Toxicity - Dog

An acceptable 90-day oral toxicity study in the dog was not submitted. However, this data requirement is satisfied by an acceptable chronic toxicity study in the dog with propanil (see Section 4.5 below).

870.3200 21-Day Dermal Toxicity – Rabbit

In a 21-day dermal toxicity study (MRID 41777001, 41961800), New Zealand white rabbits (5/sex/dose) were treated dermally with propanil at 0, 250, 500, or 1000 mg/kg/day five days/week for three weeks. The body weight gains for control, low-, mid- and high-dose females were 44, 27, 8 and -2 g. The decrease in body weight gain was associated with decreased food consumption. Body weight gains and food consumption in treated males were comparable to control values. At 1000 mg/kg/day, decreased total bilirubin was observed in both sexes at terminal sacrifice. The NOAEL was established at 250 mg/kg/day, based on decreased body weight gain (day 20) and decreased food consumption (days 14 to 20) at 500 mg/kg/day (LOAEL) in females.

This study is classified **Acceptable/guideline** and satisfies the guideline requirement for a 21-day dermal study **(870.3200)** in the rabbit.

870.3465 90-Day Inhalation – Rat

An acceptable 90-day inhalation study in the rat was not submitted. The Agency has recommended that a 28-day inhalation study be conducted with propanil. This remains a data gap.

4.3 Prenatal Developmental Toxicity

Adequacy of data base for Prenatal Developmental Toxicity: The data base for prenatal developmental toxicity is considered complete. No additional studies are required at this time. Other than slightly decreased fetal body weights (with or without accompanying delays in skeletal ossification) there was no apparent effect of *in utero* propanil exposure on the morphological development of the fetuses in the prenatal developmental toxicity studies in rats and rabbits.

870.3700a Prenatal Developmental Toxicity Study - Rat

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 prenatal developmental toxicity study in the rodent **(870.3700a).**

870.3700b Prenatal Developmental Toxicity Study - Rabbit

In an oral developmental toxicity study (MRID 00058589), 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 870.3700b).**

4.4 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The data base for reproductive toxicity is considered complete. No additional studies are required at this time. In the two-generation reproduction study in rats, delayed vaginal perforation and balanopreputial separation was observed in F1 adolescents, and decreased mean testicular sperm count and production rate was noted in F1 adult males. These findings are highly suggestive of neuroendocrine disruption, although hormonal measurements in the two-generation reproduction study did not identify specific alterations in testosterone, luteinizing hormone (LH), or estradiol levels in F0 males at

study termination. Nevertheless, the delays in sexual development are supported by a number of other considerations, including: the presence of treatment-related testicular interstitial cell tumors in the rat chronic/oncogenicity study with propanil (often related to neuroendocrine disruptions), and the similarities between the reproductive toxicity profiles of propanil to linuron and flutamide, two structurally-related chemicals with a demonstrated neuroendocrine mode of action affecting the hypothalamic-pituitary-testicular (HPT) axis.

870.3800 Reproduction and Fertility Effects - Rat

Propanil 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 two-generation reproduction study in the rat is classified **Acceptable/guideline** and satisfies the guideline requirement for a reproduction and fertility effects study in rats **(OPPTS 870.3800)**.

4.5 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. In the most recent, acceptable chronic toxicity assessments with propanil, long-term dietary exposure resulted in evidence of treatment-related methemoglobinemia and hemolytic anemia. In the chronic toxicity/carcinogenicity study in Sprague-Dawley rats, this evidence consisted of increased methemoglobin levels, decreased packed cell volume and red blood cells, and enlarged spleens at the LOAEL; additional hematological findings, with increased severity, were observed at higher dose levels. Histopathological findings (brown pigment in hepatic Kupffer cells and in the proximal convoluted tubules of the kidney) were also presumed to be related to the methemoglobinemia. Evidence of hepatic toxicity included centrilobular liver cell enlargement and hepatic granulomatous inflammation. Kidney toxicity was demonstrated by increases in blood urea nitrogen (BUN). Toxicity to the reproductive system included hypoplastic prostate and seminal vesicle, epididymal aspermia, and interstitial cell adenomas of the testes in males, and endometrial polyps, mammary galactocoeles, dilated uteri, and cystic ovaries in females. These findings are consistent with a neuroendocrine etiology. Other observed toxicity to the nervous system consisted of axonal degeneration of the sciatic nerve at the highest dose tested.

In beagle dogs, macrocytic, regenerative methemoglobinemia was observed as decreased levels of RBCs, hemoglobin, hematocrit, and MCHC and increased levels of MCV, methemoglobin, and reticulocytes. Hemosiderin deposition was observed in the bone marrow, kidney, and liver. Kidney toxicity was evidenced by increases in BUN, creatinine, and potassium, and hepatic toxicity was evidenced by increased absolute and relative liver weights.

870.4300 Combined Chronic Toxicity/Carcinogenicity Study - Rat

In a chronic toxicity/carcinogenicity study (MRID 43303201), randomized groups of 70/sex/dose Sprague-Dawley rats were fed diets containing 0, 200, 600, or 1800 ppm of technical Propanil (96.5-99.5% a.i) (9.0, 27.7, 88 mg/kg/day, males; 11.5, 38.3, 145 mg/kg/day, females) for 104 weeks (MRID 43303201). 20/sex/dose were sacrificed after 52 weeks. All rats were examined daily for toxicity and mortality and weekly for detailed clinical findings. Clinical pathology data were taken at 13, 26, 52, 78, and 104 weeks. All sacrificed animals were necropsied and organ weights were taken at 52 and 104 weeks. Histopathological examination was conducted on all animals which died on study or were sacrificed at 52 or 104 weeks.

At 200 ppm, the following treatment-related effects were observed: statistically significantly increased methemoglobin at weeks 13, 26, and 52, ranging from 33-45% above control levels, significantly decreased packed cell volume and red blood cells at weeks 26 and 52 ranging from 4-6%, significantly increased absolute weight of spleen (14%) in females at 52 weeks, enlarged spleens in 104 week necropsied females, small seminal vesicles and prostates in 104 week necropsied males, hemosiderosis in spleen of males, brown pigment (probably hemosiderin) in proximal convoluted tubules of females and 8% incidence of endometrial polyps in females (compared to 4% in controls).

