CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
HUMAN HEALTH ASSESSMENT BRANCH

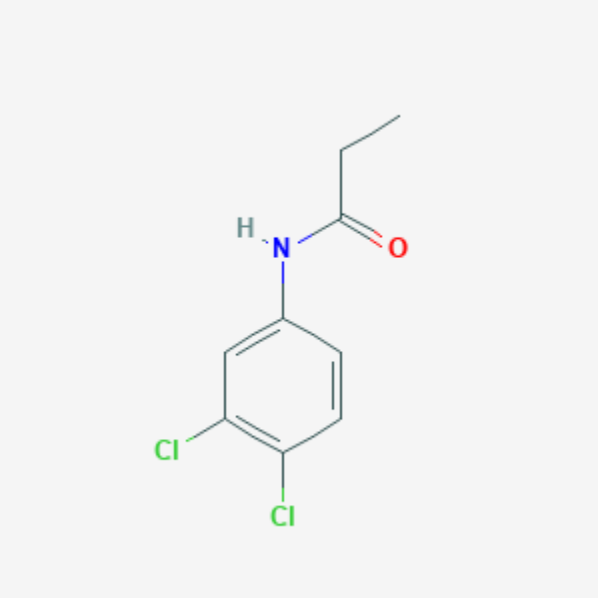
SUMMARY OF TOXICOLOGY DATA

Propanil
Chemical Code # 503**, Document Processing Number (DPN)** 274
SB 950 # 829
July 23, 1998
Revised: 10/26/99, 8/14/00, 1/29/03, 7/22/14, 4/14/15, 5/5/2016, 5/12/2016, 4/27/2020

Propanil, CAS No. 709-98-8
Trade name: Stam
Chemical MW : 218.08 mg/mol
Density: 1.25 g/ml at 25^{o} C
Vapor Pressure: 9.08 x10^{-7} mm Hg at 25^{o} C
Melting Point: 92^{o} C
Boiling Point: 351^{o} C
Oil/Water Partition Coefficient: 3.07 (log Kow)
Water solubility: 130 mg/l at 20^{o} C
Use: herbicide used for the treatment of numerous grasses and broad-leaved weeds in rice.

Source of information: https://pubchem.ncbi.nlm.nih.gov/compound/propanil

[redacted] 12/17/2020



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SUMMARY:

The primary target of propanil is hematopoiesis. Methemoglobinia and hemolytic anemia were evident in the multidosing treatment regimens (subchronic and/or chronic dosing regimens in mice, rats and dogs). Other significant effects of testicular interstitial cell tumors and hepatocellular adenomas (rat oncogenic) and retinal degeneration (mouse oncogenic) were noted. The indicated acute toxicity hazards are Category II (eye irritation), III (oral toxicity) and IV (other endpoints). Effects on neuromuscular coordination and sensory reactivity were evident in the acute neurotoxicity study. No indication of immunotoxicity was demonstrated. The rat and rabbit developmental toxicity and rat two-generation reproductive toxicity studies did not reveal any toxic effects upon the offspring at levels which were not maternally toxic. The genotoxicity battery did not demonstrate any genotoxic effects.

In the ADME study, 79 to 90% of the administered dose was recovered in the urine. Absorption of the active ingredient ranged from 85 to 90% of the administered dose (2.5 mg/kg treatment level). Metabolism of the parent compound proceeded with the oxidation of the carbons in the propoxy moiety of the molecule and subsequent hydrolysis of propanil into the propoxy component and 3,4-dichloroaniline.

Toxicology one-liners are attached.

All record numbers for the study listed types through 323574 (Document No. 274-0122) were examined. This includes all relevant studies indexed by DPR as of 4/27/20.

In the 1-liners below:
** indicates an acceptable study.

File name: T200427
Revised by [redacted], 4/27/20

This record contains summaries of studies. Individual worksheets may be useful for detailed assessment.

METABOLISM AND PHARMACOKINETICS

274-0045; 152695; "Metabolism of ^{14}C-Propanil in Rats – Part II: Analysis, Quantitation, and Structure Elucidation of Metabolites in Urine and Feces"; (D. Wu; XenoBiotic Laboratories, Inc., Princeton, NJ; Study No. 88072; 1/31/91); Urine and fecal samples collected in the mass balance study (rec. no. 152696) were analyzed for metabolites in this study. Metabolites in samples collected in the first 24 hours from animals in Groups A (2.5 mg/kg), B (2.5 mg/kg/day) and D (0.7 mg/kg, iv) and in the first 72 hours from animals in Group C (300 mg/kg) were isolated and purified by HPLC. Structural identification was accomplished by various mass spectrographic analytical techniques. Urinary metabolites constituted approximately 90% of the total radiolabel which had been administered thus demonstrating that the test material had been well absorbed. Oxidation of the carbons on the propoxy moiety of the molecule and subsequent hydrolysis of these oxidized carbons was a primary pathway of metabolism. Hydroxylated sites on either the benzyl ring or the propoxy moiety were also subject to conjugation with glucuronide. Sulfation of the nitrogen and the phenyl hydroxyl group was also observed. Less than 1% of the parent compound was recovered in either the urine or the feces even at the 300 mg/kg treatment level. Any of the metabolites recovered from the feces constituted less than 1% of the administered dose except for metabolite M12 (4%), which was a sulfonic acid analogue of acetanilide. Study supplemental (study included only the identification of the metabolites.). ([redacted], 1/15/13)

274-0045; 152696; "Metabolism of ^{14}C-Propanil in Rats: Definitive FIFRA Study, Part I: Material Mass Balance Study"; (D. Wu; XenoBiotic Laboratories, Inc., Princeton, NJ; Study No. 88072; 5/31/90); Five or six Crl:CD(SD)/sex/group were assigned to one of 4 groups (designated A to D) and treated with ^{14}C-Propanil technical (lot no. C048204E, specific activity: 19.39 uCi/mg (see rec. no. 152695), radiochemical purity: 99.09%). Unlabeled propanil (no lot no., purity: 96.73%) was used to adjust the specific activity of the dosing preparations or as the dosing preparation in the multiple dose regimen. In Groups A, B and C, the rats were dosed orally by gavage. In Group D, they were injected intravenously with the test material. The Group A animals received a single dose of 2.5 mg/kg. The animals in Group B received 14 daily doses of 2.5 mg/kg of unlabeled propanil and on the 15th day, a single dose of 2.5 mg/kg of the radiolabeled test material. In Group C, the animals received a single dose of 300 mg/kg. The Group D animals were dosed once with 0.7 mg/kg. The primary route of excretion was via the urine with the percentage of administered dose recovered from the urine ranging from 79 to 90 by the conclusion of the 7-day collection period irrespective of the dosing regimen. Recovery in the feces ranged from 2 to 13% of the administered dose. These data indicate that approximately 85 to 90% of the administered dose is absorbed. Analysis of the tissues at 7-days post dose or post-final dose revealed the primary site of radiolabel recovery to be the liver followed by blood, spleen and kidneys. Study supplemental (study protocol did not include metabolite analysis or pharmacokinetics). ([redacted], 1/14/13)

GUIDELINE ACUTE STUDIES ON ACTIVE INGREDIENT

Acute oral toxicity, rat

274-0034; 152673; "Acute Oral Toxicity (LD50) Study in Albino Rats with Propanil"; (D.J. Naas; Wil Research Laboratories, Inc., Ashland, OH; Study No. WIL-141001; 9/5/89); Five Sprague-Dawley rats/sex/group were dosed orally by gavage with 750, 1080 or 1555 mg/kg of Propanil technical (batch no. 1; purity not reported). The following mortality resulted from the treatment; 750 ((M/F: 1/5), 1080 (M: 2/5, F: 3/5), 1555 (M: 3/5, F: 5/5). Deaths occurred within 2

days of dosing. Clinical signs included lethargy, ataxia, decreased limb tone, tachypnea, prostration, body cool to touch, clear ocular discharge, cyanosis, salivation and bradypnea. The necropsy examination for those which died during the study revealed mottled lungs, dark red adrenal glands and kidneys. The contents of the urinary bladder and gastro-intestines were dark red. Red foci were noted in the thymus. No treatment-related lesions were evident in those animals which survived the 14-day observation period. LD50 (M/F) (95% confidence limit): 1080 (868 to 1343) mg/kg; Toxicity Category III; Study acceptable. ([redacted], 12/26/12)

