APPENDIX M: PROPANIL HED SUMMARY OF DATA [HED PROPANIL HUMAN HEALTH RISK ASSESSMENT (REVISED) 2002]

Table 1. Acute Toxicity of Propanil, Technical

Guideline No.	Study Type	Results	Toxicity Category
81-1	Acute Oral (Rat)	LD_{50} = 1080 mg/kg	III
81-2	Acute Dermal (Rabbit)	LD_{50} > 2000 mg/kg	IV
81-3	Acute Inhalation (Rat) STAM 80G (78.3% a.i.)	LC_{50} = 6.1 mg/L	IV
81-4	Primary Eye Irritation	Iritis, conjunctivitis present in all rabbits, cleared by day 14; corneal opacity cleared by 4 days	II
81-5	Primary Skin Irritation	Slightly irritating P.I.I. = 0.2/4.0	IV
81-6	Dermal Sensitization	Negative	N/A
81-8	Acute Neurotoxicity	Not required	

Table 2. Toxicity Profile

Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
SUBCHRONIC TOXICITY STUDIES		
870.3100 90-Day oral toxicity rodents (Wistar rat)	MRID 00015459, 00046259 (1961) 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) 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) 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) 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 non-rodents (NZW rabbit)	MRID 00058589 (1980) 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)/ Doses	Results
870.3800 Reproduction and fertility effects (SD rats, 2-generations)	MRID 44604301 (1998) 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) 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) 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)/ Doses	Results
870.4300 Combined chronic toxicity/carcinog-enicity (SD rat; 104-wk)	MRID 43303201 (1994) 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)	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)	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)	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).

Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
Cytogenetics 870.5385 Mammalian bone Marrow chromosome aberration test	MRID 00155083 (1983)	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 DNT damage or repair tests	MRID 00028625 (1979)	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)	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)	In an unscheduled DNA synthesis assay in WI-38 human fibroblasts, propanil was **negative** up to an insoluble level (1000 µg/mL).

Guideline No./ Study Type	MRID No. /(year)/ Doses	Results
METABOLISM STUDIES		
870.7485 Metabolism and pharmacokinetics (SD rat)	MRID 41796400, 41796402 (1991) 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.