At 600 ppm, the following treatment-related effects were observed: decreased weight gains ranging from 7-15% in males and 24-32% in females (excluding the 41% decrease in males and 47% decrease in females during the first week), decreases in food consumption ranging from 5-7% in males and 1-6% in females, increases in food efficiency in males and females (17.9 ♂and 18.6 ♀) in comparison to controls (16.7% ♂ and 10.5 % ♀), decreases in packed cell volume ranging from 7.6-12.5% at all sampling intervals in females, decreases in hemoglobin ranging from 7.5-13.5% at all sampling intervals in males, decreases in red blood cells ranging from 9.5-11.3% at all sampling intervals in females, increases in methemoglobin ranging from 61-119% at all sampling intervals in females, increases in methemoglobin ranging from 31-62% at all sampling intervals in males, significant increases in BUN and decreases in triglycerides at weeks 26 and 52 in males, increases in BUN at all sampling intervals and decreases in triglycerides at weeks 52 and 78 in females, significantly increased absolute and relative spleen weights for males and females at weeks 52 and 104, enlarged spleens at week 104 in both sexes, testicular masses at week 104, macrophage aggregations in the mesenteric lymph nodes (F), centrilobular liver cell enlargement (M), hepatic granulomatous inflammation (F), pericholangitis (M,F), brown pigment in Kupffer cells (M,F), bile duct hyperplasia (M,F), brown pigment in kidney

proximal convoluted tubule epithelium (M), sperm absent in epidydimides, reduced secretion from seminal vesicles, 16% incidence of benign interstitial cell tumors in testes of males (6% in controls) and 13% incidence of endometrial polyps in females.

At 1800 ppm, the following treatment-related effects were observed: discoloration of upper and lower incisors in females, increased survival in both sexes (62% ♂, 66% ♀ in comparison to controls: 30% ♂, 38% ♀; p = 0.013 ♂, 0.010 ♀), decreased weight gain ranging form 24-30% in males and 27-65% in females, decreased food consumption ranging from 11-16% in males and 2-5% in females, food efficiency increases of 20.2% for males and 50.3% for females, decreased packed cell volume ranging from 6-9% in males and 13-22% in females, decreased hemoglobin ranging from 8-15% in males and 15-22% in females, decreased RBC ranging from 9-15% in males and 18-23% in females, increased methemoglobin ranging form 58-64% in males and 106-196% in females, increased bilirubin in males at weeks 26, 52, and 104, increased BUN and decreased triglycerides at weeks 26 and 52 in males, increased bilirubin and BUN at all sampling intervals in females, decreased triglycerides at weeks 52 and 788 in females, increased absolute and relative spleen weights in both sexes at weeks 52 and 104, enlarged and darkened spleens in both sexes at weeks 52 and 104, liver masses in females, testicular masses in males, broken incisors in both sexes at week 52 and 104, ovarian cysts and thickened uteri in females at week 104, macrophage aggregations in the mesenteric lymph nodes (M), hemosiderosis of the spleen (F), hepatic centrilobular enlargement (F), hepatic granulomatous inflammation (M), focal interstitial cell hyperplasia with marked tubular atrophy, atrophy of prostate, galactoceles in mammary gland, azonal degeneration of sciatic nerve, dilatation of uterus, cystic ovarian bursa, 58% incidence of benign interstitial cell tumors in testes of males, 12% incidence of hepatocellular adenomas in females, 13% incidence of endometrial polyps in females. The incidence of testicular interstitial cell adenomas in the male historical controls ranged from 1-11% and the historical control range for female hepatocellular adenomas ranged from 0-2%.

A NOAEL was not established in this study for systemic effects due to the findings at 200 ppm (LDT).

This study is classified **Core-minimum** and satisfies the guideline requirement for a combined chronic toxicity/carcinogenicity study **(870.4300)** in the rat.

870.4100b Chronic Toxicity - Dog

Randomized groups of 4/sex/dose outbred beagle dogs were fed continuously via the diet at levels of 0, 200, 1600, or 3200 ppm (0, 5, 45, or 79 mg/kg/day for males and 0, 6, 42, or 85 mg/kg/day for females) of propanil technical, 96.9-98.5% a.i., for 12 months (MRID 42962901). Criteria evaluated were clinical signs, body weight, food consumption, clinical pathology, gross necropsy observations, organ weights, and histopathology.

No NOAEL was established in this study. Treatment-related and dose-related effects in both sexes consisted of decreased levels of RBC, hemoglobin, hematocrit, and MCHC and increased

levels of MCV, methemoglobin, and reticulocytes at the mid- and high-doses and to some extent at the low-dose at most sampling intervals. The macrocytic, regenerative, methemoglobinemia was considered moderate to severe at the mid- and high-doses and mild (up to 13% difference from controls) at the low-dose. Evaluation of reticulocyte smears from week 25 and 51 samples showed increased incidences of Heinz bodies in the mid- and high-dose dogs of both sexes and low-dose females at week 51. There was no NOAEL for endogenous pigment (hemosiderin) found in the bone marrow, kidney, and liver at the mid- and high-dose of both sexes and at the low-dose in the kidney of males and females and the liver of males. The incidence and grades of hemosiderin deposition were dose-related.

There were no mortalities and all dogs survived to terminal necropsy. During the first week of dietary exposure to propanil technical, males showed statistically significant decreased weight gains of up to 500 grams at the high-dose. In females, all groups had decreased body weight gains during the first week, but the high-dose females were more than double the controls (-190 g in controls bs. -480 g in high-dose). For body weight means, decreases up to 1-% in males and 4% in females were observed during the 4th week at the high-dose. Body weight gains returned to control levels by week 4 for high-dose females and week 7 for high-dose males. Mean body weights of high-dose dogs of both sexes were comparable to control by week 26 in females and week 39 in males, and mean body weight remained comparable between controls and high-dose dogs of both sexes for the remainder of the study. The decreases in body weight and body weight gain at the high-dose in both sexes are considered compound-related.

Food consumption in males was decreased in the high-dose during the first 6 weeks, whereas in high-dose females, food consumption was decreased only during the first week. These decreases in the food consumption of high-dose dogs are considered compound-related.