Acute dermal toxicity

274-0034; 152674; "Acute Dermal Toxicity (LD50) Study in Albino Rabbits with Propanil"; (D.J. Naas; Wil Research Laboratories, Inc., Ashland, OH; Study No. WIL-141002; 9/5/89); The skin of five New Zealand White rabbits/sex was exposed to 2000 mg/kg of Propanil technical (batch no. 1; purity not reported) for 24 hours under a semi-occlusive wrap. The test material was moistened into a paste with deionized water prior to application to the skin. No deaths resulted from the treatment. No treatment-related systemically toxic signs were noted. Moderate erythema and slight edema were noted at the site of application, clearing by study day 5. No treatment-related lesions were evident in the necropsy examination. LD50 (M/F) > 2000 mg/kg; Toxicity Category III; Study acceptable. ([redacted] 12/27/12)

274-0112; 280730; "Acute Dermal Toxicity Study"; (J. Durando; Eurofins PSL, Dayton, NJ; Study No. 6320; 10/15/98, amended, 6/8/10); The skin of five Sprague-Dawley-derived rats/sex was treated with 5000 mg/kg of Propanil Technical (lot no. 98-050; a.i.: 97.5%) for 24 hours under an occlusive wrap. The test material was moistened into a paste with distilled water prior to application on the skin. No deaths resulted from the treatment. No clinical signs nor dermal irritation at the site of application were evident. No gross lesions were evident in the necropsy examination. LD50 (M/F) > 5000 mg/kg; Toxicity Category IV; Study acceptable. ([redacted], 2/23/15)

Acute inhalation toxicity, rat

274-0034; 152675, 152676; "STAM M-4 Formulation (XF-84052): Acute Inhalation Toxicity Study in Rats"; (J.R. Fisher, J.V. Hagan, R.C. Baldwin; Toxicology Department, Rohm and Haas Company, Spring House, PA; Report No. 84R-271; 3/15/85); Ten Sprague-Dawley rats/sex were exposed whole-body to 5.0 mg/l (gravimetric) of STAM M-4 (lot no. JR-9038; a.i.: 54.1%) for 4 hours. The mean MMAD (GSD) were 4.25 (2.2) um. One male and one female rat died as a consequence of the exposure. The deaths occurred on study days 2 and 4, respectively. Clinical signs included ataxia, bradypnea, dyspnea, gasping, rales, prostration, dry cornea, corneal opacity, exophthalmos, red and/or brown stain muzzle, red and/or yellow stained anogenital region, thriftless appearance, and red exudate around eyes. In the necropsy examination of the two animals which died, their lungs were either bright red or mottled red and the liver of the male was mottled. The male also had a gas-filled stomach and intestines. LC50 (M/F) > 5.0 mg/l; Toxicity Category IV; Study acceptable. ([redacted], 12/27/12)

274-0112; 280731; "Acute Inhalation Toxicity Limit Test"; (J. Durando; Eurofins PSL, Dayton, NJ; Study No. 6321; 10/15/98, amended, 6/8/10); Five Sprague-Dawley derived rats/sex were exposed whole-body to 2.13 mg/l (gravimetric) of Propanil Technical (lot no. 98-050; a.i.: 97.5%) for 4 hours. The mean MMAD (GSD) was 3.6 (1.79) µm. No deaths resulted from the exposure. In-chamber clinical observations included ocular and nasal discharge, irregular respiration, hunched posture, and hypoactivity. Animals recovered from these signs by day 2 post-exposure. No lesions were evident in the necropsy examination. LC50 (M/F) > 2.13 mg/l; Toxicity Category IV; Study acceptable. ([redacted], 2/23/15)

Primary eye irritation, rabbit

274-0034; 152677; "Primary Eye Irritation Study in Albino Rabbits with Propanil"; (D.J. Naas; Wil Research Laboratories, Inc., Ashland, OH; Study No. WIL-141004; 9/5/89); The eyes of 6 New Zealand White rabbits were treated by ocular instillation with 100 mg/eye of Propanil technical (batch no. 1; purity not reported). Corneal opacity, grade 2 (1/6), was noted at 1 hour post-dose, increasing to grade 2 (3/6) at 24 hours, diminishing to grades 2 (2/6) and 1 (1/6) at 48 hours, grade 1 (1/6) at 72 hours and clearing by 4 days. Iritis, grade 1 (2/6), was evident at 1 hour, increasing to grade 1 (3/6) at 24 hours, diminishing to grade 1 (2/6) at 48 hours, grade 1 (1/6) at 72 hours through 7 days, clearing by day 14. Conjunctival redness, grades 3 (2/6) and 2 (4/6), was noted at 24 hours, diminishing to grades 2 (4/6) and 1 (2/6) at 48 hours, grades 2 (2/6) and 1 (4/6) at 72 hours, grade 1 (6/6) at 4 days, grade 1 (3/6) at 7 days, clearing by day 14. Chemosis, grades 3 (1/6), 2 (2/6) and 1 (3/6), was noted at 24 hours, grades 2 (1/6) and 1 (4/6) at 48 hours, grade 1 (2/6) at 72 hours, clearing by 4 days, reappearing with grade 1 (1/6) at 7 days and clearing again at 14 days. Discharge, grades 2 (2/6) and 1 (1/6), was evident at 24 hours, clearing by 48 hours. Toxicity Category II; Study acceptable. ([redacted], 12/27/12)

274-0112; 280732; "Primary Eye Irritation"; (J. Durando; Eurofins PSL, Dayton, NJ; Study No. 6322; 10/15/98, amended, 6/8/10); The eyes of 6 New Zealand albino rabbits were instilled with 0.1 ml (approx.. 0.10 g)/eye of Propanil Technical (lot no. 98-050; a.i.: 97.5%). No corneal opacity nor iritis were evident. Conjunctival redness, grades 2 (1/6) and 1 (2/6), was exhibited at 24 hours, diminishing to grade 1 (2/6) at 48 hours, and clearing by 72 hours. Chemosis, grade 1 (3/6), was noted at 24 hours, and clearing by 48 hours. Discharge, grade 1 (3/6), was exhibited at 24 hours, clearing by 48 hours. Toxicity Category III; Study acceptable. ([redacted], 2/23/15)

Primary dermal irritation

274-0034; 152678; "Primary Dermal Irritation Study in Albino Rabbits with Propanil"; (D.J. Naas; Wil Research Laboratories, Inc., Ashland, OH; Study No. WIL-141003; 9/5/89); The skin of 6 New Zealand White rabbits was exposed to 0.5 g/site, one site/animal, of Propanil technical (batch no. 1; purity not reported) for 4 hours under a semi-occlusive wrap. The test material was moistened with deionized water. Erythema, grade 1 (4/6), was noted at 1 hour post-exposure, clearing by 24 hours. Edema, grade 1 (1/6), was evident at 1 hour post-exposure, clearing by 24 hours. Toxicity Category IV; Study acceptable. ([redacted], 12/27/12)

274-0112; 280733; "Primary Skin Irritation"; (J. Durando; Eurofins PSL, Dayton, NJ; Study No. 6323; 10/15/98, amended, 6/8/10); The skin of 6 New Zealand albino rabbits was exposed to 0.5 ml/site, one site/animal of Propanil Technical (lot no. 98-050; a.i.: 97.5%) for 4 hours under a semi-occlusive wrap. No erythema nor edema were evident over the 72-hour observation period. Toxicity Category IV; Study acceptable. ([redacted], 2/24/15)

Dermal sensitization

274-0034; 152679; "Skin Sensitization Study in Albino Guinea Pigs with Propanil"; (D.J. Naas; Wil Research Laboratories, Inc., Ashland, OH; Study No. WIL-141005; 9/5/89); During the induction phase, the skin of 6 Hartley albino guinea pigs/sex was treated with 0.4 ml/site, one site/animal of a 25% (w/v) preparation of Propanil technical (batch no. 1; purity not reported) in acetone, for 6 hours under an Hilltop chamber, 3 times/week for 3 weeks. Fourteen days after the final induction, the skin of each animal was exposed to 0.4 ml/site of a 2.5% preparation of the test material in acetone for 6 hours. A naïve control group of 3 animals/sex was exposed to the same preparation under the same conditions. None of the twelve animals in the treated group demonstrated a positive response to the challenge treatment at 24 or 48 hours post-exposure. None of the six control animals exhibited a positive response as well.

The test material is not a dermal sensitizer as evaluated in a modified Buehler protocol. The positive control was functional. Study acceptable. ([redacted], 12/28/12)

274-0112; 280734; "Dermal Sensitization Test-Buehler Method"; (J. Durando; Eurofins PSL, Dayton, NJ; Study No. 6324; 10/15/98, amended, 6/8/10); The skin of 20 male Hartley albino guinea pigs was treated with 0.4 g/site of a 80% (w/w) preparation of Propanil Technical (lot no. 98-050; a.i.: 97.5%) in distilled water, using an occlusive Hilltop chamber, for 6 hours, once per week for 3 weeks in the induction phase. Twelve days after the last induction treatment, 0.4 g of the 80% (w/w) preparation of the test material in distilled water was applied to a naive site on each animal for 6 hours using the same procedure and the sites were evaluated for a sensitization response at 24 and 48 hours post-application. Ten control animals were treated in the same manner at this time as well. None of the challenged or control animals exhibited signs of positive dermal irritation over the 48- hour observation period. The test material is not a dermal contact sensitizer in accordance with the Buehler procedure. The positive control was functional. Study acceptable. ([redacted], 2/24/15)

SUBCHRONIC STUDIES

Rat Subchronic Dietary Toxicity Study

274-0001; 5113; Groups of 10 young female albino rats were exposed to 0, 0.01, 0.033, 0.10, 0.33, 1.0 and 5% of Stam F-34 in diet for 3 months. Motality: all in 5% group died within first three weeks since dosing started. One female at 0.33%, 1 male at 0.01% and 1 male at 1.0% died later during the study. Decreased food intake at 0.33% and 1.0% levels were observed at 13 week. Hemolytic anemia was indicated at these levels due to hematologic data. Urinary excretion of sugar and protein was not affected. Elevated relative spleen weight at 0.1% and above in female and at 0.33% and 1.0% in males was observed. No treatment related histologic findings were observed. Study supplemental. ([redacted], and [redacted]. 7/18/2014)

274-0036; 152683; "Propanil Technical: Dose Range Finding Toxicity Study by Dietary Administration to Rats for 13 Weeks"; (R. Billington, *et. al.,* Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England; Report No. PTF 2/9187; 6/22/92);); Five Crl:CD(SD)BR rats/sex/group were treated in the diet with 0, 300, 1000, 2000 or 4000 ppm of Propanil Technical (batch no. 01; purity: 97.2 to 98.3%) for 13 weeks ((M): 0, 23.2, 76, 151, 318 mg/kg/day, (F): 0, 27.8, 93, 184, 364 mg/kg/day). One female died as a consequence of blood collection at the conclusion of the study. The mean body weights and food consumption of both sexes in the 1000 ppm group and above were less than the control group values throughout the study. In the hematology evaluation, the hematocrit, and red blood cell count for the males in the 2000 and 4000 ppm groups and the females in the 1000, 2000 and 4000 ppm groups were less than the control values ($p<0.05$ or 0.01). The hemoglobin concentrations in the blood of the 1000 ppm females and above were less than that of the control group ($p<0.01$). These effects on the red blood cells were reflected in increases in the mean corpuscular hemoglobin content (MCHC), the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin (MCH) of both sexes in the 2000 and 4000 ppm groups. The methemoglobin content was increased in a dose-related manner in the blood of both sexes in the 2000 and 4000 ppm groups (NS, $p<0.05$ or 0.01). The serum levels of bilirubin were increased for both sexes in the 2000 and 4000 ppm groups and for the 1000 ppm females. In the necropsy evaluation, the mean absolute and relative spleen weights were increased for both sexes in the 2000 and 4000 ppm groups and for the 1000 ppm females. Histological examination of the spleens revealed the presence of hemosiderosis for both sexes in the 4000 ppm group and for the females in the 1000 and 2000 ppm groups. The incidence of splenic vascular congestion was present in both sexes of the 2000 and 4000 ppm groups and the females in the 1000 ppm groups. In the liver, centrilobular hepatocytic enlargement was noted for both sexes in the 4000 ppm group and for

the males in the 2000 ppm group. Deposits of brown pigment were evident in the Kueffer's cells of the liver for both sexes in the 1000, 2000 and 4000 ppm groups, Similar brown pigment was also observed in the proximal convoluted tubular epithelium of the kidneys of both sexes in the 2000 and 4000 ppm groups and the females in the 1000 ppm group. Effects on the spleen and the pigment deposition in the liver and kidneys were secondary to the toxic effect which the test material had on the red blood cells and their subsequent breakdown. Possible adverse effects: elevated methemoglobinemia; Rat Subchronic Dietary NOEL: (M/F) 300 ppm (23.2 mg/kg/day, (F) 27.8 mg/kg/day) (based upon the reduced mean body weight and food consumption of both sexes in the 1000 ppm group and the treatment related-effects on the red blood cells of the females in the 1000 ppm treatment group). Study supplemental (based in the limited number of animals/sex/group which were included in the study). ([redacted], 1/3/13)

274-0117, 290171 "A repeated dose 30-day oral (diet) toxicity study in rats", supp, rats, O'Neill, T., et al. WIL Research Laboratories, Inc., Ashland, Ohio. 12/27/2002. Project No. WIL-464001. Propanil, Batch No. 2, Aliquot: 21, light brown crystalline solid containing small black particulates, considered 100% pure, was ground and mixed with appropriate amounts of basal diet. The test diets were fed to rats (10M/10F per group) daily at dosage levels of 0 (basal diet only), 300, 500, and 700 ppm for 30 consecutive days (corresponds to 25, 41 and 57 mg/kg/day for males, respectively; and 28, 41 and 67 mg/kg/day for females, respectively). Administration of the test diets was terminated on day 17 due to increased methemoglobin values and recovery from this effect was evaluated. Significant reduction of body weight gain was observed at 500 and 700 ppm group treated male rats, with recovery after dosing termination. Increased methemoglobin values in treated male and female rats were observed from days 5 to 15, in a dose dependent manner. Partial recovery was observed on days 21-30, with a trend towards total recovery. NOEL (No Observed Effect Level): < 300 ppm (25 mg/kg/day for male rats, 28 mg/kg/day for female rats), due to methemoglobin level. Supplemental. ([redacted] & [redacted], 4/4/2016)

Rat 21-Day Repeated Dosing Dermal Toxicity Study

274-0112; 280741; "21-Day Dermal Toxicity Study in Rabbits"; (D.J. Margitich, LJ. Ackerman; Pharmakon Research International, Inc., Waverly, PA; Study No. PH 430-PT-001-89; 3/14/90); The skin of 5 New Zealand White rabbits/sex/group was exposed to 0, 250, 500 or 1000 mg/kg/day Propanil Technical (lot no. and purity of the test material was not included in the report) for 6 hours/day, 5 days per week for 3 weeks. The test material was applied directly to the skin and then moistened gauze patches were placed over the application site. One female in the 250 mg/kg group, one male in the 500 mg/kg group and one female in the 1000 mg/kg group were found dead on days 14, 19 and 15, respectively. The cause of their deaths was not considered to be related to the test material. The mean body weight gain of the 500 and 1000 mg/kg group females was less than that of the control group (NS). Food consumption for these animals was less than that of the control group during the last week of the study (NS). One female in the 1000 mg/kg group demonstrated abnormal gait, abnormal stance diarrhea and flaccid body tone from day 14 onward. Due to the presence of a protozoan infection, it is not possible to ascertain whether the signs exhibited by this animal were related to the treatment or not. There was no apparent treatment-related effects upon the clinical chemistry or hematology parameters. There was no treatment-related effect upon the mean absolute or relative liver, kidney or testes weights. The histopathological data were not included in the study report. Oocysts of the protozoan *Eimeria stiedae* were found in the liver of two animals which resulted in hyperplasia of the bile duct. The protozoan, *Encephalitozoon cuniculi*, was found in the kidneys of 3 animals, causing nephritis in these animals. Moderate meningoencephalitis was evident in one of these animals as a consequence of this protozoan's presence. Periocholangitis was also attributed to this protozoan infection. These lesions presented a complication in assessing the possible treatment-related effects. There were no apparent

adverse effects. Reported Rat 21-day Repeated Dosing Dermal NOEL: (M/F) 1000 mg/kg/day (based upon the assessment that no treatment-related effects were evident for the 1000 mg/kg treatment group); Study unacceptable, possible upgradeable with the submission of documentation of the test material's purity and that the test material in contact with the skin was adequately moistened and the inclusion of the missing appendices in the report. ([redacted], 2/25/15)