At the high-dose in both sexes, kidney damage was represented at statistically significant increases in serum BUN, creatinine, and potassium ranging from 13-58% above control levels at most sampling intervals. The presence of hemolytic anemia in both sexes at the mid- and high-dose was seen in the statistically significantly elevated bilirubin levels at these doses in comparison to control. Although the increases in bilirubin in treated groups were not large, the findings were consistent in both sexes over the course of the study.

In males, liver weight was statistically significantly increased at the high-dose by 40% for the absolute weight and 38% for the relative weight. Low-dose and high-dose thymus weight was significantly reduced in males by 49% (absolute) and 51% (relative) at the low-dose and by 43% (absolute) and 43% (relative) at the high-dose. High-dose thyroid weight was significantly increased in males by 48% (absolute) and 55% (relative).

In females, liver weight was significantly increased by 27% (relative) and the mid-dose and by 49% (absolute) and 48% (relative) at the high-dose. The increased relative and absolute liver weights in both sexes are considered compound-related. In the absence of clinical chemistry findings related to thymus and thyroid, the changes in the weight of these organs in males are of

uncertain toxicological significance.

The study was classified **Core-Minimum** and satisfied the guideline requirement for a chronic toxicity study **(870.4100b)** in a non-rodent species.

4.6 Carcinogenicity

Adequacy of data base for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. An increased incidence of testicular interstitial (Leydig) cell adenomas was observed in Sprague-Dawley rats following 2 years of exposure and was attributed to propanil exposure. Hepatocellular adenomas in female Sprague-Dawley rats in the same study were attributed to excessive toxicity, and were not considered to be treatment-related. Evidence of a treatment-related increase in commonly-occurring malignant lymphomas in female CD-1 mice following 18 months of propanil exposure was considered to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil.

870.4300 Combined Chronic Toxicity/Carcinogenicity Study - Rat

See Section 4.5 (Chronic Toxicity) above for the executive summary (MRID 43303201).

870.4200b Carcinogenicity (feeding) - Mouse

In a 24-month oncogenicity study (MRID 43391701) propanil (97% w/w/ a.i.) was administered to 80 Crl:CD-1(ICR)BR mice/sex/dose in the feed at dose levels of 0, 500, or 1000 ppm (males: 0, 74.9, and 150.0 mg/kg/day; females: 0, 88.6, and 174.1 mg/kg/day) for up to 104 weeks. Twenty mice/sex/dose were designated for interim sacrifice at week 52.

High dose males and females had significantly ($p<0.01$) lower body weight gain during week 1 of the study, resulting in slightly lower mean body weights in high-dose animals as compared to controls beginning at week 1 and continuing through weeks 66 and 61 for males and females, respectively. These differences were occasionally statistically significant, but were always with in 5% of controls and were not considered toxicologically significant. Dose-related increases in blue-coloration of the extremities (0/0, 22/5, and 205/19 observations/# animals in control, low-, and high-dose males; 0/0, 17/3, and 142/15 observations/#animals in control, low-, and high-dose females) and corresponding increases in mean methemoglobin values were observed in treated mice when compared to controls. Methemolobin differences were statistically significant ($p<0.05$ or $p<0.01$) in 500 ppm males (7-fold increase) and 1000 ppm males (15-fold increase) and females (12-fold increase). Mean erythrocyte, hemoglobin, and hematocrit values were lower in high-dose males compared to controls at week 104; however, the differences were not statistically significant. An increase in mean reticulocyte count and mean cell volume (MCV) was observed in 1000 ppm males, suggesting the presence of a compensatory mechanism. Mean Heinz body counts were significantly increased in 500 ppm ($p<0.05$) and 100 ppm ($p<0.01$)

males when compared to control at week 104; however, the increase was of small magnitude. The systemic toxicity LOAEL for this study is 500 ppm (74.9 mg/kg/day for males and 88.6 mg/kg/day for females) based on methemoglobinemia and blue coloration of the extremities. The systemic toxicity NOAEL is not identified. The carcinogenic potential of propanil was evidenced by an increased incidence of malignant lymphomas of the spleen in females. Lymphomas were observed in 4/61 control, 4/61 low-dose, and 13/61 high-dose females. The increase was statistically significant ($p<0.05$) in 1000 ppm female mice when compared to controls. Study deficiencies included: the testing of only two doses and a control, and no identification of a NOAEL for systemic toxicity.

This study is classified **Acceptable-guideline** and satisfies the guideline requirement for an oncogenicity feeding study **(870.4200b)** in the mouse.

4.7 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for Mutagenicity is considered adequate based on the pre-1991 mutagenicity guidelines. No further testing is required at this time. Seven acceptable genetic toxicology studies with propanil have been submitted to the Agency (summarized below). Propanil was not mutagenic in bacteria or in cultured mammalian cells. There was also no indication of a clastogenic effect up to toxic doses *in vivo*. Propanil did, however, cause DNA damage in a DNA repair-deficient strain of *B. subtilis* but not in the pol A$^-$ strain of *E. coli*. The relevance, therefore, of this positive result in *B. subtilis* is unclear, since DNA damage was not manifested as point mutations in microbial systems or mammalian cells, mitotic recombinations in yeast, DNA damage in mammalian cells or chromosomal aberrations in whole animals.

Gene Mutation

870.5100 - Bacterial Reverse Gene Mutation Assay *MRID 00155085* Guideline/Acceptable	Propanil was **negative** in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and in *Escherichia coli* WP2 up to cytotoxic doses (≥1,000 µg/plate +/-S9) in independent trials.
870.5100 - Bacterial Reverse Gene Mutation Assay MRID 00028625 Guideline/Acceptable	Independent trials were **negative** in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 up to cytotoxic doses (≥1,000 µg/plate +/-S9) and in *Escherichia coli* WP2 up to the highest dose tested (1,000 µg/plate +/-S9).
870.5300 - *In vitro* Mammalian Cell Gene Mutation Test MRID 00155084 Guideline/Acceptable	In a Chinese Hamster Ovary (CHO)/HGPRT cell forward gene mutation assay, independent tests were **negative** up to cytotoxic doses without S9 activation (125 µg/mL) and with S9 activation (175 µg/mL).