Rat 4-Week Inhalation Toxicity Study

274-0122; 323573; "Repeated Dose Inhalation Toxicity (28-Day) Study of Propanil Technical in Rats"; (V. Dalal; Jai Research Foundation, Department of Toxicology, Dist. Valsad, Gujarat, India; Study No. 621-1-01-15577; 5/20/17); Ten Wistar rats/sex/group were exposed to 0, 0.101, 0.393 or 0.823 mg/l (analytical) of Propanil Technical lot no. HN00STM110; purity: 98.2%) for 6 hours/day, 5 days/week for 4 weeks. The MMAD (GSD) ranged between 2.59 to 2.95 (1.55 to 1.68) µm over the course of the exposure period. No deaths resulted from the exposure. The mean body weight gain of both sexes in the two higher exposure groups and the males in the 0.101 mg/l exposure group was less than that of the control group ($p<0.01$ or 0.05). Likewise the mean food consumption of the two higher exposure groups was less than control group values over the course of the study $p<0.01$ or 0.05). In the hematology evaluation, the red blood cell count of both sexes in the 0.101 mg/l group and above was reduced in comparison to the control values ($p<0.01$ or 0.05). The hemoglobin concentration and hematocrit were reduced for both sexes in the 0.823 mg/l group and for the males in the 0.101 and 0.393 mg/l groups ($p<0.01$ or 0.05). The mean reticulocyte count was greater for both sexes in the 0.101 mg/l and above in comparison to the control group values ($p<0.01$ or 0.05). The clinical chemistry evaluation did not reveal any apparent treatment effects. There was no treatment-related effect noted in the urinalysis. The ophthalmological examination did not indicate any treatment-related effect. In the necropsy examination the mean relative lung and spleen weights of both sexes in the 0.393 and 0.823 mg/l groups and the males in the 0.101 mg/l group were greater than the control group values ($p<0.01$ or 0.05). The relative mean thymus weight of the males in the 0.823 mg/l group was less than the control group value ($p<0.05$). In the histopathology examination, an increased incidence of extramedullary hematopoiesis was noted in the spleen of both sexes in the 0.101 mg/l group and above. The bone marrow of both sexes in the 0.101 mg/l group and above demonstrated an increased cellularity. A significant treatment effect on hematopoiesis was identified. Rat 28-Day Inhalation Toxicity NOEL: (M/F) < 0.101 mg/l (based upon the treatment-related effect noted on the hematology parameters and/or the extramedullary hematopoiesis in the spleen and increased cellularity of the bone marrow of both sexes in the 0.101 mg/l exposure group); Study supplemental (not a guideline study). (Moore, 4/13/20)

Dog 4-Week Dietary Toxicity Study

274-0001; 5111; Groups of 1 male and 1 female mongrel dog were exposed to 0, 0.2, 1.0 and 5.0% Stam F-34 in diets daily for 4 weeks. Motality: the male dog at 5.0% group died at the start of the 4th week, the female dog in this group switched to control diet at the time. Decreased body weight gain and food consumption was observed in 1.0 and 5.0% groups male and female dogs. The author recommended the following dose levels for the two-year study in dogs: 0, 100, 600 and 3000 ppm, with the high dose subject to adjustment depending on the animals' reactions during the early weeks of feeding. Study supplemental. ([redacted] and [redacted]. 7/18/2014)

Dog 8-Week Dietary Toxicity Study

274-0037; 152684; "8-Week Dietary Range-Finding Toxicity Study in Dogs with Propanil"; (E.C. Tompkins; WIL Research Laboratories, Inc., Ashland, OH; Project No. WIL-141008;

1/13/93); Two beagle dogs/sex/group received 0, 1600, 2800 or 4000 ppm of Propanil technical (batch no. 01; purity: 97.2 to 98.3%; (reported in rec. no. 152683)) in the diet for 8 weeks ((M) 0. 57, 93, 114 g/kg/day, (F) 0, 44, 99, 81 g/kg/day). The mean body weights of both sexes in the 4000 ppm group were less than those of the control throughout the study. The mean food consumption of these animals was also less than that of the control group. In the hematology evaluation, the white blood cell counts for the 2800 and 4000 ppm females were greater than that of the control group by the end of the treatment period ($p<0.01$). The red blood cell count and the hematocrit and MCHC values for both sexes in the 2800 and 4000 ppm groups and for the 1600 ppm females were lower than those of the control group during the treatment period. The MCV values for both sexes in all of the treatment groups were greater than those of the control group. The percentage of reticulocytes was elevated for both sexes in the 2800 and 4000 ppm groups after 4 weeks of treatment and for the females in all of the treatment groups after 7 weeks of treatment. The methemoglobin levels in the blood of both sexes in all of the treatment groups was elevated throughout the study (NS, $p<0.05$ or 0.01). In the clinical chemistry evaluation, the serum albumin and total protein levels for both sexes in the 4000 ppm group and for e 2800 ppm group were greater than the control values over the course of the study. The total bilirubin concentration in the serum was greater for both sexes in all of the study groups in comparison to the control levels. The urea nitrogen levels of both sexes in the 2800 and 4000 ppm groups were greater than those of the control group throughout the study. The creatinine and cholesterol concentrations in the serum of the males in the 2800 and 4000 ppm groups demonstrated a dose-related increase. The mean relative liver weights of the males in all of the treatment groups and the females in the 4000 ppm group were greater than those of the control. The mean relative spleen weights of both sexes in the 4000 ppm group were greater than the control values. However, no lesions were evident in these organs when they were examined histologically. The females in the 2800 and 4000 ppm groups exhibited myeloid hypercellularity in the bone marrow. This result corresponded to the increased white blood cell counts which were noted for these animals. Hematopoietic effect of methemoglobinemia. Dog Subchronic Dietary Toxicity NOEL (M/F) < 1600 ppm ((M) < 57 mg/kg/day, (F) < 44 mg/kg/day) (based upon increased levels of methemoglobinemia of both sexes in the 1600 ppm group). Study supplemental (not a guideline study). ([redacted], 1/11/13)

Dog Subchronic Dietary Toxicity Study

274-0038, 152685 “13-Week oral range-finding toxicity study in dogs with propanil”, supp, dogs, Tompkins, E., et al. WIL Research Laboratories, Inc., Ashland, Ohio. 10/20/92. Project No. WIL-141006. Propanil, light purple granular or light brown to dark purple solid, considered 100% pure, was ground and mixed with appropriate amounts of basal diet. The test diets were fed to dogs (2M/2F per group) daily at dosage levels of 0 (basal diet only), 1000, 5000, 10,000 and 20,000 ppm for a week (corresponds to 45, 225, 450 and 900 mg/kg/day, respectively). Administration of the test diets was discontinued for a week due to substantial drops of test diet intake at 5000, 10000 and 20000 ppm groups. Administration of the test substance was resumed in capsulated form at concentrations of 0, 45, 225, 450 and 900 mg/kg/day the following week. Significant reduction of body weight gain and food consumption was observed at 225, 450 and 900 mg/kg/day group dogs before they were found dead or sacrificed moribund within 2 weeks since the start of the capsule dosing. Enlarged gall bladder and icteric (affected with jaundice) appearance was observed in these animals at gross necropsy. Hematology and serum chemistry examinations of these dogs showed increased white blood cell, alanine transferase, aspartate transferase following the start of the capsulated dosing. A slightly lowered body weight gain was observed in the 45 mg/kg/day group dogs. The study was terminated in week 8 due to high mortality in the high dose groups. A dietary concentration of 4000 ppm was considered to be the maximum dose for the next dietary range-finding study in dogs. Supplemental. ([redacted] & [redacted], 1/8/13)

Mouse 2-Week Dietary Toxicity Study

274-0035; 152681; "Stam Herbicide – Two Week Range-Finding Dietary Study in Mice"; (L.J. Didonato, G. Cruszan; Toxicology Department, Rohm and Haas Company, Spring House, PA; Study No. Study No. 78P-34; 9/4/79); Five COBS-CD1 mice/sex/group received 0, 250, 1250, 6250 or 31250 ppm of Stam technical (lot no. LSPP3-0031R; purity: 98%) in the diet for 2 weeks ((M) 0, 110.5, 571, 2949, 15899 mg/kg/day, (F) 0, 114.5, 588, 2769, 18799 mg/kg/day). One male and one female in the 31250 ppm treatment group died during the study. Both sexes in the 1250 ppm treatment group and above demonstrated reduced body weight gain and/or body weight loss in a dose-related manner. The mean food consumptions of both sexes in the 31250 ppm group and the females in the 6250 ppm group were less than the control values over the course of the study. In the 31250 ppm treatment group, cyanosis and lethargy were noted as clinical signs. These study data indicated that a treatment level as great as 31250 ppm was too excessive for a longer term dietary study. Study supplemental. ([redacted], 1/4/13)

Mouse Subchronic Dietary Toxicity Study

274-0035; 152680; "Stam (R): A Three-Month Dietary Study in Mice"; (J.E. McLaughlin; Toxicology Department, Rohm and Haas Company, Spring House, PA; Report No. 82R-065; 3/24/83); Ten COBS-CD1 mice/sex/group received 0, 25, 200, 1600 or 12800 ppm of STAM (R) (propanil technical) (lot no. LSPP 3-0031R; purity: 98%) in the diet for 13 weeks (reported a.i. uptake (calculated by reviewer) (M) 6.55, 48.8, 442, 5325 mg/kg/day, (F) 9.48, 77.7, 566, 6467 mg/kg/day (note: these values are high due to excessive food consumption reported for study animals). No treatment-related deaths occurred during the study (note; one control male and one 12800 ppm male escaped from their cages, thereby removing themselves from the study). The mean body weights of both sexes in the 12800 ppm group were less than the control value throughout the treatment period ($p<0.05$ or 0.01). The mean food consumption of these animals was actually greater than that of the control group. The mean red blood cell counts of both sexes in the 12800 ppm group were less than those of the control group ($p<0.05$). There was no treatment-related effect on the clinical chemistry parameters which were assayed (total protein, blood urea nitrogen, and SGPT). Urinalysis did not reveal any treatment-related effects upon any of the parameters of interest. The hepatic O-demethylase and total mixed function oxidase activities were elevated 2 to 4 fold for both sexes in the 12800 ppm group. In the necropsy examination, the blood, spleen and liver of both sexes in the 12800 ppm group exhibited a dark color. This dark coloring was also evident in the spleen and liver of both sexes in the 1600 ppm group. The mean relative liver weights of both sexes in the 12800 ppm group and the females in the 1600 ppm group were greater than the control values ($p<0.01$). The mean absolute and relative spleen weights of both sexes in the 1600 and 12800 ppm groups were greater than those of the control values ($p<0.01$). The mean absolute and relative ovaries weights of the 12800 ppm females were less than the control values ($p<0.05$ or 0.01). In the histopathological evaluation, hepatocytic pleomorphism was noted in the livers of the both sexes in the 1600 and 12800 ppm groups. Pigment laden Kupffer cells were also evident in the livers of both sexes in the 12800 ppm group and the males of the 1600 ppm group. No apparent treatment-related lesions were noted in the spleen of the treated animals. Mouse Subchronic Dietary NOEL: (M/F) 200 ppm ((M) reported 48.8 mg/kg/day, (F) reported 77.7 mg/kg/day) (based upon increased liver and spleen weights and lesions in the livers of both sexes in the 1600 ppm treatment group); Study supplemental (study was incomplete in data submission and did not include an ophthalmological examination). ([redacted], 1/9/13)

274-0036; 152682; "13-Week Dietary Range-Finding Study in Mice with Propanil"; (E.C. Tompkins; Wil Research Laboratories, Inc., Ashland, OH; Study No. WIL-141009; 1/13/93); Ten CD-1 mice/sex/group received 0, 400, 650, 900 or 1150 ppm of Propanil technical (batch no.

01; purity not reported) in the diet for 13 weeks ((M) 0, 71, 120, 166, 200 mg/kg/day, (F) 0, 98, 155, 238, 266 mg/kg/day). No deaths resulted from the treatment. There was no apparent treatment-related effect upon the mean body weights or food consumption of the study animals. The red blood cells were the primary target site of toxicity. Methemoglobin was elevated at all of the treatment levels. As a consequence, the hemoglobin concentration and hematocrit for the 1150 ppm males were less than the control levels ($p<0.05$). In the histopathological examination, the incidence of megakarycytosis was increased in the spleen of both sexes in the 1150 ppm group ((M) 0: 0.10 vs. 1150: 8/10, (F) 0: 1/10 vs. 1150: 3/10). Hemosiderin pigment in the spleen was also elevated for both sexes in all of the treatment groups. Hematopoietic effect of an elevated level of methemoglobin; Mouse Subchronic Dietary NOEL: (M/F) < 400 ppm (M: < 71 mg/kg/day, F: < 98 mg/kg/day) (based upon the elevated level of methemoglobin in the red blood cells of the 400 ppm treatment group); Supplemental Study (protocol did not fully conform to guideline requirements for a subchronic toxicity study). ([redacted], 12/31/12)

Rabbit 14-Day Repeated Dosing Dermal Irritation Study

274-0001, 5109; A group of 6 adult male rabbits were exposed to average of 30 mL of Stam F-34, 3 # E. C. at 1:9 dilution on shaved skin around the trunk daily for 14 days, using a cotton cloth 6" x 12" soaked with test material. Very slight scaling on the ventral surface of 4 rabbits on the 7th day was observed. Diarrhea was observed in 4/6 rabbits starting on the 7th day, and persisted for 2-3 days. The study is deemed supplemental due to absence of individual animal data. ([redacted], and [redacted]. 7/17/2014)

CHRONIC STUDIES

Chronic, rat

** 018 132825, "Propanil Technical, Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats", (M.E. Bellringer, Huntingdon Research Centre, Study No. PTF 3, 7/1/94). Propanil (purity = 96.5-98.5%) was fed in diet to Crl:CD(SD)BR rats (50/sex/dose) at 0, 200, 600 or 1800 ppm for 104 weeks and to 20/sex/dose for 52 weeks. Chronic NOAEL = 200 ppm (Incidence of discolored incisors were increased in females at 1800 ppm. Body weight decreased 13% & 23% (M) and 20% & 45% (F) at 600 & 1800 ppm, respectively. Food consumption was decreased intermittently in both sexes at $\geq$ 600 ppm. PCV, RBC and Hb values were intermittently significantly decreased in females at $\geq$ 200 ppm throughout the study and were significantly decreased in males at $\geq$ 600 ppm through week 52. Methemoglobin values were increased for both sexes at $\geq$ 600 ppm and also intermittently in females at 200 ppm. Bilirubin and urea nitrogen levels were intermittently increased in both sexes at 1800 ppm. Triglycerides were reduced in both sexes at $\geq$ 600 ppm. Spleen weight was increased in both sexes at $\geq$ 600 ppm. Liver weights (F) and testes + epididymide weights were increased at 1800 ppm. Enlarged spleen ($\geq$ 600 ppm, M; 1800 ppm, F), congested dark spleen (1800 ppm, M & F), and testicular masses ($\geq$ 600 ppm) were observed grossly. Livers in both sexes showed increased granulomatous inflammation, pericholangitis, brown pigmented Kupffer cells, bile duct hyperplasia, eosinophilic and/or basophilic hepatocytes and centrilobular and/or generalized hepatocyte enlargement at $\geq$ 600 ppm. Testicular focal interstitial hyperplasia and marked tubular atrophy were observed at 1800 ppm. Increase in absent spermatozoa, reduced secretion and prostate atrophy occurred at $\geq$ 600 ppm. Hemosiderin was observed in the spleen and kidneys of both sexes at $\geq$ 600 ppm.) Possible oncogenic effect: testicular interstitial cell tumors and hyperplasia were increased at 1800 ppm. Females showed increased hepatocellular adenomas at 1800 ppm. ACCEPTABLE ([redacted] & [redacted], 2/4/98).