Cytogenetics

870.5385 - Mammalian Bone Marrow Chromosome Aberration Test MRID 00155083 Guideline/Acceptable	An *in vivo* bone marrow cytogenetic assay was **negative** in CD-1 male mice administered 0, 26.5, 106, or 265 mg/kg/day by oral gavage once or once daily for 5 consecutive days. Doses selected for this study represented 1/4, 1/10 or 1/40 of the acute LD_{50}, respectively. Overt toxicity was manifested as decreased spontaneous motor activity, lethargy and piloerection in animals receiving ≥ 106 mg/kg/day in both dosing regimens. No data were provided to support the claim of decreased metaphases in the high dose animals, and this deficiency compromised the acceptability of the study. However, since there was a clear indication of toxicity to the test animals, and no differences in LOAELs between male and female mice were seen in the subchronic or chronic studies, the doses should be considered adequate.

Other Genotoxicity

870.5500 - Bacterial DNA Damage or Repair Tests MRID 00028625 Guideline/Acceptable	Propanil was **negative** for differential cytotoxicity in *Escherichia coli* strains W3110/p3478 (pol A +/-) up to an equivalent cytotoxic dose (5 µg - S9) but was **positive** for the induction of preferential inhibition of repair-deficient *Bacillus subtilis* M45 (rec-) at 0.01-5 µg without S9: S9 activation was not included in this study.
870.5575 - Mitotic Gene Conversion in *Saccharomyces cerevisiae* MRID 00028625 Guideline/Acceptable	In a D3 mitotic recombination assay, propanil was **negative** for the induction of mitotic recombinants at doses up to 0.1 % with or without S9 mix. Independent trials were performed.
870.5550 - Unscheduled DNA Synthesis in Mammalian Cells in Culture MRID 00028625 Guideline/Acceptable	In an unscheduled DNA synthesis assay in WI-38 human fibroblasts, propanil was **negative** up to an insoluble level (1000 µg/mL).

4.8 Neurotoxicity

Adequacy of data base for Neurotoxicity: Although no guideline neurotoxicity studies have been submitted for propanil, there was evidence suggestive of neurotoxicity in the data base. The findings included: neuropathological lesions (sciatic nerve degeneration) in a rat chronic/carcinogenicity study, and evidence consistent with neuro-endocrine disruption (delayed vaginal opening and preputial separation) in the two-generation reproduction study in rats, and in the rat chronic/carcinogenicity study (increased incidence of testicular interstitial cell tumors). The evidence for neuro-endocrine disruption is supported by SAR considerations (the known neuro-endocrine mode of action of linuron, which is structurally related to propanil). As a result of these considerations, the developmental neurotoxicity study is required by the Agency and is considered a data gap at this time.

870.6100 Delayed Neurotoxicity Study - Hen

A delayed neurotoxicity study in hens is not required, since propanil is not an organophosphorus pesticide.

870.6200 Acute Neurotoxicity Screening Battery

An acute neurotoxicity screening battery in adult rats was not submitted.

870.6200 Subchronic Neurotoxicity Screening Battery

A subchronic neurotoxicity screening battery in adult rats was not submitted.

870.6300 Developmental Neurotoxicity Study

A developmental neurotoxicity study in rats was not submitted but is required by the Agency, as described above. This requirement is considered a data gap.

4.9 Immunotoxicity

Adequacy of data base for Immunotoxicity: There is evidence in the published literature suggesting that propanil is a potential immunotoxic compound (Barnett et al.,1989; Pruett et al., 2000; Watson et al., 2000). Therefore, the HIARC recommended that the Registrant conduct a guideline immunotoxicity study (OPPTS 870.7800) or submit a literature search to better characterize its immunotoxic potential.

870.7800 Immunotoxicity Study

An immunotoxicity study in rats was not submitted but is required by the Agency. Alternatively, the registrant can submit a literature search to better characterize the immunotoxic potential of propanil, as described above. This requirement is considered a data gap.

4.10 Metabolism

Adequacy of data base for metabolism: The data base for metabolism is considered to be complete. No additional studies are required at this time. In a metabolism study in rats, the majority of propanil and its metabolites was excreted in the urine within 24 hours, with only 2-13% excreted in the feces and minimal retention in the carcass or internal organs. Of the total of 13 metabolites identified, three major metabolites accounted for 17-44% of the radioactivity and resulted from hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3, 4-dichloroaniline, and its N-hydroxy and 6-hydroxy derivatives which are associated with methemoglobin formation.

870.7485 Metabolism - Rat

In a metabolism study (MRID 41796400, 41796402) groups of CRL:CD(SD) BR rats were given C^{14} labelled propanil or vehicle (2 rats); a single oral dose of 2.5 mg/kg; a single high oral dose of 300 mg/kg; 14 oral doses of 2.5 mg/kg; or one I.V. dose of 0.7 mg/kg. Urine and feces were collected cumulatively over 4 time periods on the day of dosing, over 2 periods on day 2, and daily thereafter for 7 days. Animals were then sacrificed and their tissues analyzed for radioactivity. The majority of the radioactivity (78-90%) was excreted in the urine, and 2-13% was excreted in the feces. Most of the radioactivity was eliminated within 24 hours for all except the high oral dose where it took 48 hours to eliminate 90%. For the i.v. data, females excreted 10% in the feces, while males excreted 2%. The carcass contained 0.18-0.71% of the radioactivity, with the liver having the highest residue.

Of the total of 13 metabolites identified, three major metabolites accounted for 17-44% of the radioactivity and were involved in hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3,4 dichloroaniline, and its N-hydroxy and 6-hydroxy derivatives, which are associated with methemoglobin formation.

This study is classified **Acceptable-guideline** and satisfies the guideline requirement for a metabolism study **(870.7485)** in the rat.

870.7600 Dermal Absorption - Rat

A dermal absorption study in the rat was not submitted.

4.11 Special/Other Studies

McMillan et al. (1990a) examined the metabolism of propanil and 3,4-dichloroaniline in rat liver microsomes. The major pathway of propanil metabolism in microsomal incubations was acylamidase-catalyzed hydrolysis to 3,4-dichloroaniline. Oxidized metabolites were identified as 2'-hydroxypropanil and 6-hydroxypropanil. Major microsomal metabolites of 3,4-dichloroaniline were 6-hydroxy-3,4-dichloroaniline and N-hydroxy-3,4-dichloroaniline. N-hydroxy-3,4-dichloroaniline was at least an order of magnitude greater than that of 6-hydroxy-3,4-dichloroaniline in producing methemoglobin.