Chronic, dog

** 016 129293, "One Year Oral Toxicity Study in Dogs with Propanil", (E.C. Tompkins, WIL Research Laboratories, Inc., WIL-141007, 9/29/93). Propanil (purity = 96.9-98.5%) was fed in diet to Beagle dogs (4/sex/dose) at 0, 200, 1600 or 3200 ppm for 12 months. NOEL < 200 ppm (Clinical findings increased (soft stool, decreased defecation and urination and increased mucoid feces in females), primarily at ≥ 1600 ppm. Food consumption and body weight gain were decreased in both sexes at 3200 ppm. Absolute and relative liver and thyroid/parathyroid weights were increased in both sexes and thymus weights were decreased in both sexes at 3200 ppm. Several hematological changes (increased methemoglobin and Heinz bodies and decreased mean RBC, hemoglobin and hematocrit) in both sexes, observed at all doses, indicated hemolysis and methemoglobinemia were occurring. At all dose levels there was increased hemosiderosis (liver, kidney and bone marrow), observed in both sexes.) NOAEL = 200 ppm/day. Hematopoietic effect: reduced RBC and Hb and hemosiderin in the kidneys; changes were apparent for mid and high dose groups and to a lesser extent for the low dose group. ACCEPTABLE. ([redacted] & [redacted], 2/23/98).

Oncogenicity, rat

See Chronic Toxicity, Rat above.

Oncogenicity, mouse

** 019 134723: "24-Month Dietary Oncogenicity Study with Propanil", (Tompkins, E.C., WIL Research Laboratories, Inc., WIL-141011; 9/9/94). Propanil (purity = 97%) was fed in diet to Crl:CD-1[7](ICR)BR mice (80/sex/dose) for 104 weeks at 0, 500 and 1000 ppm (M: 74.9 & 150 mg/kg/day; F: 88.6 & 174.1 mg/kg/day). Twenty/sex/dose were sacrificed at 52 weeks. Chronic NOEL < 500 ppm/day (There was an increase in clinical signs in both sexes at ≥ 500 ppm. Body weights and food consumption were significantly decreased throughout the study in both sexes at 1000 ppm. Methemoglobin and reticulocyte count were increased and RBC was decreased at 1000 ppm. Mean corpuscular volume (both sexes at 1000 ppm) and incidence in Heinz Bodies (males at ≥ 500 ppm) were also affected. Females had significantly increased absolute and relative spleen weights at interim sacrifice at 1000 ppm. Weights remained increased at termination, although not significantly when compared to control.) NOEL = 500 ppm/day: Hematopoietic effect: methemoglobinemia and Heinz Bodies; oncogenic effect: increased incidence of malignant lymphoma. ACCEPTABLE. ([redacted] & [redacted] 2/27/98).

**274-0113, 0116 280742, 290170 "Twenty-Four Month Dietary Oncogenicity Study in Mice, Stam Technical"; 857; Rat; Weatherholtz, W.M, Hazleton Laboratories America, Inc., Vienna, VA, Report No. 82rc-68; 12/3/83; Six groups of CD-1 mice were included in this study. There were 2 control cohorts of 66 mice/sex each. Three treatment groups of 80 mice/sex/group received 5, 30 or 180 ppm of Stam Technical (lot no. LSPP3-0031R; purities: 98.0%) (Groups 3, 4 and 5) in the diet for 2 years. A sixth group of 80 mice/sex received 180 ppm of Stam Technical (lot no. 9287, purity: 85.4%) in the diet for 2 years ((M) 5 ppm: 0.71 mg/kg/day, 30 ppm: 4.39 mg/kg/day, 180 ppm: 26.1 mg/kg/day, 180 ppm: 26.2 mg/kg/day, (F) 5 ppm: 0.88 mg/kg/day, 30 ppm: 5.35 mg/kg/day, 180 ppm: 32.4 mg/kg/day, 180 ppm: 31.5 mg/kg/day). There was no treatment-related effect on the survival of the animals. The mean body weights and food consumption were not affected by the treatment. In the hematological evaluation, there was no treatment-related effect on any of the parameters. Particularly, there was no increase in the percentage of methemoglobinemia. In the histopathological examination, an increase in the incidence of centrilobular hepatocellular enlargement was noted in the livers of the males in the 180 ppm group (Group 6). The severity of the hepatitis exhibited by these animals was also increased over that of the control animals. The males in the 180 ppm group (Group 6) also demonstrated an increased incidence of myocarditis. An increase in the

incidence and severity of retinal degeneration was reported for the males in this group. The increased presence of regenerative epithelium in the kidneys of both sexes in the 180 ppm group (Group 6) was noted. Increased concentrations of hemosiderin pigment was evident in the spleens of both sexes in the 180 ppm group (Group 5). The females in the 180 ppm group (Group 6) also exhibited an increased incidence of thyroiditis. Overall, treatment with the less pure technical grade test material resulted in an increased incidence of histological lesions in the liver, heart, eyes, kidneys and thyroid gland. Techncial grade propanil (98.0%) gave some evidence of increased hemosiderin pigment deposition in the spleen. Although no methemoglobinemia was evident at a treatment level of 180 ppm, this increase in hemosiderin pigment may have been an indication of incipient hematological effects. Possible ophthalmological effect: retinal degeneration in the eye (propanil technical, 85.4%). No oncogenicity was evident. No justification of treatment levels was provided. Mouse Chronic Dietary NOEL (Propanil Technical (98.0%): (M/F) 30 ppm ((M) 4.39 mg/kg/day, (F) 5.35 mg/kg/day) (based upon the increased hemosiderin pigment deposition in the spleens of both sexes in the 180 ppm group); Summary Report (submitted study report was incomplete with missing pages and tables). (Moore, 3/1/15) Acceptable (upon the submission of the missing pages. [redacted] & [redacted], 4/12/16).

GENOTOXICITY

Gene mutation

014 112966, "Mutagenicity of Chloroaniline/Lignin Metabolites in the *Salmonella*/Microsome Assay", (K.A. Rashid, M. Arjmand, H. Sandermann & R.O. Mumma, Journal of Environmental Science Health, B2(6), 721-729 [1987]). 3,4-DCA, a metabolite of propanil, was used at 0, 1, 10, 100 and 1000 µg/plate (+/- S-9 metabolic activation) on *Salmonella typhimurium* strains TA98 and TA100. No evidence of mutagenicity was observed is this study. No repeat study was performed. Inadequate number of *Salmonella* strains tested and insufficient information. UNACCEPTABLE, not upgradeable. (no worksheet). These data are supplemental. [redacted] & [redacted], 2/11/98).

** 025 138205: "Microbial Mutagenicity Test of DCPA Propanil"; (Shirasu, Y., Moriya, M. and Koyashiki, R.; Toxicology Division, Institute of Environmental Toxicology; February 14, 1980). Propanil (purity = 98%) was used at 0, 20, 100, 200, 500, 1000, and 2000 µg/disk with *B. subtilis* strains (H17 and M45) in a rec assay and at 0, 1, 5, 10, 50, 100, 500, 1000, and 5000 µg/plate (+/- S-9) with *Salmonella typhimurium* strains (TA1535, TA1537, TA1538, TA98 & TA 100) in reversion assays and *Escherichia coli* strain WP2 *hcr* in reversion assays, to test for DNA damage. No evidence of mutagenicity was observed in any test. ACCEPTABLE. ([redacted] & [redacted] 2/6/98).

** 022 138202 "Stam Technical CHO/HGPRT Gene Mutation Assay", (Kruszewski, F.H., K.L. McCarthy, and M.J. Byers; Report No. 83R-142; January 12, 1984). Stam Technical (purity = 87.8%) was evaluated at 0, 15, 75, 125 or 150 µg/ml (no S-9; 18-20 hour exposure or 0, 100, 115, 130 or 140 ug/ml (with S-9; 5 hour exposure) for mutagenic activity in Chinese ovary (CHO) cells. There was no increase in mutagenic activity using the CHO test system). ACCEPTABLE. ([redacted] & [redacted], 2/4/98).

Chromosome damage

** 274 - 091 182113 "Mammalian Erythrocyte Micronucleus Test", (Gudi, R., Krsmanovic, L.; BioReliance Laboratory, Rockville, MD; Study #: AA36HB.123.BTL; 6/5/01). Propanil technical (97.1% pure) was administered to ICR mice (5/sex/dose/time point) in a single intraperitoneal injection at 0 (corn oil), 100, 200, 400 mg/kg. At 24 hours post-dosing, 5/sex/dose were

sacrificed for all doses, including cyclophosphamide (positive control, 50 mg/kg) and control. At 48 hours post-dosing, 5/sex/dose at 0 and 400 mg/kg were sacrificed. After treatment, 1/15 females died at 400 mg/kg. Clinical signs observed on the days following dosing included: lethargy and piloerection in both sexes at 100, 200 and 400 mg/kg (all doses). In addition, prostration and irregular breathing in both sexes and crusty eyes in females were observed at 400 mg/kg. There was no treatment-related increase in micronuclei at any dose. ACCEPTABLE (some deficiencies). ([redacted] & [redacted], 1/29/03).

023 138203: "Stam(pede) Cytogenetic Study in Mice", (O=Neil, P.J., P.L. McLeod, K.L. McCarthy; Rohm & Haas Company, Toxicology Dept.; Report No. 82R-255, November 11, 1983). Stampede Technical (87.8% pure) was administered p.o. in a single dose to male Charles River CD-1 mice (24/dose) at 0 (corn oil), 26.5, 106, and 265 mg/kg. Bone marrow slides (chromosomal evaluation) were prepared from eight animals/group/sacrifice scheduled at 6, 24, and 48 hours post-dosing. An additional 8 animals/dose were treated po daily for five days and were sacrificed 6 hours after the final dose. A decrease in spontaneous motor activity was observed at $\geq$ 106 mg/kg. At 265 mg/kg, lethargy was observed on Day 1. Piloerection was observed at $\geq$ 106 mg/kg. NOEL = 26.5 mg/kg (Decreased motor activity, lethargy and piloerection occurred at $\geq$ 106 mg/kg. There was no increase in chromosomal aberration.) Not acceptable (Only one sex was tested without justification.) ([redacted] & [redacted], 2/11/98).

DNA damage or miscellaneous effects

274 - 092 182114 "Unscheduled DNA Synthesis in Mammalian Cells *In Vitro*", (San, R.H.C., Reece, J.D.; BioReliance, Rockville, MD; Laboratory Study Number AA36HB.380.BTL; 6/5/01). Propanil technical (purity = 97.1%) was used on primary rat hepatocytes at 1.0, 5.0, 25, 50 and 100 _g/ml to evaluate the potential for induction of unscheduled DNA synthesis *in vitro* with autoradiography (3 replicates/dose; 1 trial). Propanil technical, at doses tested, did not significantly increase the incidence in unscheduled DNA synthesis. The study is currently unacceptable but is possibly upgradeable with submission of data for nuclear and cytoplasmic grain counts for each coverslip. ([redacted] & [redacted], 1/29/03).

024 138204 "*IN VITRO* Microbiological Mutagenicity and Unscheduled DNA Synthesis Studies of Eighteen Pesticides", (Simmon, V.F., SRI International, Menlo Park, CA; 10/79). In this study, propanil (88%) was used at 10, 50, 100, 500, 1000, and 5000 µg/plate with and without metabolic activation (S-9) in a mutagenicity assay with *Salmonella typhimurium* (TA1535, TA1537, TA1538, TA98 and TA100) and *Escherichia coli (WP2).* Propanil was toxic to *S. typhimurium* strains at 1000 µg/plate and did not increase histidine revertants at any dose level tested in three experiments. Propanil did not increase tryptophan revertants in a test with *E. coli (WP2).* In another assay, Propanil was tested *in vitro* at concentrations from 0.01 to 5.0% (+/- S-9) using *Saccharomyces cerevisiae* (D3). Propanil at $\geq$ 1.0% (+/- S-9) was toxic to the test organism. Propanil did not significantly increase mitotic recombination at the doses used in two experiments. Propanil was also tested at 0.1 to 1000 µg/ml (+/- S-9) using human fibroblasts (WI-38 cells). Precipitation was observed at 1000 µg/ml. Increases in ^{3}HTdR incorporation were not observed at tested doses. Unacceptable (insufficient details and data reporting). Not upgradeable. ([redacted] & [redacted], 2/9/98).

REPRODUCTIVE TOXICITY, RAT

** 065 162957 "A Dietary Two-Generation Reproductive Toxicity Study of Propanil in Rats", (Stump, D.G., WIL Research Laboratories, Ashland, OH; Study #: WIL-141013; 7/1/98). Propanil (purity = 98.4% aliquot #6 & 98.3% aliquot #7) was fed in diet to Sprague-Dawley Crl:CD^{7}BR (30/sex/dose/generation) at 0, 60, 150 and 600 ppm for 2 generations (pre-mating F0 through weaning of F2). Parental Systemic NOEL = 150 ppm (F0 females showed an

increased occurrence of hair loss at 600 ppm. F0 & F1 adults of both sexes showed decreased body weights at 600 ppm. During gestation and lactation F0 & F1 female body weights were significantly decreased at 600 ppm. F0 showed significantly increased food consumption (g/kg/day) throughout the study. F0 & F1 females at 600 ppm showed significantly decreased food consumption throughout gestation and lactation. F0 & F1 spleen weights were significantly increased in females at 600 ppm. F0 relative right testes weights and relative brain weights (both sexes) were significantly increased at 600 ppm. Relative female F0 ovary and adrenal glands were significantly increased at 600 ppm. F1 absolute liver and kidney weights were significantly decreased at 600 ppm in both sexes. F1 males showed significantly increased relative (to body) brain, kidney, seminal vesicle/coagulating gland, both testes, left cauda epididymus, adrenal gland and spleen weights at 600 ppm. Relative F1 brain, spleen, ovaries and adrenal glands were increased in females at 600 ppm. F1 liver weights were decreased in both sexes at 600 ppm. Female F1 relative weights for liver and pituitary were decreased and spleen weights were increased at 600 ppm. Both sexes of both generations showed increased spleen pigmented macrophages at 600 ppm (dose-related increase in severity). Reproduction NOEL = 150 ppm (The left epididymus showed decreased sperm count at 600 ppm in F0 & F1. The F1 left testis showed decreased sperm count at 600 ppm.) Pup NOEL = 150 ppm (F1 weanling males at 600 ppm showed significantly increased relative testes and liver weights. There was a significant increase in age in F1 at balanopreputial separation observed in males at 600 ppm.) Acceptable.

042 152692 "Three Generation Reproduction Study on Rats Receiving Stam F-34 in Their Diet" (Borzelleca, J.F., Ambrose, A.M. & Larson, P.S., Department of Pharmacology, Medical College of Virginia, VA; Report #: 66RC-1048; 2/7/66). Stam F-34 (Propanil; Lot #: 9315; concentration not specified) was fed in diet to Wistar rats (25/sex/dose) for 11 weeks at 0, 100, 300 and 1000 ppm. Subsequently, 20/sex/dose (F0 parental generation) were mated to produce the F1a generation. This procedure was used for 3 generations (2 litters/generation). Not acceptable (No effects at any dose in any generation. An MTD was not achieved.) Not upgradeable (Too many missing parameters. The study was performed prior to FIFRA Guidelines.) [redacted], 7/23/98.

DEVELOPMENTAL TOXICITY

Rat

** 026, 070 138206, 166892 "Original Study: Teratological Evaluation of Stam Technical in the Albino Rat; Supplemental: Snell Project 310065-008: Evaluation of Stam Technical in the Albino Rat (Teratology Study)", (Original Study: Gallo, M.A., Rohm and Haas Company, Toxicology Dept., Snell Project #10065-008; Rohm and Haas Company Report #: 81RC-027B; 2/29/80; Supplemental Study: The Propanil Task Force (c/o McDermott, Will & Emery), Washington, DC; 2/1/99). Stam Technical (purity = 85.4%) was administered by gavage at 0 (corn oil), 0.8, 4, 20 and 100 mg/kg to mated Sprague -Dawley rats (20/dose) during gestation days 6 through 15. Maternal NOEL = 100 mg/kg/day. Developmental NOEL = 100 mg/kg/day (Minimal effects were observed as decreased fetal weights at 100 mg/kg but they were not statistically significant.) Acceptable, based on submitted rangefinding/dose justification data. No adverse effect. ([redacted], 8/10/00).