Propanil (3,4-dichloropropionanilide) also has been reported to be contaminated with the cytochrome P450 enzyme inducers 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), which are structural analogs of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). McMillan et al. (1990b) determined if treatment of rats with TCAB, TCAOB, propanil, 3,4-dichloroaniline, TCDD, or phenobarbital induced the hepatic microsomal metabolism of propanil and 3,4-dichloroaniline. Acylamidase-catalyzed hydrolysis of propanil to 3,4-dichloroaniline was not induced by any of the pretreatments. However, hydroxylation of propanil at the 2'-position was induced by TCDD, TCAB, TCAOB, propanil, and 3,4-

dichloroaniline pretreatments. Ring- and N-hydroxylations of 3,4-dichloroaniline were induced by TCDD, TCAB, TCAOB, and 3,4-dichloroaniline pretreatments. Propanil- and 3,4-dichloroaniline may be weak inducers of cytochrome P450 isozymes. Propanil undergoes hydroxylation to form N-hydroxyaniline which oxidizes hemoglobin to form methemoglobin. The metabolism of propanil and resulting reactions involved in methemoglobin formation are presented in Figure 1.

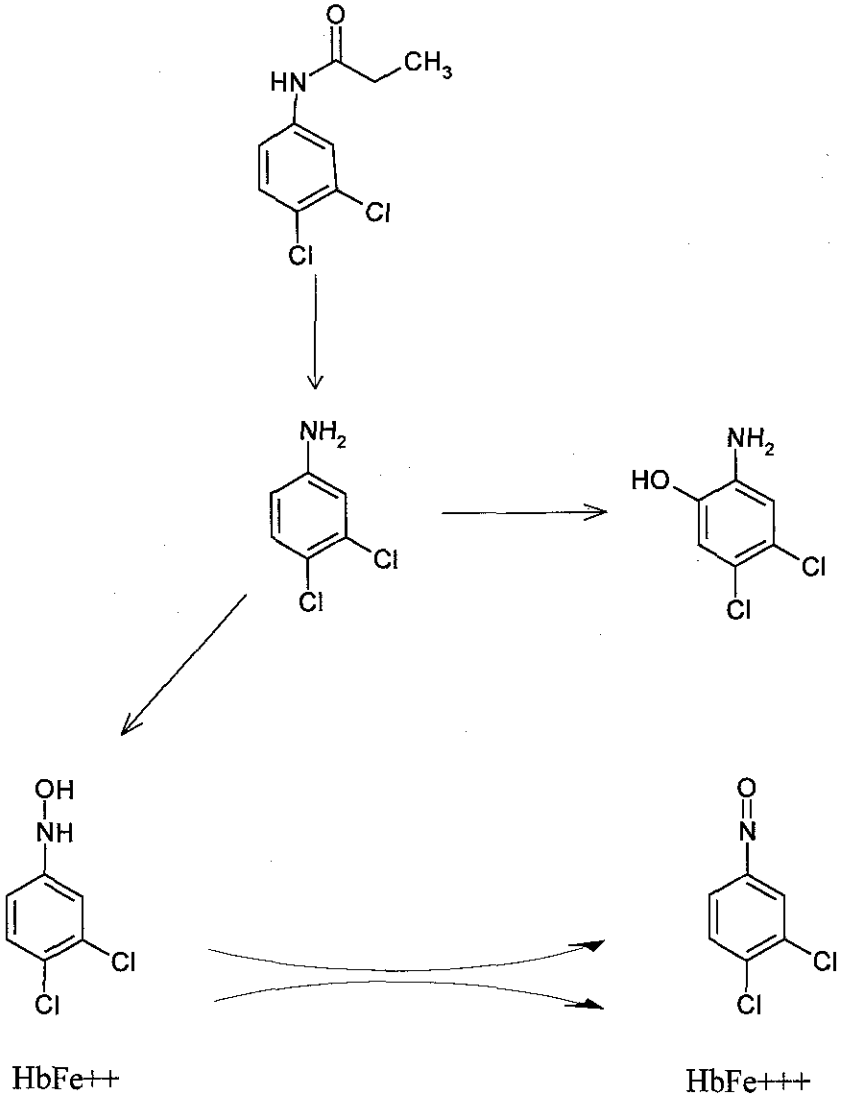

Figure 1. Biotransformation of propanil

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 9.2 for Endpoint Selection Table.

5.2 Dermal Absorption

Dermal Absorption Factor: 20 %

The estimation of a dermal absorption factor of 20% was extrapolated using the maternal LOAEL of 100 mg/kg/day from the developmental toxicity study in rabbits (MRID 00058589) and the LOAEL of 500 mg/kg/day from the 21-day dermal study in rabbits (MRID 41777001, 41961800); the ratio of 100/500 or 20%. This dermal absorption factor is supported by a dermal absorption study with linuron, a structurally-related aniline compound, for which 16% dermal absorption was observed over an eight-hour exposure.

The dermal absorption factor is required for short-, intermediate-, and long-term dermal risk assessments since oral doses were selected for these exposure periods.

5.3 Classification of Carcinogenic Potential

5.3.1 On May 9, 2001, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs met to evaluate the carcinogenic potential of propanil. The studies evaluated included combined chronic toxicity and carcinogenicity studies in Wistar (1972) and Sprague-Dawley rats (1994) and in CD-1 mice (1983; 1994) .

The earlier studies with Wistar rats and CD-1 mice were considered to be unacceptable because of study deficiencies and inadequate dosing to test the carcinogenic potential of propanil. Since then, acceptable studies in Sprague-Dawley rats and Crl:CD-1 (ICR) BR mice were submitted by the registrant. In the 1994 rat study, Sprague Dawley rats (50/sex/dose) were fed diets containing 0, 200, 600, or 1800 ppm of propanil (0, 9, 27.7, or 88 mg/kg/day for males and 0, 11.3, 38.3, or 145 mg/kg/day for females, respectively) for 104 weeks. In the 1994 mouse study, propanil was administered to 60 Crl:CD-1 (ICR) BR mice/sex/dose at dietary levels of 0, 500, or 1000 ppm (0, 74.9, 150 mg/kg/day for males and 0, 88.6, 174 mg/kg/day for females, respectively) for up to 104 weeks. For both rat and mouse studies, an additional 20 animals/sex/dose were designated for interim sacrifice at week 52.