Rabbit

** 027, 070 138207, 166895 "Stam Technical Teratogenicity study in Rabbits, Report Supplement: Rohm and Haas Report NO. 81RC-015B", Original Report: Florek, C.M.; Argus Research Laboratories, Inc., Argus Project 018-001, Rohm and Haas Report No. 81RC-015; 12/17/80; Supplement: O=Neill, P.J.; Rohm and Haas Company, Toxicology Dept., Spring House, PA; 6/4/93). Stam Technical (purity = 85.4%) was administered to artificially

inseminated New Zealand white rabbits (20/dose) by gavage at concentrations of 0 (corn oil), 4, 20 and 100 mg/kg/day (approximately 4.7, 23.4 & 117.1 mg/kg/day) during gestation days 6 through 18. Maternal mortality was 25% at 100 mg/kg/day. Maternal NOEL = 20 mg/kg/day (There was increased mortality and decreased body weight observed at 100 mg/kg/day.) Developmental NOEL >100 mg/kg/day (There were no significant fetal effects observed at any dose.) This study is now complete and has been upgraded to acceptable. [redacted] 8/10/00.

NEUROTOXICITY

Acute neurotoxicity, rat

** 274-0122; 323574; "Acute Neurotoxicity Study of Propanil Technical in Wistar Rats"; (K.N. Shah; Jai Research Foundation, Department of Toxicology, Dist. Valsad, Gujarat, India; Study No. 498-1-02-15800; 7/26/17); Ten Wistar rats/sex/group were dosed orally by gavage with 0 (vehicle: aqueous 0.5% carboxymethyl cellulose), 100, 1000 or 2000 mg/kg of Propanil Technical (lot no. HN00STM110; purity: 98.2%). The functional domains of the study animals were assessed in the Functional Observation Battery (FOB) and motor activity evaluations prior to study initiation and on study days 1 (8 hour post-dose), 8 and 15. Two females in the 2000 mg/kg group were found dead on the day of dosing. The necropsy examination revealed that they had been misgavaged. One female in the high dose group was euthanized on day 3 due to moribundity and one female in the 1000 mg/kg group was found dead on day 3. In the clinical observations, on the day of dosing, 7 males and 8 females in the 2000 mg/kg group and 6 females in the 1000 mg/kg group demonstrated lethargy. Weakness was evident in one female from the 1000 and 2000 mg/kg groups on the 2nd day, persisting in one female in the high dose group on the 3rd day. Catalepsy was identified in one female in the 1000 mg/kg group on day 2 and in one female in the 2000 mg/kg group on day 3. The mean body weights of both sexes in the 1000 and 2000 mg/kg treatment groups were less than the control group values through day 4 ($p<0.01$ or 0.05). The mean food consumption of both sexes in the 1000 and 2000 mg/kg groups was less than that of the control group ($p<0.01$ or 0.05) through day 7. In the FOB on day 1, in the open field assessment, females in the 1000 and 2000 mg/kg group demonstrated slight to moderately impaired gait and mobility. The arousal level for animals of both sexes in these two groups was also low or very low in contrast to the control group animals. The mean number of rearings of both sexes in these groups was also less than the control group values ($p<0.01$). The sensory reactivity of both sexes in these groups was diminished. The mean forelimb grip strength values of both sexes in the 1000 and 2000 mg/kg groups were less than the control group values ($p<0.01$). The mean hindlimb grip strength manifested by both sexes in the 2000 mg/kg and the females in the 1000 mg/kg was less than that of the control group ($p<0.05$). In the motor activity assessment on day 1, the activity, both fine and ambulatory, of both sexes in the 1000 and 2000 mg/kg groups was reduced in comparison to that of the control group ($p<0.01$). The mean activity (both fine and ambulatory) of the females in the 100 mg/kg group was also less than that of the control group during the first twenty minutes of the assessment period ($p<0.01$). However, the reduced motor activity in the low dose group was not supported or correlated with other muscular activities (rearing counts or arousal). Therefore it was not considered to be treatment-related. The histopathological examination did not reveal any treatment-related effects. Rat Acute Neurotoxicity NOEL: 100 mg/kg (based upon treatment-related effects on the neuromuscular coordination and sensory reactivity domains and in the motor activity assessment of both sexes in the 1000 mg/kg group); No positive control study data were submitted nor are on file with DPR from this laboratory to substantiate the competency of the staff to perform the neurological assessments required for the study; however, the study data were sufficient to document a neurotoxic response in the study animals, thereby supporting the staff's abilities to identify neurologically important endpoints; Study acceptable. [redacted], 4/7/20)

90-day neurotoxicity, rat

Study not submitted.

Developmental neurotoxicity, rat

Study not submitted.

IMMUNOTOXICITY

** 274-0118 290172, “A splenic antibody study in rats following dietary exposure to propanil for 28 days”; 857; Rat; WIL Research Laboratories, Inc., Ashland, Ohio, Padgett, E., Study No. WIL-141014: 12/7/06; Propanil, Lot No.SJ0588R301, 99.7% pure, an irregular, off-white flake was administered to 10 /sex rats by diet at 0, 50, 200 or 600 ppm [mean test substance intake: 4, 16, and 48 mg/kg/day, respectively for 50, 200 or 600 ppm group male rats; 5, 19 and 56 mg/kg/day, respectively for 50, 200 or 600 ppm group female rats] for 28 days. An additional group of 10/sex rats were given control diet for 24 days followed with 50 mg/kg of cyclophosphamide via intraperitoneal injection for 4 consecutive days before euthanasia. All rats were administered 0.5 mL, 2 x 10^8 sRBC (sheep Red Blood Cells) via intravenous administration once 4 days before euthanasia (on day 25 of study). The rats were observed for vitality, general appearance, body weight and food consumption. At the end of the 28-day treatment period, all rats were euthanized by carbon dioxide asphyxiation, and organ weights were measured. The splenocyte suspension was prepared and its viability was tested. A primary IgM response to sRBC was enumerated using a modified hemolytic plaque assay, permitting the number of antibody-forming cells (AFC) present in the whole spleen to be calculated. No mortality. Reduction of body weight gain in high dose group male and females, changes in hematology parameters, including decreased hemoglobin, red blood cells, hematocrit and APTT, increased absolute and relative reticulocyte, in high dose male and females, and decreased hemoglobin, red blood cells, and hematocrit in 200 ppm group females were observed at the end of the treatment. Positive control group animals demonstrated decreased body weight gain, decreased hematology parameters including platelet, absolute neutrophil, lymphocytes, monocytes, eosinophils, basophils, and large unstained cells. Decreased spleen and thymus weights, decreased spleen cells and splenic antibody forming cells were observed in positive control group animals. Test substance treatment did not induce changes in spleen cell numbers or the humoral immune responses evaluated in the IgM antibody-forming cell response to the T-dependent antigen, sheep erythrocytes. NOEL (No Observed Effect Level) for immunotoxicity: 600ppm (48 and 56 mg/kg/day for male and female rats, respectively) after 28 day treatment. Acceptable ([redacted] & [redacted], 4/12/16).

ENDOCRINE DISRUPTOR STUDIES

Study not submitted.

SUPPLEMENTAL STUDIES

Study not submitted.

DATA GAP STATUS

Combined, rat:	No data gap, testicular tumors, hepatocellular adenomas
Chronic toxicity, dog:	No data gap, hematolytic anemia, methemoglobinemia
Oncogenicity, mouse:	No data gap, malignant lymphoma, methemoglobinemia, retinal degeneration
Reproduction, rat:	No data gap, no significant effect
Developmental toxicity, rat:	No data gap, no significant effect
Developmental toxicity, rabbit:	No data gap, no significant effect
Gene mutation:	No data gap, no significant effect
Chromosome effects:	No data gap, no significant effect
DNA damage:	Data gap, inadequate study, no significant effect
Neurotoxicity:	No data gap, neuromuscular coordination, sensory reactivity affected.