The CARC concluded that:

- **In Sprague-Dawley rats, there was a treatment-related increase in testicular adenomas** because: 1) There was a statistically significant positive trend and a statistically significant increase by pair-wise comparisons of the 600 and 1800 ppm dose

groups with the controls for testicular interstitial cell adenomas in males (21% and 72%, respectively). 2) The incidences of these tumors in both dose groups were outside the range for the historical controls (0%-11%), and 3) These tumors were associated with an increased incidence of minimal interstitial cell hyperplasia. There was a difference of opinion among the Committee members regarding whether the highest dose in male rats was adequate or excessive. Decreased body weight gains (30% decrease compared to controls at week 13) and a marked increase in methemoglobin level (MeHb; range: 84%-132% increase over the course of study) were considered by some Committee members to be indicative of excessive toxicity while the remaining members were of the opinion that despite these changes, there were no clinical signs of toxicity and survival of the animals was not affected by the treatment.

In females, there was a statistically significant positive trend and a statistically significant increase by pair-wise comparison of the 1800 ppm dose group with the controls for hepatocellular adenomas. The incidence of these tumors (13%) was outside the historical control range (0%-2%). The non-neoplastic changes in the liver were not severely adverse. **However the CARC determined that these tumors occurred at an excessively toxic dose based on decreased body weight gain (42% decrease compared to controls at week 13) and a marked increase in MeHb level (range: 106%-196% increase over the course of study).**

Although there was a borderline increasing trend, there was no significant increase by pairwise comparisons of the 600 and 1800 ppm dose groups with the controls for endometrial polyps. The increased trend was considered by the CARC to be skewed because not all animals in 200 and 600 ppm dose groups were microscopically examined. The changes in the uterine wall were not severely adverse. Moreover, the endometrial polyps are not tumors but are considered simply as a proliferative response of the endometrium to the damaging effects of steroid sex hormones.

The CARC concluded that the testicular tumors observed in male rats in this study were treatment-related. There was no treatment-related increase in tumors in female rats.

- **In Crl:CD-1 (ICR) BR mice, there was a treatment-related increase in commonly occurring malignant lymphomas in females** as evidenced by a statistically significant positive trend and a statistically significant increase by pair wise comparison of the 1000 ppm dose group with the controls for malignant lymphomas. There was an increase in the incidence of malignant lymphomas from controls in the high dose group only. Usually the CARC prefers historical control data from the performing laboratory of same study duration and performed within two years of the study under review. In this case the historical control data from the performing laboratory was based on only one study of comparable duration of 24 months. The historical control data from 4 other studies from the same laboratory was for 18 months. Therefore, the CARC considered historical control data cited by the registrant, published between 1982-1995, from different

laboratories which ranged from 0%-28%. The incidence of 17% at the high-dose was within this historical control range. Moreover, this tumor occurs spontaneously in this sex and strain of mice. Therefore, the finding of malignant lymphomas at the high-dose was considered by the CARC to have a limited impact on the overall conclusion regarding the weight-of-the-evidence for the carcinogenic potential of propanil. No treatment-related tumors were observed in male mice.

The highest dose level tested was considered by the CARC to be adequate and not excessive because there were no treatment related adverse effects on the body weight gain, non-neoplastic histopathological findings or survival of the mice. However, there was an increase in MeHb levels, relative spleen weights and blue coloration of extremities in both sexes.

- A battery of pre-1991 acceptable Mutagenicity assays indicated that propanil was not genotoxic. No new studies were requested by the Committee.

- No mode of action studies related to the mechanism of tumor induction in rats or mice were available.

5.3.2 Classification of Carcinogenic Potential

In accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified propanil into the category **"Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential."** There was an increase in benign tumors in male rats. But considering the non-mutagenicity of propanil the available evidence for carcinogenicity did not reach the level of concern associated with category "Likely to be carcinogenic in humans." The Committee's decision was based on the following weight-of-the-evidence considerations:

1. Propanil induced testicular interstitial cell adenomas in male rats. The hepatocellular adenomas in female rats occurred only at an excessively toxic dose. The increase in commonly occurring malignant lymphomas in female mice added little to the overall weight of evidence for the carcinogenic potential of propanil.

2. Propanil was not genotoxic in a battery of acceptable mutagenicity assays.

5.3.3 Quantification of Carcinogenic Potential

The dose-response assessment is not indicated for agents when the evidence is "suggestive" of carcinogenic potential.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

There was no evidence for quantitative susceptibility following *in vivo* exposures to rats and rabbits or following pre/post natal exposure to rats for two-generations. However, there was evidence consistent with neuro-endocrine disruption (delayed vaginal opening and preputial separation) in the 2-generation reproduction study which indicated a qualitative susceptibility to the offspring.

6.2 Recommendation for a Developmental Neurotoxicity Study

There was evidence suggestive of neurotoxicity in the propanil data base. The findings included: Neuropathological lesions (sciatic nerve degeneration) in a rat chronic/carcinogenicity study. Evidence consistent with neuro-endocrine disruption (delayed vaginal opening and preputial separation) in the two-generation reproduction study in rats, and in the rat chronic/carcinogenicity study (increased incidence of testicular interstitial cell tumors); this evidence is supported by SAR considerations (the known neuro-endocrine mode of action of linuron, which is structurally related to propanil). A developmental neurotoxicity study in rats for propanil is required.

7.0 OTHER ISSUES

Propanil has been reported to be contaminated with the cytochrome P450 enzyme inducers 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB), which are structural analogs of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). A summary of short-term bioassays compiled by the National Toxicology Program (NTP) states that "3,3'-4,4'-tetrachloroazobenzene caused typical dioxin-like effects, such as thymic atrophy, an increase in liver weights, induction of hepatic cytochrome P4501A, and decreased mean body weight gains. Furthermore, in the 13-week studies, a sharp decrease in circulating thyroxine concentrations was observed even at the lowest dose (0.1 mg/kg) tested in rats. Other effects included a decrease in epididymal spermatozoal concentration in mice, major effects on the hematopoietic system, and increased incidences of hyperplasia of the forestomach in 3 and 30 mg/kg males and 30 mg/kg females. A no-observable-adverse-effect-level (NOAEL) was not reached in rats. The NOAEL in mice was 0.1 mg/kg. Comparison of various dioxin-like effects in these studies with those reported in the literature indicate that 3,3',4,4'-tetrachloroazobenzene is six to two orders of magnitude less potent than 2,3,7,8-tetrachlorodibenzo-*p*-dioxin." (TOX-65, 1998) It is unknown to what extent the toxicological response to treatment with propanil is attributable to contaminent exposure.

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9.0 APPENDICES
Tables for Use in Risk Assessment

9.1 Toxicity Profile Summary Tables

9.1.1 Acute Toxicity Table - See Section 4.1

9.1.2 Subchronic, Chronic and Other Toxicity Tables

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
SUBCHRONIC TOXICITY STUDIES		
870.3100 90-Day oral toxicity rodents (Wistar rat)	MRID 00015459, 00046259 (1961) Core-supplementary 0, 0.01, 0.033, 0.10, 1.0, 5.0 % (diet) (0, 10, 33, 100, 1000, 5000 mg/kg/d)	NOAEL = 33 mg/kg/day LOAEL = 100 mg/kg/day based on increased relative spleen weight in females and decreased hemoglobin in males.
870.3100 90-Day oral toxicity rodents (CD-1 mouse)	MRID 40402901 (1983) Core-minimum 0, 25, 200, 1600, 12800 ppm (diet) (M: 0, 6.6, 49, 442, 5325 mg/kg/d) (F: 0, 9.6, 78, 566, 6467 mg/kg/d)	NOAEL = 6.6/9.6 (M/F) mg/kg/day LOAEL = 49/78 (M/F) mg/kg/day based on histopathological findings in the liver (hepatocytic pleomorphism and hepatocytic multifocal necrosis).
870.3200 21-Day dermal toxicity (NZW rabbit)	MRID 41777001, 41961800 (1990) Acceptable/guideline 0, 250, 500, 1000 mg/kg/d 6 hrs/day; 5 days/week	NOAEL = 250 mg/kg/day LOAEL = 500 mg/kg/day based on decreased body weight gain (day 20) and decreased food consumption (days 14-20).
DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES		
870.3700a Prenatal developmental toxicity in rodents	MRID 00058588 (1980) Acceptable/guideline 0, 0.8, 4.0, 20, 100 mg/kg/d Gavage; GD 6-15	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on decreased body weight gain during treatment. **Developmental** NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on decreased mean fetal weight and delayed ossification in the sternebrae and cervical vertebrae.
870.3700b Prenatal developmental toxicity in nonrodents (NZW rabbit)	MRID 00058589 (1980) Acceptable/guideline 0, 4, 20, 100 mg/kg/d Gavage; GD 6-18	**Maternal** NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on mortality, clinical signs of toxicity, and weight loss during treatment. **Developmental** NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on slightly decreased mean fetal weight.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.3800 Reproduction and fertility effects (SD rats, 2-generations)	MRID 44604301 (1998) Acceptable/guideline 0, 60, 150, 600 ppm (diet) (F0 M: 0, 4, 11, 43 mg/kg/d) (F0 F: 0, 5, 13, 51 mg/kg/d)	**Parental/Systemic** NOAEL = 11/13 (M/F) mg/kg/day LOAEL = 43/51 (M/F) mg/kg/day 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. **Reproductive** NOAEL = 11/13 (M/F) mg/kg/day LOAEL = 43/51 (M/F) mg/kg/day based on delayed vaginal perforation and balanopreputial separation in F1 adolescents, and decreased mean testicular sperm count and production rate in F1 adult males. **Offspring** NOAEL = 11/13 (M/F) mg/kg/day LOAEL = 43/51 (M/F) mg/kg/day based on reduced F1 and F2 pup weights, delayed vaginal perforation and balanopreputial separation in F1 adolescents, and organ weight changes 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 males and females).
CHRONIC TOXICITY AND CARCINOGENICITY STUDIES		
870.4100a Chronic toxicity rodents	See 870.4300, Combined chronic toxicity/carcinogenicity	
870.4100b Chronic toxicity dogs (beagles, 1-yr)	MRID 42962901 (1993) Core-minimum 0, 200, 1600, 2300 ppm (diet) (M: 0, 5, 45, 79 mg/kg/d) (F: 0, 6, 42, 85 mg/kg/d)	NOAEL = < 5/< 6 (M/F) mg/kg/day LOAEL = 5/6 (M/F) mg/kg/day based on macrocytic, regenerative, methemoglobinemia (decreased erythrocytes, hemoglobin, hematocrit, and mean cellular hemoglobin concentration; increased mean cell volume, methemoglobin, and reticulocytes.; increased Heinz bodies in females at week 51), and endogenous pigment (hemosiderin) in the kidney of both sexes and the liver of males
870.4200 Carcinogenicity (CD-1 mice; 104-wk)	MRID 43391701 (1994) Guideline/acceptable 0, 500, 1000 ppm (diet) (M: 0, 74.9, 150 mg/kg/d) (F: 0, 88.6, 174.1 mg/kg/d)	NOAEL = < 74.9/< 88.6 (M/F) mg/kg/day LOAEL = 74.9/88.6 (M/F) mg/kg/day based on methemoglobinemia (increased methemoglobin and Heinz bodies in males) and blue discoloration of the extremities. **Evidence of carcinogenicity:** malignant lymphomas in females at 174.1 mg/kg/d

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300 Combined chronic toxicity/carcino-genicity (SD rat; 104-wk)	MRID 43303201 (1994) Core-minimum 0, 200, 600, 1800 ppm (diet) (M: 0, 9.0, 27.7, 88 mg/kg/d) (F: 0, 11.5, 38.3, 145 mg/kg/d)	NOAEL = < 9.0/< 11.5 (M/F) mg/kg/day LOAEL = 9.0/11.5 (M/F) mg/kg/day based on clinical chemistry findings in both sexes (increased methemoglobin at weeks 13, 26, and 52; decreased packed cell volume and red blood cells at weeks 26and 52), increased spleen weight in females at 52 weeks, and gross- and histo-pathological findings at 104 weeks (enlarged spleen in females, small seminal vesicles and prostate in males, hemosiderosis in spleen of males, brown pigment [probably hemosiderin] in proximal convoluted tubules of females and endometrial polyps in females). **Evidence of carcinogenicity:** testicular interstitial cell adenomas in males at 27.7 and 88 mg/kg/d.
MUTAGENICITY STUDIES		
Gene Mutation 870.5100 Bacterial reverse gene mutation assay	MRID 00155085 (1980) Guideline/acceptable	Propanil was **negative** in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and in *Escherichia coli* WP2 up to cytotoxic doses (≥1,000 µg/plate +/-S9) in independent trials.
Gene Mutation 870.5100 Bacterial reverse gene mutation assay	MRID 00028625 (1979) Guideline/acceptable	Independent trials were **negative** in *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 up to cytotoxic doses (≥1,000 µg/plate +/-S9) and in *Escherichia coli* WP2 up to the highest dose tested (1,000 µg/plate +/-S9).
Gene Mutation 870.5300 *In vitro* mammalian cell gene mutation test	MRID 00155084 (1984) Guideline/acceptable	In a Chinese Hamster Ovary (CHO)/HGPRT cell forward gene mutation assay, independent tests were **negative** up to cytotoxic doses without S9 activation (125 µg/mL) and with S9 activation (175 µg/mL).
Cytogenetics 870.5385 Mammalian bone marrow chromosome aberration test	MRID 00155083 (1983) Guideline/acceptable	An *in vivo* bone marrow cytogenetic assay was **negative** in CD-1 male mice administered 0, 26.5, 106, or 265 mg/kg/day by oral gavage once or once daily for 5 consecutive days. Doses selected for this study represented 1/4, 1/10 or 1/40 of the acute LD_{50}, respectively. Overt toxicity was manifested as decreased spontaneous motor activity, lethargy and piloerection in animals receiving ≥106 mg/kg/day in both dosing regimens.

Guideline No./ Study Type	MRID No. (year)/ Classification /Doses	Results
Other Genotoxicity 870.5500 Bacterial DNT damage or repair tests	MRID 00028625 (1979) Guideline/acceptable	Propanil was **negative** for differential cytotoxicity in *Escherichia coli* strains W3110/p3478 (pol A +/-) up to an equivalent cytotoxic dose (5 µg - S9) but was **positive** for the induction of preferential inhibition of repair-deficient *Bacillus subtilis* M45 (rec-) at 0.01-5 µg without S9: S9 activation was not included in this study.
Other Genotoxicity 870.5575 Mitotic gene conversion in *Saccharomyces cerevisiae*	MRID 00028625 (1979) Guideline/acceptable	In a D3 mitotic recombination assay, propanil was **negative** for the induction of mitotic recombinants at doses up to 0.1 % with or without S9 mix. Independent trials were performed.
Other Genotoxicity 870.5550 Unscheduled DNA synthesis in mammalian cells in culture	MRID 00028625 (1979) Guideline/acceptable	In an unscheduled DNA synthesis assay in WI-38 human fibroblasts, propanil was **negative** up to an insoluble level (1000 µg/mL).
METABOLISM STUDIES		
870.7485 Metabolism and pharmacokinetics (SD rat)	MRID 41796401, 41796402 (1991) Acceptable/guideline A: single oral low dose (2.5 mg/kg) B: multiple oral low dose (2.5 mg/kg for 15 days) C: single oral high dose (300 mg/kg) D: intravenous dose (0.7 mg/kg in saline)	The majority of the radioactivity (78-90%) was excreted in the urine, and 2-13% was excreted in the feces. Most of the radioactivity was eliminated within 24 hours for all except the high oral dose where it took 48 hours to eliminate 90%. For the i.v. data, females excreted 10% in the feces, while males excreted 2%. The carcass contained 0.18-0.71% of the radioactivity, with the liver having the highest residue. Of the total of 13 metabolites identified, three major metabolites accounted for 17-44% of the radioactivity and were involved in hydroxylation and oxidation of the propanamide moiety. Other metabolites included 3,4 dichloroaniline, and its N-hydroxy and 6-hydroxy derivatives, which are associated with methemoglobin formation.

9.2 Summary of Toxicological Dose and Endpoints for Propanil for Use in Human Risk Assessment [1]

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	No appropriate endpoint attributed to a single dose was identified. Therefore, an acute RfD was not established.		
Chronic Dietary	LOAEL = 9 UF = 300	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostates in males.	Chronic toxicity/ carcinogenicity study in rats [2]
		Chronic RfD = 0.03 mg/kg/day	
Cancer	Suggestive evidence of carcinogenic potential by all routes of exposure, but not sufficient to assess human carcinogenic potential.	(1) Propanil induced testicular interstitial cell adenomas in male rats. The hepatocellular adenomas in female rats occurred only at an excessively toxic dose. The increase in commonly occurring malignant lymphomas in female mice added little to the overall weight of evidence for the carcinogenic potential of propanil. (2) Propanil was not mutagenic.	Chronic toxicity/ carcinogenicity study in rats; carcinogenicity study in mice [2]
Incidental Oral; short- and Intermediate-Term	LOAEL= 9	Increased methemoglobin.	Chronic toxicity/ carcinogenicity study in rats [2]
Dermal; Short-Intermediate-Term [3]	LOAEL= 9	Increased methemoglobin.	Chronic toxicity/ carcinogenicity study in rats [2]
Dermal; Long-Term [3]	LOAEL= 9	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostates in males.	Chronic toxicity/ carcinogenicity study in rats [2]
Inhalation; Short-, Intermediate-Term [4]	LOAEL= 9	Increased methemoglobin.	Chronic toxicity/ carcinogenicity study in rats [2]
Inhalation; Long-Term [4]	LOAEL = 9	Increased methemoglobin and increased spleen weight in females, and small seminal vesicles and prostates in males.	Chronic toxicity/ carcinogenicity study in rats [2]

1 UF = uncertainty factor, LOAEL = lowest observed adverse effect level, RfD = reference dose.
2 Chronic carcinogenicity study in rats: MRID 43303201; carcinogenicity study in mice: MRID 43391701.
3 An oral endpoint was used for dermal exposure: a dermal absorption factor of 20% of oral exposure will be used.
4 An oral endpoint was used for inhalation exposure: inhalation exposure assumed equivalent to oral exposure.

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Chemical:	**Propanamide, N-(3,4-dichlorophenyl)-**
PC Code:	**028201**
HED File Code	**13000 Tox Reviews**
Memo Date:	**11/09/2001**
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